SP 133
TCGA − success story in ovarian cancer

P. Spellman. *Lawrence Berkeley National Laboratory, USA*

TCGA has committed to the systematic analysis of the molecular nature of more than 20 human cancer types. The first TCGA project to be completed was of high-grade serous ovarian cancer, a deadly malignancy with poor treatment options. TCGA completed the complete sequencing of protein coding genes from more than 300 ovarian cancers and their matched germline genomes. Additionally, TCGA completed complete molecular profiles of mRNA expression, DNA copy number, DNA methylation, and miRNA expression from more than 500 ovarian cancers. These data have been distributed to the entire community in near real time and provide the most comprehensive examination of the complexities associated with the analysis of integrative human cancer genomic data. The major findings from TCGAs study serve to remind the cancer research community about the complexities of the disease. First, it is confirmed that high grade serous ovarian cancer is a disease of p53 and BRCA1/2. Second, the study highlighted the "long tail" of mutations, wherein there are likely to be a great many driving oncogenes where the somatic mutation frequency is very low (1% or less). Third, ovarian cancer contrasts with other human cancers wherein the disease shows an extraordinary dependence on structural changes to the genome, which likely contribute the majority of oncogenic events. Fourth, TCGA describes epigenetic states that predict outcome, and distinct tumor biology that must be further analyzed to understand how to exploit these biologies for clinical benefit. Finally, TCGA provides some preliminary looks at how to integrate multidimensional genomics data to highlight pathways that contribute to disease.

SP 114
Predictive and pharmacodynamic (PD) markers of PI3K pathway inhibitors: focus on PI3K, AKT and mTOR inhibitors

J. Tabernero. *Vall d'Hebron University Hospital, Spain*

PI3K pathway is commonly disregulated in human cancer and is critical for progression and resistance to other antineoplastic agents. Several molecular aberrations affect key components, including genetic mutations and amplifications (PIK3CA, AKT) and loss of function of negative regulators (PTEN). Rationally designed drugs targeting key elements of this pathway include: (a) pure pan-PI3K inhibitors, targeting all isoforms of PI3K; (b) dual PI3K/mTOR inhibitors; (c) AKT inhibitors; (d) mTOR complex 1 and 2 inhibitors; and (e) isoform-specific PI3K inhibitors, including the α isoform activated in *PIK3CA* mutants and the δ isoform upregulated in hematologic neoplasms. Biomarker studies were implemented in the early phases of clinical development of these agents in order to assist in optimal dose determination − PD markers − and to identify patients likely to benefit from treatment − predictive markers. Preliminary reports of PD effects have shown downregulation of key pathway readouts, such as pAKT, pPRAS40, pGSK3β, pS6K and p4EBP1, in the range of 50 to 90% both in tumor and surrogate tissues. These included platelet rich plasma (pAKT, pPRAS40, and pGSK3£]), skin (pS6K), hair follicles (pPRAS40), and PBMCs (p4EBP1). Significant decline in proliferation marker Ki67 reassures that the targets are being hit. There appears to be correlation of drug exposure and pathway inhibition. Other biomarkers of pathway inhibition include increase in serum glucose or plasma C-peptide levels and reduction of glucose avidity on FDG-PET scans. Regarding predictive markers, clinical activity with PI3K pathway inhibitors have been reported in multiple tumor types, including breast, ovarian, endometrial, prostate, lung, mesotheliomas, sarcomas and lymphomas. Importantly, clinical benefit has not been restricted to patients whose tumor harbor PI3K pathway activation and the PD markers have not shown predictive value. The degree and duration of pathway inhibition that is necessary for clinical effects has not been established with the current agents and biomarker studies. Recognizing that PI3K pathway operates in complex networks in which the outcomes of pharmacologic modulation may be difficult to predict is of paramount importance. It is now clear that inhibition of PI3K pathway increases the activity of ERK signaling. Therefore, the next generation of trials with PI3K pathway inhibitors is focusing in combination strategies, including MEK inhibitors and EGFR/HER2 inhibitors.

