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No abstract available

O1.2
No abstract available

O1.3
Bayesian Adaptive Designs for Precision Medicine: Promise, Progress and Challenge
J. Jack Lee
University of Texas MD Anderson Cancer Center, Houston, TX, USA

Clinical trial is a prescribed learning process for identifying safe and effective treatments. In recent years, rapid advancements in cancer biology, immunology, and genomics demand innovative methods to identify better therapies for the most appropriate population in a timely, efficient, accurate, and cost-effective way. In my talk, I will first illustrate the concept of Bayesian update and Bayesian inference, a superior alternative to the traditional frequentist approach. Bayesian methods take the “learn as we go” approach and are innately suitable for clinical trials. Then, I will give an overview of Bayesian adaptive designs in the areas of adaptive dose finding, posterior and predictive probability calculations, outcome adaptive randomization, multi-arm platform design, and hierarchical modeling, etc. Finally, real world applications will be discussed. Bayesian adaptive clinical trial designs increase the study efficiency, allow more flexible trial conduct, treat more patients with more effective treatments in the trial, and provide early stopping for futility or efficacy when sufficient evidence accumulates. Perspectives will be given on translating theory to practice to enhance the clinical trial success and speed up drug approval. We have developed Shiny applications and other software tools to assist the learning and implementation of Bayesian adaptive designs such that we can turn promise into progress. Many useful software can be found at the followings two sites:
https://biostatistics.mdanderson.org/softwareOnline/
https://biostatistics.mdanderson.org/softwareDownload/

O1.4
No abstract available
PLENARY SESSION 2: New avenues for target discovery

O2.1
No abstract available

O2.2
Chromatin dynamics – epigenetic parameters and cellular fate
Genevieve Almouzni
Institut Curie, Paris, France

Chromatin organization in the nucleus provides a large repertoire of information in addition to that encoded genetically. A major goal for my group involves understanding how histones, the major protein components of chromatin, the bricks, can mark functional regions of the genome through their variants or post-translational modifications, along with non-coding RNA and other chromatin regulators. Errors in the establishment and propagation of these chromatin components, possibly involving imbalance in their deposition pathways, can lead to mis-regulation of genome functions and pathological outcomes, such as cancer. The propagation of centromeric identity represents a model of choice for the study of epigenetic mechanisms. Our work has focused on histone chaperones, as architects of chromatin organisation. We will present our latest findings.

References:

O2.3
DNA damage response pathway inhibition – a pipeline and the phase 1 experience
Giorgio Massimini¹, Frank Zenke¹, Astrid Zimmermann¹, Lubo Vassilev², Lars Damstrup¹, Jan Cosaert², Mary Ruisi²

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²EMD Serono, Inc., Billerica, United States

Damage to DNA in humans is constantly occurring, is variable, and depends on inherent cell DNA stability and the environmental conditions that induce DNA damage. DNA damage events can happen at a rate between 1,000 and 10,000 damage events per cell per day, depending on species, requiring sophisticated mechanisms to recognize and repair the multitude of different damage types. Aberrations in DNA damage and repair pathways are even more frequent in cancer cells, and the DNA damage response (DDR) has emerged as an attractive intervention point for the development of new molecules for the treatment of cancer. New insight into DDR mechanisms has allowed a number of new druggable targets to be identified. We are developing a number of DDR small molecule inhibitors targeting different components of the DDR, such as DNA-PK, ATM, and ATR. An overview of their development, of the approach taken to define a biologically efficacious dose, and of the experience in their development will be presented.
PLENARY SESSION 3: Immunological approach to personalized medicine

O3.1
No abstract available

O3.2
No abstract available

O3.3
The Complex Challenges of Stratifying Patients for Immunotherapy
Steven Anderson
Covance, Durham, NC, United States

With an increasing focus on the delivery of precision medicine, biomarkers for patient stratification play a critical role in both immunotherapy drug development and the subsequent diagnostic testing of patient specimens. In the area of immunotherapy, a variety of cell, tissue and genomic based biomarkers are currently used for purposes ranging from exploratory assessments to patient stratification during the various stages of the drug development process. Recent examples include as PD-L1 status which is considered a companion diagnostic for certain therapeutic approaches and clinical indications; tumor mutation burden; neo-antigen burden; genomic instability; and cytokine/chemokine expression patterns. The use of biomarkers in trial design for individual immunotherapeutic approaches, as well as combination therapies, is increasingly relevant in this very complex and competitive area of drug development. The topics covered in this presentation will include a review of relevant biomarkers for immunotherapies; the impact of biomarkers on trial design and execution; and the role of companion diagnostics in the development and commercialization of specific immunotherapies.

O3.4
No abstract available
03.5
Patient-specific peptide vaccination
Hans-Georg Rammensee

University of Tuebingen, Institute for Cell Biology, Tuebingen, Germany

Therapeutic cancer vaccination trials reaching phase 3 until very recently were either complete failures or showed only marginal benefit. In contrast, there is a large number of phase II or earlier clinical trials, and case reports, reporting therapeutic vaccination with tumor antigens, viral, mutated, tumor-associated or tissue-specific, leading to antigen specific T cell responses associated with clinical benefit, especially when efficient adjuvants had been used. Since analysis of T cell responses of melanoma patients responding to checkpoint inhibition indicated neoantigens as targets of such therapeutically effective T cells, efforts are now concentrating on developing vaccination strategies against such antigens. Based on various sources, it can now be estimated that only between 0.1 and 1 percent of exome mutations can be detected as neoantigens.

However, tumors regularly present non-mutated tumor associated peptides with highly tumor specific expression. For both categories, the approach needs to be personalized with few exceptions, since both mutated as well as non-mutated tumor specific HLA ligands are different in every patient. Analyzing the entire detectable landscape of HLA ligands on tumor samples, consisting of 1000 through 5000 non-mutated peptides per sample, we do find dozens to hundreds of peptides in germline sequence with apparently tumor specific expression, based on the absence of these peptides on adjacent autologous benign tissue and absence on a large number of normal tissue samples from all organs and tissue types available for analysis, all, of course, within the sensitivity limits of our technology, tandem mass spectrometry. The population of these tumor peptides is highly different between patients. Many of these apparently tumor specific peptides are immunogenic, as tested by in vitro priming experiments with human T cells from healthy donors. We suggest that germline sequence HLA ligands with tumor specific expression should be efficient as targets for personalized antigen specific immunotherapy, combined with neoantigens, if one finds them. Critical will be the use of efficient vaccine delivery, powerful adjuvants, and combination with checkpoint inhibition or other immunomodulation.
PLENARY SESSION 4: Next great steps in cancer therapy

O4.1
No abstract available

O4.2
Proteogenomics: New Opportunities in Cancer Biology and Precision Medicine
Henry Rodriguez
National Cancer Institute, National Institutes of Health, Bethesda, MD, United States

Despite significant progress in understanding cancer through massively parallel sequencing genome programs, the complexity that comprises its diseases remains a daunting barrier. Today we know that molecular drivers of cancer are derived not just from DNA alterations alone, but from protein expression and activity at the cellular pathway level - proteomics. To predict the downstream effects of gene alterations, orthogonal technologies such as next-generation proteomics are needed. This proteogenomics approach (interplay between proteome and genome) is anticipated to transform oncology care from one that relies mainly on trial-and-error treatment strategies based on the anatomy of the tumor, to one that is more precisely based on the tumor’s molecular profile. This seminar will discuss how genomics, transcriptomics, and proteomics must all be brought together in the quest to understand the etiology of cancer, in addition to highlighting efforts by the U.S. National Cancer Institute’s Clinical Proteomic Tumor Analysis Consortium (CPTAC) program in this area of biomedical research. CPTAC began with the purpose of developing standardized (rigor & reproducibility) proteomic assays and workflows, in order to complement genomic and transcriptomic analyses. CPTAC’s proteogenomics approach was recently successful in demonstrating the scientific benefits of integrating proteomics with genomics to produce a more unified understanding of cancer biology and possibly therapeutic interventions for patients, while creating open community resources that are widely used by the global cancer community. This seminar will also highlight the recently announced APOLLO (Applied Proteogenomics Organizational Learning and Outcomes) program and the efforts of the International Proteogenomic Consortium. APOLLO brings together the U.S. National Cancer Institute, U.S. Department of Defense, and the U.S. Department of Veterans Affairs to create the nation’s first healthcare system in which cancer patients will be routinely screened for genomic abnormalities and proteomic information with the goal of matching their tumor type to a specific targeted therapy.

O4.3
No abstract available
Cancer Genome Sequencing in a Multi-Institutional Clinical Setting: The MASTER Study of the German Cancer Consortium

Stefan Fröhling

National Center for Tumor Diseases (DKFZ), Heidelberg, Germany

Precision oncology implies the ability to predict which patients will likely respond to specific cancer therapies based on increasingly accurate, high-resolution molecular diagnostics as well as the functional and mechanistic understanding of individual tumors. While molecular stratification of patients can be achieved through different means, a promising approach is next-generation sequencing of tumor DNA and RNA, which can reveal genomic alterations that have immediate clinical implications. Furthermore, certain genetic alterations are shared across multiple histologic entities, raising the fundamental question of whether tumors should be treated by molecular profile and not tissue of origin. We here describe MASTER (Molecularly Aided Stratification for Tumor Eradication Research), a clinically applicable platform for prospective, biology-driven stratification of younger adults with advanced-stage cancer across all histologies and patients with rare tumors. We illustrate how a standardized workflow for selection and consenting of patients, sample processing, whole-exome/genome and RNA sequencing, bioinformatic analysis, rigorous validation of potentially actionable findings, and data evaluation by a dedicated molecular tumor board enables categorization of patients into different intervention baskets and formulation of evidence-based recommendations for clinical management in a multi-institutional clinical setting. Critical next steps will be to increase the number of patients that can be offered comprehensive molecular analysis through collaborations and partnering, to explore ways in which additional technologies can aid in patient stratification and individualization of treatment, to stimulate clinically guided exploratory research projects, and to gradually move away from assessing the therapeutic activity of targeted interventions on a case-by-case basis towards controlled clinical trials of genomics-guided treatments.
PLENARY SESSION 5: Predict: what and how?

O5.1

No abstract available

O5.2

No abstract available

O5.3

Augmented Intelligence in the clinical set of Precision Oncology – A IBM Watson perspective

Vanessa V. Michelini

IBM Watson Health, Boca Raton, FL, United States

Watson for Genomics is a cloud-based tool that can help clinicians deliver precision medicine to cancer patients by providing evidence-based tumor analysis and therapeutic options. Watson for Genomics is trained and validated in collaboration with more than 20 leading cancer institutes and diagnostics labs world-wide. Watson uses relevant information extracted from massive volumes of medical literature and clinical trials to provide a genetic analysis of a patient’s cancer-causing mutations. Watson’s report includes recommendations for potential targeted therapies that are relevant to the unique DNA profile of a patient’s tumor. Using Watson for Genomics, clinicians are empowered with insights to create personalized treatment plans for their cancer patients.

This session will discuss how a cognitive tool like Watson speeds up the analysis of sequenced DNA in a clinical set and working side by side with clinicians, increase the number of cancer patients that can have access to genomic analysis.

O5.4

No abstract available
PLENARY SESSION 6: Using new knowledge in clinical trials

O6.1
No abstract available

O6.2
No abstract available

O6.3
Molecular medicine in lung cancer - Insights in molecular pathogenesis driving better therapies
Reinhard Büttner

University Hospital of Cologne, Cologne, Germany

Traditionally, tumors are classified by histopathological criteria, i.e., based on their specific morphological appearances. Consequently, current therapeutic decisions in oncology are strongly influenced by histology rather than underlying molecular or genomic aberrations. The increase of information on molecular changes, however, enabled by the Human Genome Project and the International Cancer Genome Consortium as well as the manifold advances in molecular biology and high-throughput sequencing techniques, inaugurated the integration of genomic information into disease classification. We have therefore introduced multiplex deep sequencing of informative gene sets into routine histopathological diagnostics and molecular pathology. This comprehensive approach integrating morphological and molecular information is currently changing cancer diagnostics in five categories: (1) Somatic genomic or epigenomic alterations acquired during cancerogenesis may be used for disease classification as we show this approach adding important information to conventional morphological classifications. (2) A significant portion of solid tumors depend on oncogenic driver lesions, which provide molecular targets for prediction of effective and selective therapies. (3) Genomic alterations in signal transduction cascades and gene expression pattern may be used as prognostic parameters predicting the need and extent of adjuvant therapy. (4) In the case of multiple syn- or metachronous tumors, genomic profiling assists allocation of metastases from tumors with unknown primary (CUP) and correct staging as multiple small primary tumors and systemic metastases are reliable being discriminated. (5) Finally, mutational profiling of tumor circulating tumor DNA may facilitate monitoring the response of tumors to therapy and development of secondary resistance. In addition, immune checkpoint inhibitor therapies have been implemented and proved to provide significant benefit for tumors lacking drugable oncogeneic driver lesion. We therefore have implemented hybrid capture-based NGS and expression profiles of PD-L1 to select specifically patients for immune checkpoint inhibitor therapies. Taken together, comprehensive molecular tumor pathology and oncology paves the way for a new rational and.

O6.4
No abstract available
Prostate cancer (CaP) remains the most common male malignancy worldwide. Although some localized cancers can be indolent, others can manifest aggressive biology with abnormal cancer metabolism and genetic instability. These men need intensified treatment to prevent metastatic castrate-resistant disease (mCRPC). However, the genomic landscape of prostatic cancer heterogeneity relative to outcome is not known. We analyzed the whole-genomes and methylomes of close to 500 men with sporadic prostate cancers treated by surgery or radiotherapy. Unlike mCRPC, these tumours have few clinically-actionable mutations despite a high level of important genomic rearrangements associated with chromothripsis and kataegis. Even pathologically similar cancers have great heterogeneity in clinical outcome and this associated with a unique 5-feature signature consisting of mutations, copy-number alterations and altered methylation. We have broadened our genomics approach to two other aggressive features of prostate cancer: (1) aggressive sub-pathologies such as intraductal carcinoma with cribriform architecture (IDC-CA), and (2), BRCA2-associated prostate cancers. The poor outcome associated with IDC and CA sub-pathologies was found to be associated with a constellation of genomic instability, SChLAP1 expression, and hypoxia. We posit a novel concept in IDC/CA+ prostate cancer, “nimbosus” (gathering of stormy clouds, Latin), which manifests as increased metastatic capacity and lethality. Prostate cancers that develop in mtBRCA2-carriers are associated with an aggressive course with 50% mortality at 5 years. We observed increased genomic instability and a mutational profile that more closely resembles metastatic, rather than localized sporadic disease, in mtBRCA2 PCa. These tumours also show genomic and epigenomic dysregulation of the MED12L/MED12 axis, which is involved in beta-catenin-WNT signaling-usually only dysregulated in mCRPC. Our data strongly suggests that novel therapeutic approaches should also focus on recurrent non-mutation targets in sporadic, localized prostate cancer in order to improve cures a priori. IDC-CA and BRCA2 prostate cancer variants should be further treated with intensification.
06.6 Concluding Remarks

Systems Medicine, Big Data and Scientific Wellness are transforming Healthcare

Leroy Hood

Institute of Systems Biology and Providence Health and Services, Seattle, WA, United States

Systems medicine, the application of systems approaches to disease, places medicine at a fascinating tipping point—promising a revolution in the practice of medicine. I will discuss how systems biology approaches have framed systems medicine and I will discuss some of the new systems-driven technologies and strategies that have catalyzed this tipping point. Moreover, four converging thrusts—systems medicine, big data (and its analytics), the digitalization of personal measurements and patient-activated social networks—are leading to a proactive medicine that is predictive, personalized, preventive and participatory (P4). I will contrast P4 medicine with contemporary medicine and discuss its societal implications for healthcare. P4 medicine has two central thrusts—wellness and disease.

I will discuss our successful effort to introduce P4 medicine into the current healthcare system with a P4 pilot program on scientific wellness—a longitudinal, high-dimensional data cloud study on each of 108 well patients over 2014. The preliminary results both with regard to data analyses and patient responses from these studies are striking. They point to the emerging discipline of scientific wellness—and the fact that it will catalyze several new thrusts in healthcare: 1) optimizing wellness, 2) identifying the earliest disease transitions for all common diseases and learning how to reverse them and 3) employing the dense, dynamic, personal data cloud approach to study diseases (e.g. cancer, Alzheimer’s, diabetes) and their responses to therapy. Scientific wellness will also pioneer N=1 experiments to deconvolute the staggering complexity of human biology and disease. We started Arivale, a company focused on scientific wellness for the consumer, in 2015 and already have 1500 individuals enrolled. I will also discuss some preliminary results from the Arivale studies.

My institute, the Institute for Systems Biology (ISB), in 2016 affiliated with Providence St. Joseph Health to become its research arm and LH its Chief Science Officer. Providence is one of the largest non-profit healthcare systems in the US—and ISB/Providence will be initiating a series of “translational pillars” moving applications of systems (P4) medicine from the bench to the bedside. These pillars include scientific wellness, bringing scientific wellness to cancer survivors, making Alzheimer’s a reversible and preventive disease, rather than a relentlessly progressive disease, taking a systems approach to type 2 diabetes and exploring how the deep, dynamic, personal data clouds can be used to gain a deep understanding of glioblastoma and provide new diagnostic and therapeutic approaches to this inevitably fatal tumor. It is fair to say that dense, dynamic, personal data clouds followed longitudinally on hundreds of thousands of patients will allow us to see the earliest wellness to disease transitions for all of the common cancers—and generate biomarkers for early detection and identify the drug targets or strategies (e.g., immunotherapy) that will allow us to reverse the disease before it ever manifests itself as a disease phenotype.

Thus scientific wellness will catalyze a transformation in contemporary healthcare and it will provide eventually millions of dense, dynamic, personal data clouds that will present striking new opportunities for pharma, biotech, nutrition and diagnostic companies to identify biomarkers and drug target candidates. As the cost of the assays for the dense, dynamic, personal data clouds decline; scientific wellness can be brought to the developing world leading to a democratization of healthcare unimaginable even a few years ago.
Molecular Investigation of Wild and Mutant Active Binding Site Expression of GPR15 in Cancer using Computational Approach

Aman Chandra Kaushik¹, Eitan Rubin²

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²Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Background: GPCRs play a key role in many signal transduction pathways and are significant as drug targets. GPCRs with unknown ligands and/or target pathway are known as “Orphan GPCRs”. GPR15 is an important orphan GPCR that plays a crucial role in many physiological functions. The E144V mutation in GPR15, which is often observed in cancer, makes it an attractive target for therapeutic intervention. Here we present in silico screening for potential compounds that bind the ligand binding site of the wild type and mutant structures of GPR15.

Method: An approximate structure of the mutant GPR15-E144V was created by setting amino acid 144 to Valine. Grid box was generated around 5Å area of the pocket E144 in wild and V144 in mutant. A library of 55,975 compounds obtained from Maybridge Library was used for the screening of compounds for affinity with both wild and mutant structures. Top hits were selected based on scoring function (Chem score + G Score + D Score + PMF Score). We also applied a cutoff (Total score >5) on the docking score function to eliminate false positives. Molecular Dynamics simulation was done for top two potential inhibitors to check their stability and interaction fraction during Molecular Dynamics Simulations. Finally, affinity to the wild-type and mutated version of GPR15 was estimated computationally.

Results:
Similarly, we present analyzes of the drugs used for the WINTHER trial. We present a comparison of each compound affinity to wild-type and normal GPR15, showing which has the potential to offer specific inhibition of the mutated version of GPR15. Top five potential compounds were obtained from wild type model using screening approach and top five potential compounds were obtained from mutant type model using screening approach; and then compare with each other using Docking score. It means mutation in E144 can affect the binding mode of inhibitors.

Conclusions:
We present top five potential compounds which could be considered in the development of new therapeutic agents for colon cancer.

Keywords: Cancer Medicine; GPCRs; GPR15; Molecular Modeling; Molecular Dynamics Simulation
**POSTER SESSION 2: Biomarkers (prognostic and predictive)**

**P2.2**

Bioinformatic/MS proteomic approach to identify a panel associated with the response to therapy in drug-resistant ovarian cancer tissue.

Maria Paola Costi, Leda Severi, Lorena Losi, Gaia Gozzi, Gaetano Marverti, Sergio Fonda, Fulvio Magni, Clizia Chinello, Martina Stella, Jalid Sheouli, Ioana Braicu, Filippo Genovese, Chiara Maraccini, Domenico D’Arca, Stefania Ferrari

1. University of Modena and Reggio Emilia Modena, Italy
2. University of Milano Bicocca, Milano, Italy
3. European Competence Center for Ovarian Cancer, Berlin, Germany
4. Centro Interdipartimentale grandi strutneti, Modena, Italy
5. Ospedale Sanat Maria, Reggio Emilia, Italy

Ovarian cancer is the seventh most common cancer and the eighth most common cause of cancer-related death in women. The most frequent subtype is high-grade serous carcinoma. Therapy relies on debulking surgery and platinum-based chemotherapy. Despite the initial high response rates to platinum drugs, most patients relapse, develop resistance to classical chemotherapy, and subsequently die from the disease. Tools for the identification of a sub-population of patients who respond to a specific treatment are needed. In our studies on anticancer drugs targeting the folate pathway, tissue samples collected from patients to whom pemetrexed was administered after failure of the first-line carboplatin-based chemotherapy suggested the possibility of identifying a protein panel to predict the response to pemetrexed-based therapy.

The investigational protein panel was discovered using a mass spectrometry (MS) label-free proteomic relative quantification approach. Statistical metrics of the experimental MS data were combined with a knowledge-based approach that included bioinformatics and a literature review to design a protein set of reference (PSR). The PSR provides feedback for the consistency of MS proteomic data because it includes known validated proteins. The method was applied to three tissue samples from patients with ovarian cancer.