SP 118
MDM2 inhibitors to reactivate p53 in human cancer

L. Vassilev. *Roche, USA*

The p53 tumor suppressor is controlled by MDM2 and MDMX that bind p53 and negatively modulates its transcriptional activity and stability. Many tumors overproduce MDM2 or MDMX to impair p53 function. Small-molecule MDM2 antagonists, the nutlins, interact specifically with the p53-binding pocket of MDM2 and can release p53 from negative control. Treatment of cancer cells expressing wild-type p53 with nutlins stabilized p53 and activated the p53 pathway, leading to cell cycle arrest and apoptosis in vitro and in vivo. However, nutlins do not inhibit the p53-MDMX interaction and their effectiveness can be compromised in tumors overexpressing MDMX.
MDM2 antagonist, nutlin-3, and a novel dual MDM2/MDMX antagonists, RO-5963 are used as molecular tools to study p53 regulation and identification of biomarkers for p53 activation.
Nutlin disrupt p53-MDM2 autoregulatory circuit leading to upregulation of both proteins. They selectively block MDM2-p53 binding but do not affect E3 ligase activity of MDM2. As a result, nutlin treatment facilitates the degradation of MDMX in many cancer cell lines. However, tumor cells that overexpress MDMX are resistant to nutlin. We identified small molecules that potently block p53 interaction with both MDM2 and MDMX by inhibitor-driven homo- and/or hetero-dimerization of MDM2 and MDMX proteins. Structural studies revealed that the inhibitors bind into and occlude p53 pockets of MDM2 and/or MDMX by inducing the formation of dimeric protein complexes kept together by a dimeric small-molecule core. This mode of action effectively stabilized p53 and activated p53 signaling in cancer cells, leading to cell cycle arrest and apoptosis. MIC-1 is a p53 transcriptional target and secreted protein universally induced by nutlin in cancer cells that offers an easily accessible pharmacodynamic biomarker for p53 activation. Its blood levels were assessed during the clinical Ph I evaluation of RG7112, a member of the nutlin family of MDM2 antagonists, and found to correlate with drug exposure, suggesting effective p53 activation.
The dual MDM2/MDMX antagonist, RO-5963, restored p53 apoptotic activity in the presence of high levels of MDMX and may offer a more effective therapeutic modality for MDMX overexpressing cancers. Early clinical data with RG7112 validated MIC-1 as a p53 activation biomarker.

SP 120
Various molecular forms of ALK predict sensitivity to targeted therapy in hematological and solid tumors

M.A. Wasik. *University of Pennsylvania, USA*

Anaplastic lymphoma kinase (ALK) is expressed in a diverse spectrum of malignancies including T- and B-cell lymphomas, lung, breast, renal and thyroid carcinomas, neuroblastomas, and inflammatory myofibroblastic tumors. ALK, which is physiologically expressed solely in immature neural tissues, is aberrantly expressed in these malignancies as either a full-length protein or, much more frequently, a chimeric protein encoded by two gene loci fused together as a result of chromosomal translocations involving the ALK gene and one of a number of partner genes. The nucleophosmin (NPM)-ALK fusion protein, the prototypic member of this group, is expressed in 60−80% of anaplastic large T-cell lymphomas and displays potent cell-transforming properties, both in vitro and in vivo. Echinoderm microtubule-associated-like 4 (EML4)-ALK has been recently identified in 4−6% of non-small cell lung carcinoma and also found to be highly oncogenic. Indeed, lung carcinomas positive for ALK expression have been the first to be therapeutically targeted by the newly developed small molecule ALK inhibitor PF2341066/Crizotinib. The presentation will focus on the expression of ALK as a biomarker and therapeutic target in lung carcinoma, lymphoma, and other malignancies. It will discuss the importance of ALK detection as well as the various diagnostic methods to detect ALK expression including FISH, PCR, and immunohistochemistry. It will summarize the current status and future directions of clinical trials with ALK inhibitors. It will also discuss the mechanisms of malignant cell transformation induced by ALK including immune evasion and epigenetic silencing of tumor suppressor genes as well as how understanding of these oncogenic mechanisms could be incorporated into the future therapeutic strategies.

SP 112
Integration of metabolic imaging (PET CT) into clinical trials

W. Weber. *Department of Nuclear Medicine, University Hospital Freiburg, Germany*

Positron emission tomography with the glucose analogue fluorodeoxyglucose (FDG PET) has been used as clinical imaging modality for about 20 years. FDG PET is also increasingly used in clinical trials of new therapeutic agents. The aim of this presentation is to provide an overview of the requirements for successfully using FDG-PET/CT in clinical trials.
The literature on qualitative and quantitative analysis of FDG-PET alone or in combination with x-ray computed tomography (FDG PET/CT) was reviewed. A special focus was the use of FDG PET for assessing the prognosis of patients and to monitor tumor response to therapy.
Guidelines for FDG PET/CT imaging have been presented by the National Cancer Institute and the European Association of Nuclear Medicine (EANM). These guidelines provide detailed information on