A panel of 24 proteins with levels that were significantly different in pre-treatment samples from patients who responded differently to the pemetrexed treatment was identified. The global interpretation of the MS data was performed using a bioinformatic analysis and was driven by the purposely designed PSR with the aim of providing internal experimental validation.

The final panel should be tested in retrospective clinical trials to validate the ability of the identified tool to predict the response of patients with platinum-resistant ovarian cancer to pemetrexed.

**Reference:**

**Acknowledgment:**
The Authors acknowledge AIRC2010 IG16944, AIRC2015 IG 16977 and EUTROC (European Translational Research In Ovarian Cancer), http://eutroc.org/.
A novel 3′UTR panel to predict axillary lymph node involvement in operable triple-negative breast cancer

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²Shanghai Advanced Research Institute, Chinese Academy of Sciences, Shanghai, People's Republic of China

Background: Triple-negative breast cancer (TNBC) is known for its clinical and molecular heterogeneity. Sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) are standard surgical staging approaches for operable TNBC. In this study, we developed a novel 3′UTR panel to predict axillary lymph node involvement (ALNI) in TNBC patients with the aim of exempting low-risk patients from the invasive axillary staging surgery.

Methods: We evaluated 3′UTR profiles using currently available microarray data from 327 patients with TNBC. Samples were randomly divided into either a training set (n = 164) or a validation set (n = 163) according to chip batch stratification. We constructed a 15-member 3′UTR-panel (consisting of APOL2, IL21R, BID, DGCR14, UST, ADD2, SNN, NRCAM, PKP2, YIPF6, NUMB, KCMF1, TFB2M, OSBPL1A and COL1A1) using an elastic net model to predict the risk of ALNI after initial feature filtering. Receiver operating characteristic (ROC) and logistic analyses were used to assess the predictive power of the panel.

Results: In the training set, ALNI occurred in 50% of high-risk patients (odds ratio [OR] 10.6, 95% CI 4.48-25.1; p<0.001), and in 8.6% of low-risk patients. The panel showed a high distinguishing power with an area under the curves (AUC) of 0.829 (95% CI 0.748-0.909). In the validation set, 37.7% of high-risk patients had nodal involvement (OR 5.01, 95% CI 2.22-11.3; p<0.001) whereas 10.7% of subjects in the low-risk group had an AUC of 0.772 (95% CI 0.684-0.861). After adjustment by clinical factors, the 15′3′UTR-panel retained significant predictive accuracy (OR 8.54, 95% CI 4.56-16.0; p<0.001). A combinatorial analysis of the 3′UTR panel and tumor size increased the AUC to 0.784 (95% CI 0.729-0.839).

Conclusions: This study revealed a 15′3′UTR-panel as a promising predictor for ALNI in operable TNBC. Our results may permit a non-invasive personalized management of ALN staging in TNBC patients.
Circular RNA profile identifies circLMTK2 is upregulated and as a proliferative factor and prognostic marker in gastric cancer

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Background: Despite many advances in the diagnosis and treatment of gastric cancer (GC), the prognosis of patients with GC remains poor. Circular RNAs (circRNAs), a new star of the non-coding RNA network, have been identified as critical regulators in various cancers. There is increasing evidence that circRNAs represent a class of widespread and diverse endogenous RNAs that may regulate gene expression. However, the role of circRNAs in GC remains elusive. Here, we aimed to determine the circRNA expression profile and investigate the functional and prognostic significance of circRNA in GC.

Materials and Methods: In this study, we investigated the expression profile of circRNAs in three GC samples and paired adjacent normal tissues using ribo-minus RNA sequencing and a bioinformatics analysis. Furthermore, quantitative reverse transcription polymerase chain reaction (qRT-PCR) was performed to identify circRNA candidates. Molecular and cellular techniques were used to explore the biological function and mechanism of circRNA in GC cells. The prognostic significance was analyzed using the Kaplan-Meier method and the Cox proportional hazards model.

Results: We first characterized circular RNA transcripts using RNA-seq analysis of ribosomal RNA-depleted total RNA from three paired normal and cancerous gastric tissues. In all, 15623 distinct circRNA candidates were found in these tissues and at least 5500 distinct circRNAs are differently expressed in GC tissues compared with matched normal tissues. We further characterized one abundant circRNA derived from the LMTK2 gene, termed circLMTK2. The expression of circLMTK2 is often upregulated in GC tissues and the silencing of circLMTK2 significantly inhibits gastric cancer cell growth. Furthermore, the level of circLMTK2 was observed as an independent prognostic marker for overall survival and disease-free survival of patients with GC.

Conclusions: Our study revealed the circular RNA profile of GC tissues and characterized a differentially expressed circRNA derived from the LMTK2 gene. circLMTK2 may serve as a new proliferative factor and prognostic marker in gastric cancer.
Figure. (A-C) RNA-seq analysis of circular RNAs in gastric cancer tissues. (D) Clustered heatmap of the differentially expressed circRNAs. (E) Circos plots showing the differentially expressed circRNAs and their host genes in GC tissues. (F) The genomic loci of the LMTK2 gene and circLMTK2. (G) qRT-PCR analysis of circLMTK2 in either the cytoplasm or the nucleus. (H) qRT-PCR analysis of circLMTK2 after treatment with Actinomycin D. (I) Schematic representation and target sequences of the siRNAs and qRT-PCR analysis of circLMTK2 expression after treatment with two siRNAs. (J and K) Assessment of proliferation of MGC-803 and AGS cells transfected with control or circLMTK2 siRNAs by CCK-8 assay. (L) circLMTK2 is frequently up-regulated in gastric cancer. (M) Kaplan-Meier analysis of the correlation between circLMTK2 expression and overall survival in gastric cancer patients.
A Novel Splice Variant to NCOR2 as Biomarker for Tamoxifen Resistant Breast Cancer

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More than two-thirds of all breast cancers are estrogen receptor (ER) positive for which Tamoxifen revolutionized their management as adjuvant treatment to prevent cancer recurrence. Almost half of these patients eventually develop resistance. The mechanisms underlying tamoxifen resistance are not yet well understood. There is no robust biomarker to reliably predict those who will be resistant. By the time drug resistance is established, the cancer has already progressed and sometimes metastasized. We have identified a novel splice variant, BQ323636.1 which retains only the N-terminus repression domain 1 of the NCOR2 wild-type protein. Overexpression of BQ conferred resistance to tamoxifen in both in vitro and in orthotopic mouse model. Mechanistically, co-immunoprecipitation showed BQ could bind to NCOR2 and inhibit the formation of co-repressor complex for suppression of the ER signaling. Consistently, BQ overexpression compromised the suppressive role of NCOR2 in regulating estrogen-response element activity and rescued transcriptional suppression of tamoxifen on ER-target genes. We generated a monoclonal antibody specific for BQ used to predict patients' responses to tamoxifen treatment. Immunohistochemistry was performed on tissue microarray of 355 patients with clinical follow-up data of more than 10 years, who had ER positive primary breast carcinoma and had received adjuvant tamoxifen treatment. Nuclear BQ overexpression was significantly associated with tamoxifen resistance by Chi-square test, \( p=3.90 \times 10^{-6} \) with a sensitivity of 51.4% and specificity of 72.9%. In tamoxifen treated patients, nuclear BQ overexpression was significantly correlated with cancer metastasis, \( p=1.72 \times 10^{-6} \), and also significantly associated with disease relapse, \( p=3.47 \times 10^{-4} \). Consistent with its role in predicting tamoxifen resistance, nuclear BQ was significantly associated with poorer survival by Kaplan-Meier estimate (Log-rank test) \( p=6.28 \times 10^{-5} \) and \( p=1.31 \times 10^{-4} \) for overall survival and disease-specific survival respectively. The development of such reliable biomarker would enable appropriate alternative therapy to be given at an early stage, thus saving the patient from the side effects as well as risk of inappropriate treatment by tamoxifen.

Proposed mechanism of how BQ323636.1 may induce tamoxifen resistance in breast cancer
Assessment of the response to neoadjuvant Chemo-Radiation in rectal cancer patients based on a metabolomics approach

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Purpose: We report a metabolomics study to identify potential metabolite biomarkers in predicting pathological response after neoadjuvant chemo-radiation therapy (NCRT) for locally advanced rectal cancer (LARC).

Methods: The ultraperformance liquid chromatography quadrupole time-of-flight mass spectrometry (UPLC-QTOF/MS)–based metabolomics was used to analyze 106 serum samples, which were collected from patients treated with NCRT in Fudan University Shanghai Cancer Center (FUSCC) between July 2014 and January 2016. Differential metabolites were identified between sensitive and resistant patients to NCRT evaluated based on tumor regression grade (TRG) according to univariate analysis and multivariate analysis. The predictive performance was evaluated by area under receiver operating characteristic curve (AUC).

Results: A total of 4810 metabolites were identified and 57 significant metabolites were selected. With the 57 metabolic biomarkers, we were able to differentiate sensitive patients from resistant patients using partial least-squares discriminant analysis (PLS-DA) in a sample set of 56 sensitive patients and 49 resistant controls. The combination of these 57 biomarkers had the AUC value of 0.88, 0.81 and 0.84 in the PLS, Random Forest, and support vector machine prediction model, respectively. The results demonstrate that a panel of metabolite biomarkers is of great potential for the prediction of response after NCRT for LARC. Furthermore, the fifteen highest-ranking significantly metabolites were finally identified. A PLS model constructed with fifteen markers also has an ideal discriminant performance with an AUC of 0.80.

Conclusion: Through a systematic metabolomics analysis, we are able to build a model to predict the response after NCRT for LARC. These results show promise for larger studies that could produce more personalized treatment protocols for LARC.

(a) Fifty seven featurea are selected (the cutoff values of fold change is set as larger than 1.2 or less than 0.83); (b) Those 57 features can separate most resistant from most sensitive group sample; (c) The combination of these 57 biomarkers had the AUC v
**P2.7**

Oncogenetic key signal RANTES/CCL5 - „Cytokine cross talk“ in tumors and silent inflammation of jawbone

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**Background:** The importance of the microenvironment surrounding the tumor cells with "silent inflammation" increases. Objective: To check the suspected tumor-relevant inflammatory cytokine sources in fatty-degenerative osteonecrotic jawbone (FDOJ), we analyze these conspicuously altered jawbone areas to assess quantification of cytokine expression.

**Material and Method:** In 38 tumor patients we determine the levels of cytokines by bead-based Luminex® analysis in samples of FDOJ. Results: Striking is the high content of chemokine RANTES/CCL5 (R/C) in all 38 tissue samples on average at 35 fold higher compared to healthy jawbone. A single case is reported by high R/C levels in FDOJ sample and simultaneously by metastasizing cells inside the FDOJ sample.

**Discussion:** R/C interacts on several levels in immune responses and is considered in scientific literature as pathogenetic key point in tumor growth. The study supports a potential mechanism where FDOJ is a mediating link specifically in breast cancer (MaCa) and its metastasis.

**Conclusion:** The authors conclude from the data of FDOJ analysis that these areas express hyperactivated signal transduction of the chemokine R/C, induce pathogenetic autoimmune processes in tumors, MaCa and its metastasis and serve as a possible cause. It may be suggested to involve FDOJ in an integrative therapy concept for tumor therapy.

Graph shows signaling overexpression of RANTES/CCL5 compared to healthy jawbone. Photographs in left panel shows sample of fatty-degenerative medullary jawbone (FDOJ); right panel shows extent of osteolytic and softened jawbone by contrast medium.
The Expression and Clinical Significance of PERK and p-eIF2α in Pancreatic Ductal Adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest malignancies with a dismal five-year survival rate of 6.0%. Previous studies showed that endoplasmic reticulum (ER) stress plays an important role in PDAC development and chemoresistance. ER stress activates unfolded protein response, which subsequently lead to the phosphorylation of eukaryotic initiation factor 2 alpha (eIF2α) by protein kinase R-like ER kinase (PERK). However the expression and clinical significance of phospho-eIF2α (p-eIF2α) and PERK in PDAC have not been examined.

Materials and methods: We examined the expression of p-eIF2α and PERK in 84 PDAC and their paired normal pancreas samples from patients who underwent surgical resection with curative intent using tissue microarrays and immunohistochemical staining. We also examined PERK and p-eIF2α expression by Western blot using paired frozen samples of normal pancreas and PDAC. The results of p-eIF2α and PERK expression were correlated with clinicopathologic parameters and survival using SPSS Statistics.

Results: The mean H score for PERK expression in PDAC was 140.8 compared to 82.1 in normal pancreas (p<0.001). Using the median H-score in PDAC as a cut off, 42 (50%) PDAC had high level of PERK expression. High level of p-eIF2α expression was present in 47 (56%) PDAC, but only in 5 (7.6%) matched normal pancreas. The expression levels of p-eIF2α and PERK was higher in PDAC than those in normal pancreas, which was validated by Western blots. PERK expression in PDAC correlated significantly with p-eIF2α expression (p=0.008). High levels of PERK and p-eIF2α expression were associated with shorter survival (p=0.048 and p=0.03 respectively). By multivariate analysis, high level of p-eIF2α (p=0.01), positive margin (p=0.002) and lymph node metastasis (p=0.01) were independent predictors for shorter survival in PDAC patients.

Conclusions: Our results show that the expression levels of PERK and p-eIF2α are higher in PDAC than those in normal pancreas. High levels of PERK and p-eIF2α expression are predictors of shorter survival in PDAC patients. Our data suggest that PERK and eIF2α could be promising targets for PDAC.
P2.9
Assessing tumor heterogeneity and biomarkers of therapeutic resistance using a multi-omics strategy in metastatic colorectal cancer patients

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Background: Colorectal cancer (CRC) is the 2nd leading cause of cancer relating-death in Canada and therapeutic resistance remains a major obstacle in metastatic (m)CRC. Studies aiming at understanding mechanisms of resistance have largely investigated primary tumors. However, selective pressures during therapy can lead to tumor heterogeneity. This highlights the need to characterize the molecular changes of metastasis and plasma over time of treatment and response to decipher tumor evolution and therapeutic resistance mechanisms.

Material and methods: Eighty-eight (88) metastatic liver tissue samples were collected at baseline (pre-biopsies) and at relapse (post-biopsies) in sixty-one (61) responder and non-responder mCRC patients undergoing the same standard first-line treatment. Four (4) patients had multiple post-biopsies, to allow the assessment of intra- and inter-tumor heterogeneity after treatment exposure. Biopsies were profiled using exome and transcriptome sequencing as well as high-density SNP array analysis to capture chromosomal anomalies, loss of heterozygosity and copy number variations (CNV). Serial blood samples were also collected for proteomic and ctDNA analysis.

Results: Exome sequencing allowed the characterization of recurrent mutations and the clonal dynamics over time of treatment. Integrated analysis of matched SNP array analysis and transcriptome datasets of successive pre- and post-biopsies revealed genomic anomalies associated with consistent gene expression changes, allowing the identification of robust candidates. In chemo-naïve biopsies, specific CNV regions have been found significantly associated with patient progression free survival by Kaplan-Meier analysis. Immune gene expression analysis identified a subgroup of patients with putative immune-reactive metastases. Plasma-derived ctDNA analysis was performed to investigate the mutational status during treatment and whether they correlate with their relative levels in biopsies.

Conclusion: Our study, using a multi-omic approach to profile liver metastasis samples and serial liquid biopsies in mCRC patients, constitutes an innovative approach to identify clinical biomarkers and molecular signature of resistance, which may enhance the development of personalized therapy.
We questioned whether the expression dynamics of the entire CTA family in cancer could serve to improve our ability to assess the disease. We employed especially designed computational ranking methods to study the expression of all known CTAs, measured using microarrays and deep sequencing, in close to 15000 samples, including more than 100 types of solid cancers. CTA provided an expression signature that was consistently sufficient to determine the existence and staging of all solid cancers tested, with close to perfect accuracy. We found two CTA uncorrelated components that coexist in all solid cancers—One component of genes that are part of the mitotic cell cycle appearing in most known cancer prediction signatures, not located on the X chromosome and consistently appearing up regulated in the order of 2 to 5. The second component, CTA genes mostly residing on chromosome X, aberrantly highly expressed in the order of 5 to 100, and not strongly correlated to other genes. Treating cell lines, with B-raf and Egfr inhibitors affected the first component. 5-aza-2'-deoxycytidine treatment of cell lines, affected the second component. Residing.
POSTER SESSION 3: Clinical trial design

P3.1
Criteria for futility and efficacy evaluation in interim analyses and final evaluation of phase II-trials

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A phase II trial is typically a small-scale study to determine whether an experimental treatment should continue further clinical evaluation. In this setting, interim analyses are commonly performed to allow for early stopping for futility and/or efficacy. The use of Bayesian posterior probability as decision rule for early stopping and for final analysis has been suggested, especially in the context of biomarker-targeted therapies with small numbers of patients. In comparison to traditional hypothesis testing-based approaches the advantage is the flexibility with respect to number and timing of interim analyses as well as the final number of patients included in the study. Using a Bayesian hierarchical model, borrowing of information across similar study arms is possible.

The INFORM2 phase I/II trial series addresses individualized therapy for relapsed malignancies in childhood using next-generation diagnostics. The trials have a dichotomous endpoint and will include interim futility and/or efficacy evaluations. They are one-arm trials or have several arms run in parallel. Sample size is restricted by recruitment rate and duration and hence identical evaluation criteria for interim and final analyses will be used. We will show a workflow for planning of the trials and show the impact of the choice of the Bayesian model and the prior distributions for decision making.
POSTER SESSION 4: Diagnostic

P4.1
The value of CT texture analysis for evaluating response to neoadjuvant chemotherapy for colorectal liver metastases

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Objective: To explore whether the computed tomography (CT) histogram analysis of baseline CT portal images before treatment can help predict the response of patients with colorectal liver metastases (CRLM).

Materials and Methods: Thirty-four patients (A total of 132 lesions) diagnosed with CRLM were retrospective enrolled and underwent contrast-enhanced CT before and after neoadjuvant chemotherapy (FOFOX, FOLFIRI or CapeOX). All patients underwent pre-treatment CT baseline scan within four weeks for primary tumor assessment and a second CT scan in 2 to 3 month for response evaluation. Histogram analysis of CT portal images of patients with CRLM and response is mainly assessed using Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1). The texture parameters of the metastatic tumor were analyzed statistically to find the differences in baseline CT histogram parameters between the two groups before and after treatment. The ROC curves were depicted to characterize each parameter value for evaluating the treatment outcome. The optimal cut-off values (obtained according to the maximal Youden index = sensitivity + specificity-1), the corresponding sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy could be calculated. ROIs (regions of interest) were manually drawn on the largest cross-sectional area of the primary lesions by two radiologists in consensus.

Results: 21 responding and 13 non-responding patients were evaluated. The value of mean, variance, skewness and percentile (10th, 50th, 90th, 99th) in patients with respond were much lower than that in non-respond (p < 0.05). The kurtosis and 1st percentile values between two groups exhibited no significant difference (p=0.769, p=0.06, respectively). The optimal cutoff value for the accurate identification of patients with respond was 167 for 90th percentile (74.42% sensitivity, 91.3% specificity, 66.67% PPV, 66.67% NPV, 81.82% accuracy, and 0.854 AUC, respectively).

Conclusion: The computed tomography (CT) histogram analysis of baseline CT portal images before treatment can help predict the response of patients with colorectal liver metastases.
P4.2
Differential diagnosis of pulmonary metastasis from non-metastasis in patients with colorectal cancer by histogram parameters based on CT

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Objective: To determine whether whole-lesion histogram parameters of pulmonary nodules based on computed tomography (CT) images can distinguish between lung metastasis and non-metastasis in patients with colorectal cancer (CRC).

Methods: We analyzed the chest CT images of 276 CRC patients with pulmonary lesions between January 2010 and October 2016. Patients were divided into two groups: metastasis group which was confirmed by pathology and non-metastasis group which was confirmed by follow-up and tissue samples. Whole-tumor volumetric texture analysis was performed on CT images by semi-automatically contouring a region of interest around the tumor outline for each slice by using proprietary software. Histogram parameters including kurtosis, skewness, mean, volume, sphere value and standard deviation were derived from the pixel distribution histogram by software algorithm. Multivariate logistic regression analysis was performed to build a discriminating model with histogram parameters to investigate the differentiating factors of LM from NM. Receiver operating characteristic curve analysis were generated to evaluate its discriminating performance.

Results: Of 276 nodules, pathologic analysis confirmed 141 LMs, 15 NMs and follow-up confirmed 30 LMs, 90 NMs. Multivariate analysis revealed that kurtosis and sphere value were significantly higher (0.73 versus -0.79, OR=0.77, P<.0001; 1.59 versus 0.65, OR=15.17, P<.0001, respectively) while skewness was significantly lower (-1.03 versus 0.13, OR=0.25, P<.0001) in LM compared to NM. Area under the ROC curves (AUC), to discriminate between LM and NM, were significantly higher for sphere value (AUC=0.87, 95% CI 0.82–0.90), skewness (AUC=0.85, 95% CI 0.80–0.89) and kurtosis (AUC=0.67, 95% CI 0.61–0.72) compared to all other parameters. With median attenuation, the standard deviation, volume, kurtosis, skewness and sphere value, the logistic regression model showed excellent accuracy in the differentiation of LM from NM (AUC=0.92, 95% CI 0.88–0.94, 88.9% sensitivity, 81.9% specificity).

Conclusion: In patients with CRC, higher kurtosis, sphere value and lower skewness are significant differentiators of LM from NM, and LM can be accurately differentiated from NM by using CT histogram analysis.
P4.3
Development of Novel Sodium Fluoride-PET Response Criteria for Solid tumors (NAFCIST) in Osteosarcoma: From RECIST to NAFCIST

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**Purpose:** The development of osteosarcoma therapeutics has been challenging, in part because of the lack of appropriate criteria to evaluate responses. We developed a novel criteria in clinical trial of radium-223 dichloride (223RaCl2) for response assessment in osteosarcoma: NAFCIST.

**Experimental Design:** Patients received 1-6 cycles of 223RaCl2, and cumulative doses varied from 6.84 MBq to 57.81 MBq. Molecular imaging with technetium (Tc)-99m phosphonate scintigraphy, fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) or sodium fluoride-18(Na18F)PET was used to characterize the disease. Correlation of biomarkers and survival was analyzed with NAFCIST measure from Na18F-PET.

**Results:** Of the 18 patients, 17 had bone lesions visible in at least one of the imaging studies. In 4/7 patients with multiple skeletal lesions (>5), FDG-PET and NaF-PET studies could be compared. The skeletal tumor locations varied in our patient population: [Cranium = 2, extremities =7, pelvis =10, spine =12, and thorax= 9].

The 18F-FDG-PET and Na18F-PET studies could be compared in all four patients who had multiple lung lesions (>5). Overall RECIST response was seen in one patient, but four patients experienced mixed responses better defined by Na18F-PET. Changes in NAFCIST were correlated with changes in bone alkaline phosphatase levels ($r = 0.54$), and negatively with cumulative dose of 223RaCl2. ($r = -0.53$). NAFCIST correlated with survival ($p$ value 0.037), versus PERCIST did not ($p$-value 0.19).

**Conclusions:** Our results indicate that Na18F-PET should be used in osteosarcoma staging. NAFCIST may be a promising criteria for high-risk osteosarcoma response evaluation, and correlates with survival. Further validation studies are needed.
P4.4
The Clinical Impact of New AJCC Stage for Treated Pancreatic Ductal Adenocarcinoma

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Background: The new AJCC stage (8th edition) for pancreatic ductal adenocarcinoma (PDAC) stratifies the patients by tumor size [pT1, ≤2 cm (pT1a, ≤0.5 cm; pT1b, >0.5 cm and ≤2 cm, and pT3, >4 cm] and the number of positive lymph nodes (N0, no regional nodal metastasis; N1, 1-3 positive nodes; ≥4 positive nodes). However the prognosis of this new T stage system has not been validated in patients who received neoadjuvant therapy and pancreaticoduodenectomy (PD).

Materials and methods: Our study population consists of 398 patients (176 females and 222 males; median age: 64.1 years) who received neoadjuvant therapy and underwent PD for PDAC at our institution from 1999-2012. All PD specimens were processed using a standardized pathologic evaluation system. The T and N stages were correlated with clinicopathologic parameters and survival using SPSS Statistics.

Results: There were 9 ypT0 (pathologic complete response with no residual carcinoma, 2.3%), 152 ypT1 (38.2%: 16 ypT1a [4%], 14 ypT1b [3.5%], and 122 ypT1c [30.7%]), 203 ypT2 (51%), and 34 ypT3 (8.5%) patients. The ypN0, ypN1 and ypN2 disease was present in 183 (46.0%), 142 (35.7%) and 73 (16.3%) patients respectively. Both the new ypT stage and ypN stage correlated significantly with disease-free survival (DFS) and overall survival (OS). The new T stage correlated with nodal metastasis (p<0.001) and tumor regression grade (p<0.05). In multivariate analysis, new ypN stage was a significant predictor for both DFS (p<0.001) or OS (p<0.001)

Conclusions: Our study shows that the new ypT stage and ypN stage are significant prognostic factors in patients who received neoadjuvant therapy and PD. Our study suggests that tumor size cutoff for T2 should be 1.0 cm for patients with PDAC who received neoadjuvant therapy.
P4.5

The preliminary study of 18F-FES PET in predicting metastatic breast cancer patients receiving fulvestrant with docetaxel

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Purpose: We aimed to evaluate the efficacy of combining fulvestrant with docetaxel in hormone-receptor positive and HER2-negative metastatic breast cancer, and the clinical prediction value of 18F-FES PET/CT.

Methods: Twenty-two patients with pathology confirmed ER/PR+, HER2- metastatic breast cancer were prospectively enrolled and randomly divided into two groups (T: docetaxel, n=8 and TF: docetaxel+fulvestrant, n=14). Among them, six patients in group TF and 9 patients in group T underwent both 18F-FES and 18F-FDG PET/CT before and after two cycles of treatment.

Results: The median PFS was numerically longer in TF group than that in T group (12.3 vs. 9.9 months). The percentage of patients without disease progression after 12 months was 62.5% in the combination arm compared with 21.4% in the single-agent docetaxel arm (P=0.08). According to 18F-FES PET/CT scans, SUVmax of all metastatic lesions decreased in group TF after 2 cycle of treatment. However, 6/9 patients in group T had at least one lesion with higher post-treatment SUVmax (P=0.028). In group TF, the patients with PFS>12 months had significant greater SUVmax changes of 18F-FES than those with PFS<12 months: 91.0±12.0 versus PFS<12 months: 20.7±16.2; t=4.64, P=0.01). In addition, the SUVmax changes of 18F-FES showed good agreement with PFS (correlation coefficient=0.946, P=0.004), which reflected its potential to predict prognosis.

Conclusions: Our preliminary study showed that the addition of fulvestrant to docetaxel might improve PFS in metastatic breast cancer patients. 18F-FES PET/CT, as a noninvasive method, could be utilized to predict its prognosis.
Quantification of PI3K p110α, PTEN, and AKT I and II in colorectal cancer cell lysate and tissue samples using immuno-MALDI (iMALDI)

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Colorectal cancer is one of the most common cancers in both incidence and cancer-related deaths (PMID:28248415). The PI3K/AKT/mTOR pathway is commonly upregulated in colorectal cancer and is the target of many anti-cancer therapies (PMID:25591826), but current patient stratification methods for targeted therapy are based mostly on genomic data and are often unsatisfactory. The goal of this project was to develop immuno-MALDI (iMALDI) mass spectrometry (MS) assays to quantify the expression and phosphorylation levels of proteins in the PI3K/AKT/mTOR pathway.

iMALDI combines antibody enrichment with MALDI-MS detection (PMID: 21136662). After enzymatic digestion of the sample, analyte-specific endogenous peptides (END) and their stable-isotope labeled (SIS) analogues are enriched using antibodies immobilized on magnetic beads. The beads are magnetically separated from the sample, washed, and spotted on a MALDI target. Matrix is added and the target peptides are analyzed. Protein quantification is based on the END: SIS ratio. Quantification of phosphorylation level is achieved by splitting the sample into two aliquots, and treating one with phosphatase (PMID:20524616). The amount of phosphorylated END originally in the sample is determined from the resulting increase in the amount of unphosphorylated END.

Unique tryptic peptides containing the cancer-related phosphorylation sites in PI3K p110α, PTEN, and AKT I and II were selected, confirmed experimentally, and used to raise polyclonal antibodies. Quantification of AKT I and II expression and phosphorylation levels were achieved in various cancer cell lines, as well as in flash-frozen and formalin-fixed tumour tissue samples, using 10 µg cell lysate. Endogenous PI3K p110α and PTEN were detected in 25 µg MDA-MB-231 breast cancer cell lysate. The next steps of this project include combining the PI3K p110 α, PTEN, and AKT assays into a single multiplexed assay, as well as adding additional protein targets from the PI3K/PI3K/mTOR pathway. After the method has been fully validated, it will be automated and used for the analysis of colorectal cancer xenograft mice and patient samples. Combined with genomic data, these levels can be used to build a predictive model for a patient’s response to targeted therapy.
POSTER SESSION 6: Drug resistance and modifiers

P6.1

Not all TLE are the same- phosphorylation dependent different effects TLE3 versus TLE1 in adipose tissue and cancer

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Background: In mammals, there six Groucho orthologs, TLE 1-6 which may modulate MAPK and WNT signaling. They are considered to be structurally and functionally equivalent. We demonstrated that non-phosphorylatable TLE1 derivative suppresses tumorigenic effects induced by KRAS activation. TLE3 has a role in adipocyte differentiation and has been proposed as a marker for taxane sensitivity. Only 1 out of 8 possible MAPK phosphosites in TLE1 only one is divergent in TLE3. Here we studied the functional differences of TLE3 and TLE1. The possible effects of manipulation of the proximal putative phosphosite on these functions.

Methods: Retroviruses expressing TLE1, TLE3 or TLE1 modified in the proximal phosphosite to TLE3 (TLE1-p3) or TLE3 modified to resemble TLE1 (TLE3-p1) were transduced into preadipocytes and lung cancer cell line (a549). These cells were treated by either PPARgamma activator containing differentiation media or taxanes and analyzed for differentiation or cell death. mRNA array analysis was performed on adipocytes.

Results: TCGA analysis revealed differential relationship between TLE1,4 overexpression (correlated with poor survival) and TLE3 overexpression (no correlation to survival) in colon cancer. In pre-adipocytes TLE1 had higher effects on differentiation than TLE3. However TLE1-p3 influenced differentiation similarly to TLE3 and vice versa TLE3-p1 influenced differentiation similarly to TLE1. These changes were also reflected in analysis of mRNA arrays from these samples. In A549 cells transduction with TLE3 resulted in greater sensitivity to chemotherapy than in TLE1 transduced cells which was lost when we used TLE3-p1 (Fig.1). In contrast to that TLE1-p3 effected taxane sensitivity similarly to TLE3.

Conclusion: There are some functional differences between TLE1 and TLE3 in differentiation and cancer. The different functions may be modulated by a specific phosphorylation. Further mechanistic understanding of this proteins may provide new insights to basic signal transduction events and provide novel targets for modulation of anticancer therapy.

Fig 1 TLE3 transduction sensitizes A549 cells to Taxanes while TLE3 modified in its proximal phosphosite to resemble TLE1 (TLE3 (PLTP) inhibits taxanes.
POSTER SESSION 7: Early diagnosis of cancer

P7.1
Breast Tissue Dynamics in BRCA1/2 Mutation Carriers

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Introduction: Circulating free DNA (cfDNA) is released to the bloodstream from dead cells in different tissues. Today, most of the detection methods are based on sequencing and pathologic changes in the genetic code. We use a method based on the methylation pattern of cfDNA, thus allowing us to measure normal tissue turnover in various clinical scenarios. BRCA1/2 gene mutation is a common cause of hereditary breast and ovarian cancer worldwide. Previous data suggests that healthy carriers of the BRCA1/2 mutation have an increased turnover of cells in the breast tissue. Therefore, we believe that increased cell turnover is a potential early mark of tumorigenesis in this population.

Methods: Using Illumina methylation array we have identified three sites with breast unique methylation pattern. Then, three cohorts of pre-menopausal United States women were identified: healthy controls (n=27), healthy BRCA1/2 mutation carriers (n=10) and BRCAmut/+ metastatic breast cancer patients (n=5). 20 ml of peripheral blood were drawn during the menstrual cycle at days 1-3 (Time point 1= TP1), days 9-11 (TP2) and days 21-23 (TP3).

Results: Average levels of total cfDNA (ng/ml) in healthy controls were: TP1=3.50, TP2=3.64 and TP3=3.23. Average levels of total cfDNA in healthy BRCA1/2 mutation carriers at previously mentioned time points were: 3.45, 2.84, and 3.51, respectively. Fraction of breast specific cfDNA at different time points in healthy controls were as following: TP1=0.3%, TP2=0.05%, TP3=0.2%. Fraction in healthy BRCAmut/+ women were: TP1=0.3%, TP2=0.1%, TP3=0.6%. Total cfDNA levels and fraction of breast-specific cfDNA in metastatic breast cancer patients were considerably higher, representing extensive burden of disease in this group.

Conclusion: Our data suggests that turnover of body tissues and breast tissue change during the menstrual cycle, with potential variation between healthy women and BRCA1/2 mutation carriers. The difference can reflect differential hormonal sensitivity of tissues. Surprisingly, we have not identified increased turnover of breast tissue of BRCA1/2 carriers. This finding may imply that BRCA1/2 tumorigenesis is due to damaged cell-removal mechanism (such as apoptosis or senescence) instead of uncontrolled proliferation on the background of DNA repair defect.
P8.1
The effect of reflexology on quality of life in breast cancer patients

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Background and Aim: Breast cancer is one of the most prevalent cancers among women. Physical and mental symptoms of cancer affect the quality of life in patients. Use of complementary therapies for patients infected by pain and emotional distress arising out of cancer may result in relaxation in breast cancer. One of the complementary therapies is reflexology. This paper has been provided with the objective of determining the effect of reflexology on quality of life in breast cancer patients under chemotherapy in the breast disease center of the University of Tehran in 2012.

Material and method: This study was a randomized clinical trial which has been applied on 60 patients suffering from breast cancer. The patients were selected randomly in three groups, test, control, and placebo. In the test group, reflexology was implemented for 3 weeks and each session lasted half an hour. In the placebo group, only relaxation techniques were implemented for 3 weeks, each session lasting 20-30 min. The control group received the routine therapies of the breast cancer center.

Result: Data were collected by standard questionnaires of EORTC QLQ-C30.V.3 and EORTC QLQ-BR23.V.3. The questionnaires were filled before intervention and two weeks after applying study. There was no significant difference in demographic characteristics or quality of life score of three groups before intervention. Total score of quality of life was higher in the interventional group compared to the placebo group before and two weeks after intervention (p<0.001). Results also indicated a significant difference in total score of quality of life between the three test, placebo, and control groups after intervention (p<0.001). A considerable improvement was noticed in the different aspects of quality of life in the test group compared to the other placebo and control groups.

Conclusion: Using reflexology in patients suffering from breast cancer may improve the quality of life, as an effective method and can be recommended to breast cancer patients.

Keywords: Breast Cancer, Reflexology, Quality of Life
P8.3
Antitumor activity of RET inhibitor vandetanib with mTOR inhibitor everolimus in patients with Non-small cell Lung Cancer with RET fusion.

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**Background:** RET fusion kinases (RET+) occur in 1-2% of NSCLCs and are oncogenic drivers. Tumors eventually become refractory to monotherapy. We evaluated the activity of V in combination with the mTOR inhibitor everolimus (E) in RET+ cancer cells and NSCLC patients in a phase I study.

**Methods:** We performed cell viability assays and analyzed protein phosphorylation with western blot in CCDC6-RET fusion+ LC-2/ad (NSCLC) and TPC1 (papillary thyroid cancer) cells treated with vehicle, V, E, or V + E. We evaluated the activity of V + E in NSCLC pts in a phase Ib study (NCT01582191). RET fusions were detected by FISH and/or comprehensive genomic panel (CGP) in tumor tissue.

**Results:** V suppressed RET and MEK activation, but not mTOR signaling. E suppressed mTOR but had not effect on impact on RET and MEK activation. V + E blocked RET, MEK and mTOR signaling and had the greatest inhibitory effect on cancer cell proliferation. To date, 19 stage IV NSCLC patients have been treated. Median age was 59 years and 8 patients (42%) were males. The combination was well-tolerated: G3-4 toxicities included diarrhea (21%), thrombocytopenia (16%). Thirteen tumors (93%) were RET+, 8 were assessed by CGP only (CGP+/FISH N/A), 5 were assessed by CGP + FISH. Among the tumors assessed by both tests, 3 were FISH+/CGP-, 2 were CGP+/FISH+. Concordance rate between the two tests was 40%. The ORR in 13 RET+ patients was 54% (7 PR). RET+ by CGP was associated with response: ORR was 75% (6 PR) in CGP+/FISH N/A patients (n=8), and 50% (1 PR) in CGP+/FISH+ patients (n=2). No responses were seen in RET+ tumors by FISH only (0/3=0%). The combination was active in RET+ NSCLC brain metastases, nivolumab progressor and cabozantinib progressor. The median PFS of 13 RET+ patients was 4.4 months (95% CI 3.4, NR); the median PFS of RET CGP+ patients (n=10) was 8 months (95% CI 0.1, 1.1).

**Conclusions:** V and E combination is superior to single agent in abrogating cell division and RET, MEK and mTOR activation in RET+ cancer cells. The combination of V (300 mg) and E (10 mg) was well-tolerated and demonstrated significant antitumor activity in 10 patients with RET rearranged NSCLC by CGP with an ORR of 70% and a median PFS of 8 months, including in patients with CNS and cabozantinib-refractory disease.
Anticancer activity of melatonin analogues

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Introduction: Melatonin plays fundamental roles in diverse physiological functions ranging from the regulation of circadian rhythms to tumor inhibition, owing to its antioxidant, immunomodulatory and anti-aging properties [1-3]. The therapeutic potential of melatonin and its analogues [4,5] prompted us to investigate the in vitro and in vivo antitumor activity of new melatonin derivatives on melanoma and breast cancer cells, and explore the underlying molecular mechanisms.

Materials and methods: New indole melatonin analogues were synthetized and tested for their ability to inhibit proliferation and induce apoptosis in DX3 melanoma cells and in MCF-7 and MDA-MB231 breast cancer cells by viability and apoptosis assays. The oncostatic effect of melatonin analogues was also measured on a human melanoma xenograft mouse model. The changes in the expression levels of different proteins in cancer cell lines during treatment with melatonin analogues were investigated by Western blot analysis.

Results: The experiments revealed that the new melatonin analogues inhibited the growth of DX3 melanoma cells in a dose- and time-dependent manner. In addition, the study demonstrated that low concentrations (0.1 mM) of the melatonin analogue UCM 1037 exhibited antiproliferative and cytotoxic effects also in MCF-7 and MDA-MB231 breast cancer cells. The suppression of DX3 tumor growth by the melatonin analogues was further demonstrated in vivo in a xenograft mice model. Caspase 3 resulted to be involved in the pro-apoptotic mechanism induced by UCM 1037 in DX3 and MDA-MB231 cells. A decrease in the activation of both Akt and MAPK pathways was observed in breast cancer cells following UCM 1037 treatment.

Conclusions: This study describes melatonin derivatives showing promising antiproliferative and cytotoxic activity in melanoma and breast cancer cells.

References and acknowledgements:
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Keywords: Melatonin, melatonin receptors, melatonin analogues, melanoma, breast cancer
P10.1
The Roles of MUS81 in progression of Ovarian Cancer Associated with Dysfunctional DNA Repair Systems

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Ovarian cancer (OC) is characterized by heterogeneity and genome instability, and has the highest mortality rate in gynecological malignancy. Novel insights into OC is required to minimize the mortality rate and drug resistant disease. MUS81, a structure-special endonucleases, plays an important role in the genome instability of cancer cells and DNA damage repair system. To investigate whether MUS81 participates in the genome instability of OC, we firstly detected the expression level of MUS81 in OC tissues (n=49) and matched adjacent cancer tissues (n=49) by RT-PCR. The result indicated that MUS81 was significantly overexpressed in OC tissues, and this data was consistent with the TCGA database. Then, the expression of MUS81 in OC cell lines was down-regulated by lentiviral-mediated RNAi, and RAPD analysis, comet assay, IFC technique etc were applied to assess the status of genome instability and DNA damage repair pathway. Interestingly, we observed that down-regulation of MUS81 in OC cells induced remarkable genome instability and decreased activity of HR, and were unable to elicit RAD51 foci formation. Furthermore, transcriptional profile analysis and interaction protein chips screening array showed that MUS81 was involved in the molecular network and pathway of DNA repair in OC cells. Further experiments proved that MUS81 had the impact on resistance to CPT and PARP inhibitors through collaboration with RAD51 and BM28, respectively. Finally, in vivo experiment also showed the evidences that down-regulation of MUS81 could increase chemotherapy-sensitivity of tumor transplanted with OC cells. Consequently, these data suggest that MUS81 might represent a novel chemotherapy target and be associated with drug resistant.
Breast Cancer Phenotype in BRCA 1/2 carriers - preliminary analysis of three large cohorts suggests distinct subtypes based on ER status

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Background: Hereditary breast cancer (HBC) comprises more than 10% of all breast cancers (BC). BRCA1/2 genes are involved in about half of HBC. The phenotype of BRCA associated tumors differs. Most of BRCA1 associated tumors are triple negative basal-like, while BRCA2 associated tumors are mostly ER positive. In the present study we aim to further explore clinical and molecular characteristics of BRCA associated BC in 3 cohorts.

Methods: Three different BC databases (DB) were evaluated: (i) Hadassah oncogenetic BC DB (n=4429); (ii) Nick-Zainal et al. BC DB (n=560), and (iii) METABRIC BC DB (n= 1980). We tested for differences in age at diagnosis between BRCA positive (BP) and BRCA negative (BN) patients (PT), for ER positive (ER+) and ER negative (ER-) groups. Point mutations analysis was performed in cohorts ii&iii. and mRNA differential expression (DEA) and pathway analysis were performed in cohort iii, using Ingenuity Pathway Analysis (IPA).

Results: Age at diagnosis for cohorts i, ii,&iii respectively, in years for ER+:BRCA1-44, NA, 60; for BRCA2-49, 48, 64; for BN – 53, 56, 63. For ER-: BRCA1-42, 42, 47; for BRCA2-48, 52, 49; for BN-49, 54, 56. For cohorts ii&iii, higher frequencies of TP53 and PIK3Ca mutations were found among BP& BN, respectively. DEA was performed between BP&BN in ER- tumors: the major activated pathways involved cancer related processes and were highly significant (up to p=1e-7.5, FDR=1e-4.5). Surprisingly the most significant pathway was Estrogen Mediated S-phase Entry and the most activated upstream regulator was ERBB2. Similar evaluation in ER+ showed mostly differences in immune related pathways (differences not significant).

Conclusions: Younger age at presentation was observed in BRCA1 vs. BRCA2 pt. No age differences were observed between ER+&ER- PT in cohort i&ii, in cohort iii ER- BP PT were younger than ER+ BP PT (similar age as ER+ BN). BP show different mutational profile than BN. ER+ BP and BN show similar genomic characteristics. By contrast, for ER- BP differs markedly from BN. This might imply that BP associated tumors consist of two genomically distinct subtypes: (i) ER-, and (ii) ER+. The results may shed light on possible somatic factors which affect the development of BC BP and carry therapeutic implications.
CBX3 promotes proliferation and aerobic glycolysis via FBW7/c-Myc pathway in pancreatic adenocarcinoma

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Introduction: Epigenetic modifications and the related chromatin modifiers are being increasingly recognized to contribute to cancer formation and progression. More and more evidence has demonstrated that CBX3 or Chromobox 3, has important role in carcinogenesis by regulating several mechanisms, such as heterochromatin formation, gene silencing and DNA replication and repair. However, its role in pancreatic adenocarcinoma (PDAC), has seldom been discussed.

Methods and Results: By using the Cancer Genome Atlas (TCGA) dataset analysis, we demonstrated that higher expression of CBX3 predicted worse prognosis. To search for the underlying molecular mechanism, we silenced CBX3 expression in PDAC cancer cell lines and identified the positive roles of CBX3 in cancer proliferation. Furthermore, we demonstrated that silencing CBX3 in pancreatic cancer cells inhibited aerobic glycolysis, the basis for providing cancer cells with building blocks for macromolecule synthesis and ATP that required. In the end, our results uncovered that CBX3 regulated aerobic glycolysis via the FBW7/c-Myc axis in pancreatic cancer.

Conclusions: These data contribute to the body of knowledge how chromatin modifiers regulated cancer malignancies and provide a critical foundation for further investigation of the role of CBX3 in malignant characteristics like proliferation, progression, and aerobic glycolysis that sustains these malignant behaviors.

Keywords: CBX3, Aerobic glycolysis, FBW7/c-Myc pathway, Pancreatic adenocarcinoma.
The molecular heterogeneity of sporadic colorectal cancer with different tumor sites in Chinese patients

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Purpose: To assess the biological variability of clinical meaningful molecular markers and their clinical correlations in Chinese patients with colorectal cancer (CRC).

Materials and methods: In this prospective observational study, frequencies and clinico-pathological features of RAS and BRAF V600E mutations, deficiency of DNA mismatch repair (dMMR) were evaluated in patients with colorectal cancer staged I-IV. The molecular heterogeneity between right-sided and left-sided colorectal cancers was studied in our series by classifying patients with different mutations and dMMR status.

Results: Among 400 evaluable patients, mutations in KRAS exon 2, exon 3 or 4, NRAS and BRAF V600E were detected in 36%, 7.5%, 3.5% and 2.5%, respectively. RAS mutations were significantly higher in metastatic CRCs (56.4% vs. 43.1%, p=0.015) and right-sided CRCs (62.5% vs 41.7%, p=0.003) (Figure). In 212 RAS wild-type patients, V600E mutation was higher in older patients (9.5% vs. 2.2%, p=0.017), women (9.2% vs. 2.2%, p=0.021) and right-sided CRCs (10.5% vs. 3.4%, p=0.06). dMMR was detected in 7.75% of all stages of CRCs, with the highest dMMR rate of 40% in stage II right-sided colon cancer.

Conclusions: By assessing the mutations and clinical correlations of RAS and BRAF genes, and dMMR status, similar RAS mutation, dMMR frequency and lower BRAF mutation was observed in Chinese patients compared to western patients. A distinct molecular heterogeneity was found between patients with right-sided and left-sided CRCs.
P10.7
Genetic Evaluation of BRCA1 associated A Complex genes with Triple-negative Breast Cancer Susceptibility in Chinese Women

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Background: The tumor suppressor BRCA1 plays a pivotal role in maintaining genomic stability and tumor suppression. The BRCA1-A complex is required for recruitment of BRCA1 to DNA damage sites, DNA repair and cell cycle checkpoint control. Since germline mutations of BRCA1 often lead to breast tumors that are triple-negative breast cancer (TNBC) type, we aimed to investigate whether genetic deficiency in genes of the BRCA1-A complex is associated with risk to TNBC development. Similar work has never been done before in Asian.

Methods: We investigated associations between the BRCA1-A complex genes and TNBC developing risk in the first case-control study of Chinese Han Women population including 414 patients with TNBC and 354 cancer-free controls. We detected 37 common variants in ABRAXAS, RAP80, BRE, BRCC36 and NBA1 genes encoding the BRCA1-A complex and evaluated their genetic susceptibility to the risk of TNBC. An additional cohort with 652 other types of breast cancer (non-TNBC) cases and 890 controls was used to investigate the associations between TNBC-specific SNPs genotype and non-TNBCs susceptibility. We also did in silico analysis and further function examination to the investigated SNPs.

Results: We found that rs7250266 in the promoter region of NBA1 confers a decreased risk to TNBC. The allelic frequency of the G-allele of rs7250266 was 0.19 in controls compared with 0.14 in patients with significant difference (PG) and rs2278256 (T>C) down-regulate promoter activity of NBA1 in mammary epithelial cells.

Conclusions: Genetic variants of NBA1 may be an important genetic determinant of developing TNBC. The variants detected in this study had not been reported to be associated with risk to breast cancer in literature. Further investigation and validation of these SNPs in larger cohorts may facilitate in predication and prevention of TNBC and in counseling individuals for risk of TNBC development.
POSTER SESSION 11: New combinations (agents and modalities)

P11.1

A Phase Ib/IIa Study to Evaluate Safety and Activity of Oregovomab and Nivolumab in Women with Recurrent Ovarian Cancer (ORION-01)

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Background: Oregovomab is a monoclonal antibody specific for Ca 125, a tumour associated antigen expressed by more than 80% of advanced epithelial ovarian cancers (EOC). Nivolumab is a fully human monoclonal antibody that targets programmed death-1. Both agents are clinically active in advanced EOC as monotherapy. We hypothesize that the combination will elicit a systemic Ca 125 specific T cell response in a manner that is synergistic, safe and clinically efficacious.

Methods: ORION-01 is an open-label, single-arm, phase Ib/IIa, single center study with dose finding and dose expansion parts to characterize the safety and tolerability of Oregovomab in combination with Nivolumab and to establish the recommended dose for expansion (RDE). Co-primary endpoint is to evaluate the antitumor activity of this combination as assessed by overall response rate (ORR) per GCIG criteria and progression free survival. Patients with histologically confirmed epithelial ovarian carcinoma, fallopian tube and primary peritoneal carcinoma who have received 2 prior lines of cytotoxic chemotherapy are eligible for this study. Secondary endpoints include ORR per immune related response criteria, disease control rate, ORR in EOC subtypes and overall survival. Correlative studies will be performed to assess changes in immune-related pharmacodynamics characteristics at baseline and post treatment. A modified “3+3” design for dose escalation will be employed. A minimum of 6 and maximum of 18 patients will be enrolled in the dose finding part starting at a dose of 2mg every 4 weekly of Oregovomab in combination with 240mg of Nivolumab every 2 weekly. Three patients will initially be enrolled and an additional 3 if ≤1 dose limiting toxicity (DLT) is observed. If ≤1 DLT is observed then this dose level will be the RDE. Two lower dosages of Oregovomab (1mg every 4 weeks and 0.5mg every 4 weeks) are specified in case of excessive toxicities. An additional 14 patients are to enrol in the dose expansion part once RDE is determined. As per May 2017, 2 patients have been enrolled onto cohort 1. Clinical trial information: NCT03100006
POSTER SESSION 12: New treatment strategies

P12.2
Neoadjuvant biphosphonate in breast cancer

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Introduction: Clinical studies have demonstrated synergistic antitumor effects of chemotherapy (CT) and zoledronic acid (AZ). In the essay Neo-AZURE, to determine whether the addition of AZ to neoadjuvant chemotherapy gives complete histological responses. We report a prospective evaluation comparing complete pathological response between different sub-biomolecular groups.

Methods: from 2012 to 2014, 432 patients received neoadjuvant chemotherapy + AZ. The main objective is the complete histologic response. Secondary endpoints were clinical response according to RECIST criteria, estimate the overall survival of patients targeted by the study, assess bone density before and at the end of chemotherapy, the side effects associated with the treatment protocol, and Quality life.

Results: histologic complete response with zoledronic acid was 40.13%. the higher in the subgroup Her2/luminal (RH ± Her2 +) and under Her2 + (HR-Her2 +) and the lowest rate was observed in the triple negative group as classified by Sataloff, overall survival was 45.77 months for subgroups (Her2/luminal and in Her2 + group) vs 44.11 months for triple negative group.

Conclusion: These data suggest a possible direct antitumor effect of AZ in combination with CT. The studies were recently published in the Proceedings of the American Academy of Sciences (PNAS) shows that bisphosphonates namely zoledronic acid the ability to block the abnormal growth of signals transmitted via the HER receptors, these studies demonstrated that the same can inhibit zoledronic acid tyrosine kinases in case of secondary transfer and thereby potentiate and treat breast cancer became resistant primary treatment.

Keywords: antitumor activity; breast cancer; neoadjuvant chemotherapy; pCR; zoledronic acid
P12.3

Maintenance treatment of Uracil and Tegafur in responders following first-line fluorouracil-based chemotherapy in metastatic gastric cancer

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Background: Maintenance therapy proves to be effective in advanced lung and breast cancer after initial chemotherapy. However, its role in gastric cancer is not clear. The purpose of this phase II study was to evaluate the efficacy and safety of Uracil and Tegafur (UFT) maintenance in metastatic gastric cancer patients following the first-line fluorouracil-based chemotherapy.

Methods: Metastatic gastric cancer patients with stable disease or a better response after the completion of first-line chemotherapy were randomized to oral UFT (360mg/m2 × 2 weeks) every 3 weeks until disease progression/intolerable toxicity or to observation (OBS). The primary endpoint was progression-free survival (PFS); the secondary endpoints were overall survival (OS) and safety.

Results: The trial was closed after the interim analysis of the 58 enrolled (120 planned) patients. Median PFS was not significantly improved in the UFT group compared with the OBS group (3.2 months versus 3.6 months, P = 0.752). Similarly, UFT maintenance did not prolong median OS compared with OBS (14.2 months for both, P = 0.983). However, subgroup analysis showed that patients with low hemoglobin (< 120 g/L, n = 32) had a shorter PFS after the maintenance therapy (1.9 months in 17 patients of UFT group versus 3.6 months in 15 patients of OBS group, P = 0.032), whereas patients with normal hemoglobin (≥ 120 g/L, n = 26) benefit from the UFT maintenance (7.1 months in 12 patients of UFT group versus 2.4 months in 14 patients of OBS group, P = 0.008). Similar trend was also observed in the OS analysis. Patients with normal baseline hemoglobin had a better survival trend after the maintenance therapy (23.6 months versus 10.5 months, P = 0.09), whereas patients with low hemoglobin did not (14.0 months versus 21.2 months, P = 0.106). Grade 3 to 4 toxicities in the UFT group were anemia (3.4%), thrombocytopenia (3.4%) and diarrhea (6.9%).

Conclusions: This trial did not show superiority of UFT maintenance in non-selected patients responding to fluorouracil-based first-line chemotherapy. The normal hemoglobin level at baseline is a predictive biomarker for favorable patient subsets from the maintenance treatment. Safety profile of UFT was acceptable.
The discovery of novel synthetic lethal compounds for the treatment of E-cadherin deficient tumours

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The cell-cell adhesion protein E-cadherin (CDH1) is a tumour suppressor that is frequently mutated in a range of sporadic and hereditary cancers including hereditary diffuse gastric cancer (HDGC). The lifetime risk of developing advanced diffuse-type stomach cancer in individuals with pathogenic CDH1 germline mutations is approximately 70%. Additionally, female mutation carriers have an elevated lifetime risk of developing lobular breast cancer (LBC) of between 40-60% (1).

At present, prophylactic total gastrectomy is the single option to abolish an inherited risk of gastric cancer and is recommended by the age of 20 years. HDGC is characterized by multiple foci of stage T1a signet ring cell carcinomas which are relatively indolent and develop after downregulation of the 2nd CDH1 allele (2). We hypothesise that the loss of CDH1 within these early stage foci could be specifically targeted with drugs using a synthetic lethal approach (3) before they progress through the muscularis mucosa and invade the submucosa. To identify novel synthetic lethal compounds for the treatment of cancer arising from E-cadherin loss, we performed a three-staged 114,000 hit-like compound screening campaign on an isogenic pair of human mammary epithelial cell lines with and without CDH1 expression (4). The metabolism-based celltiter-blue assay and a high content imaging approach were employed to determine the impact of the compounds on cell viability and cell cycle phase distribution. This approach identified 84 lead-like compounds which were found to belong to 16 distinct pharmacophore groups. Validation of these groups identified 13 novel compounds as being highly selectively lethal to E-cadherin deficient cells, demonstrating that E-cadherin loss creates druggable vulnerabilities within tumour cells. These novel synthetic lethal compounds are now being validated in more complex in vitro and in vivo models and their targets identified.

Overall this work provides novel leads for the chemoprevention and treatment of both sporadic and familial LBC and DGC.

POSTER SESSION 13: Other topics (WIN Symposium related)

P13.1
The impact of clinicians’ perceptions and experiences of lenvatinib for differentiated thyroid cancer on adherence

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Lenvatinib is an oral tyrosine kinase inhibitor used when differentiated thyroid cancer no longer responds to radioactive iodine treatment and continues to progress. Clinical trials have demonstrated that lenvatinib reduces tumour size in c. 65% of patients and increases median progression-free survival. The efficacy of lenvatinib, however, is significantly compromised by non-persistence when patients experience side effects at the start of treatment.

This study aimed to understand clinicians’ experiences of managing patients on lenvatinib and the impact of their beliefs about lenvatinib on adherence to inform the development of a patient support programme which increases efficacy outcomes.

A focus group and five telephone interviews were conducted with clinicians which investigated their experiences prescribing lenvatinib; their patients’ concerns and their thoughts around support materials. Clinicians did not consider adherence a problem because many patients have high necessity beliefs because lenvatinib is perceived as their last treatment option. Side effects were the main concern but clinicians assumed patients would raise these during consultations. They believed lenvatinib was effective but did not understand the rationale behind the recommended dose and adjusted it, or allowed medication breaks, in cases of severe side-effects. They thought family, carers and GPs play an important support role. Practical barriers included overwhelming patients with information and older patients accessing resources online.

Clinicians’ misconception that adherence is not an issue and patients will openly discuss side effects suggests a lack of effective communication. Clinicians should highlight to patients that side effects will diminish and the treatment will improve their quality of life. Clinicians need to be provided with clear scientific evidence for the recommended dose to convey the importance of adhering to it. Providing patients with access to clear information in the form of concise materials on disease, treatment, side effects and how to manage them is key to improving adherence. To improve adherence, patient support programmes must understand and address both practical and perceived barriers which are tailored to clinician and patients’ needs.
P13.2
Individualised Molecular Profiling for Allocation to Clinical Trials (IMPACT) and Molecular Tumour Board- an Asian tertiary cancer centre

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Background: The primary aim of tumour molecular profiling (MP) is to identify clinically relevant genomic alterations that may be amenable to targeted therapeutics – either in the context of trials or existing approved agents. Here, we describe our single-centre multidisciplinary MP experience, culminating with a monthly molecular tumour board (MTB). We also describe the barriers to trial enrolment.

Methods: Following consent, archival or new tissue samples of patients (pts) with advanced cancers were obtained and submitted for testing. A panel of assays across multiple platforms were performed including immunohistochemistry (IHC), multiple allele specific PCR and mass spectrometry or targeted next generation sequencing (NGS) panels (29 gene and 143 genes). Results were discussed at monthly MTB (held from 5/13 to 4/17) and matched to available trials/therapeutics.

Results: A total of 738 samples were processed under IMPACT, involving 710 pts. Median age at consent was 58 (Range 18-83), 44% were female. Ethnic characteristics: Chinese (n=605, 82%), Malay (n=42, 6%), Indian (16, 2%) and others (75, 10%). Tumour types profiled: Lung (31%), Gastrointestinal including hepatobiliary (31%), Breast (11%) and others (27%). 34% of samples were fresh tissue biopsies. IHC was performed on 70% of samples, FISH on 23% and sequencing on 68%. 57% (n=417) of samples had actionable alterations. Common discovered mutations include: p53 mutant (n=236, 32%), EGFR (n=178, 24%), KRAS (n=96, 13%), PIK3CA (n=71, 10%). 58% (n=427) were found to be actionable.

6% (n=45) profiling events led to biomarker matched trial enrolment whilst 22% (n=161) were enrolled in other phase I trials without matched aberrations. 534 (72%) profiling events did not lead to trial enrolment. Common reasons include 38% (n = 201) when standard treatment was still effective, 19% (n = 100) progressive metastatic disease , 13% (n = 70) no trial slots available, 9% (n=47) pt declined MTB recommendations and 2% (n = 7) did not meet trial entry criteria.

Conclusions: It is feasible to perform MP and institute a MTB for allocation to trials. 6% of all MP events lead to enrolment onto molecularly matched trials. Pt education and timely application of broad, customized MP panels could improve clinical trials enrolment.
P13.3
Modulation of hepatic cancer stem cells markers following the induction of extrinsic apoptosis pathway by CD95: a preliminary study

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Background: Hepatocellular carcinoma (HCC) remains one of the lethal malignancies that have a poor prognosis and high recurrence rate. Although HCC is a heterogeneous disease, dysregulation of molecular profiling related to apoptosis also contributes to the disease progression. This study reports on a relevant function of CD95 death receptor that can induce apoptosis via modulation of apoptosis genes and cancer stem cell markers in HCC.

Materials and Methods: For the in vivo study, genes CD90, CD95, and CD95L from 47 samples (14 HCC, 9 peri-HCC, 13 cirrhosis, and 11 normal) from patients undergoing liver resection without any prior treatments were analyzed. For the in vitro study, HCC the human cell lines HepG2, JHH6, and HUH7 were used representing high to low basal CD95 expression. Apoptosis-induction was performed by using anti-CD95 (DX2) at a concentration of 250 ng/ml and 500 ng/ml for 24 hours. Flow cytometry and quantitative real-time PCR were performed to analyze the data.

Results: The expressions of CD95 and CD95 genes were highly variable in human tissues. A significant increase for CD95L was noticed in HCC as compared to normal tissues, as observed for CD90. After in vitro treatment of anti-CD95, genes TNF-α and TRAIL2R were upregulated in all cell lines in a dose-dependent manner, as well as pro-apoptotic gene Puma and BAX. Cancer stem cell marker CD24 was highly upregulated in HepG2 and to a lower extent in JHH6, while CD13 was slightly increased in all cell lines. There was a decrease of CD133 in HepG2 and no significant changes for EpCAM, CD44, and CD90.

Conclusions: We observed a modulation of apoptotic genes Puma, BAX, TNF-α, and TRAIL2R and cancer stem cell markers CD24, CD13, and CD133 after induction by CD95 antibody in acute phase treatment.

Keywords: Apoptosis, HCC, CD95, CSC, apoptotic genes

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P14.1
Combination of BRAF and EGFR inhibition in PDXs of BRAF mutant recurrent and metastatic colorectal cancer

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Purpose: To evaluate efficiency of BRAF inhibitor combined with EGFR inhibitor in PDXs of BRAF V600E-mutant recurrent and metastatic colorectal cancer.

Materials and Methods: Twenty-three PDXs models of recurrent and metastatic colorectal cancer were established by biopsy specimen, of which four ones were detected BRAF V600E-mutation. BRAF mutant PDXs were selected and cultivated to F2 generation, then each model was divided into four groups: BRAF inhibitor (Group A), EGFR inhibitor (Group B), BRAF and EGFR inhibitor (Group C), placebo (Group D). After three weeks, the efficiency was evaluated by tumor volume, immunohistochemical method and metabolic activity of small animal PET.

Results: The tumor inhibition rate of each group was 23.5%, 23.6, 72.9% and 0, respectively. Group C had the most significant reduction of tumor volume and metabolic activity (P < 0.05). Group A showed high expression of EGFR, while Group C displayed high expression of MLH1 but low expression of EGFR, Ki-67 and COX-2.

Conclusion: Combination of BRAF and EGFR inhibitor had high efficiency in PDXs of BRAF V600E-mutant recurrent and metastatic colorectal cancer, and the two showed coordination mechanism.
P14.2
Establishment of patient-derived xenografts models of recurrent and metastatic colorectal cancer based on CT-guided biopsy

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Purpose: To establish patient-derived xenografts (PDXs) models of recurrent and metastatic colorectal cancer by CT-guided biopsy. Materials and Methods: A total of thirty-four colorectal cancer patients after curative resection were performed CT-guided biopsy because of suspicion of recurrence and/or metastasis. Part of tissue specimen for histological diagnosis was reserved, the rest was cut into small pieces to transplant to nude mice subcutaneously, which was marked F0 generation. When cultivated to F2 generation, hematoxylin-eosin and immunohistochemical staining and gene mutation test were done, then compared with the biopsy specimen. Results: In the present study, twenty-three of the thirty-four biopsy specimen was confirmed recurrence and/or metastasis. Altogether sixteen PDXs models of recurrent and/or metastatic colorectal cancer were built, and the success rate was 69.6% (16/23). The PDXs models manifested high consistency with the corresponding patients’ biopsy specimen. Conclusion: Establishment of PDXs models of recurrent and metastatic colorectal cancer by CT-guided biopsy was not only minimal invasive but also had high success rate and consistency.
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