patient preparation, data acquisition and image analysis including the calculation of quantitative parameters such as standardized uptake values (SUVs). Furthermore, criteria for classifying patients as responders or nonresponders on PET have been proposed (PET response criteria in solid tumors, PERCIST). When following these guidelines reproducible measurements of changes in FDG uptake during therapy are feasible. Comparison of tumor FDG uptake across different patients is more challenging, especially when different scanners are used at different sites. Another challenge when using different PET/CT scanners is a clinical trial is the definition of a "FDG positive" lesion. Since sensitivity and spatial resolution of PET/CT scanners have significantly improved over the years, lesions can easily be "negative" on an older scanner, but "positive" on a newer scanner.
Standardization of FDG PET scans and response criteria have made considerable progress in recent years. Challenges remain when qualitative observations or absolute measurements of tumor FDG uptake need to be compared across different scanners.

References

[1] Shankar LK et al. National Cancer Institute. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med. 2006; 47: 1059−66.
[2] Boellaard R et al. EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2010; 37: 181–200.
[3] Wahl RL, et al. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med. 2009; 50(Suppl 1): 122S–150S.

SP 109
Meta-analysis of genomic datasets for robust signature discovery and disease characterization

L. Wessels. *The Netherlands Cancer Institute, The Netherlands*

Here we evaluate (1) the prognostic value of available gene signatures; (2) the benefit of integration of clinical and gene expression data for prognostication and (3) the extent to which collaborating gene interactions can be revealed from copy number and expression data.
We performed a comprehensive analysis of the performance of nine gene expression signatures on seven different breast cancer datasets. To better characterize the functional processes associated with these signatures, we enlarged each signature by including all probes with a significant correlation to at least one of the genes in the original signature. In addition we also combined data from different modalities. We generate and evaluate a single prediction model based on both expression and clinical data. We compare three different integration strategies using five classifier types. Finally we employed copy number data from breast cancer samples to detect co-occurring aberrations. Such aberrations could point to genes that collaborate in oncogenesis.
The overall classification performance of the nine gene expression signatures is very similar but show low concordance at the sample level. Functional analysis of the enlarged signatures revealed 11 functional modules with prognostic ability. Of these, proliferation is the most dominant signature. The combination of the RNA-splicing and immune modules resulted in a classifier with high prognostic performance. On NKI 295 breast cancer series, the late OR integration strategy significantly outperformed all other classifiers. Independent datasets also showed that integration resulted in clear benefits, with the intermediate and the late OR integration strategies performing the best. In the co-occurrence analysis we discovered several regions that show interactions and are associated with outcome and breast cancer subtypes. When combining these findings with gene expression data and clinical outcome data, we identified several genes that show co-occurences both at the copy number and gene expression levels and show a significant interaction effect with regard to outcome.
Integration of clinical and expression data improves prognostication, and clinical features can achieve performance comparable to gene expression signatures. Thus, there is no longer a significant performance argument to choose one data source over the other. Finally, co-occurring gene aberrations are a powerful way to reveal oncogenic pathways and stratify cancer.

SP 124
Debate on strategies for data release: controlled access

D.L. Wickerham. *National Surgical Adjuvant Breast and Bowel Project (NSABP), USA*

The National Surgical Adjuvant Breast and Bowel Project (NSABP) is one of the National Cancer Institute of the United States cooperative trials groups with a 50+ year history of conducting large scale adjuvant therapy trials in primary breast and colon cancer. In 1992 the group expanded its research agenda to include chemoprevention trials in breast and colorectal cancer. The NSABP Biospecimen Banks contain formalin-fixed, paraffin-embedded (FFPE) tumor blocks from more than 90,000 breast and colorectal cancer tumor cases and sera from 20,000 treatment trial cases. Lymphocytes and sera are also banked from 33,000 healthy high-risk women from two breast cancer prevention trials. In addition to the centrally reviewed data for participant entry, treatment, recurrence, and death, copies of protocol consent forms are collected for all trial participants. Biospecimens and the corresponding clinical data are provided, on an as needed basis, to qualified investigators from both academia and the private sector on the basis of the scientific merit of proposals. In order to preserve participant confidentiality, the final analysis file which contains the laboratory results from the qualified investigator, and the clinical data from the NSABP Biostatistical Center, is prepared by an independent third party ("Honest Broker") and contains no participant identifiers except for a new randomly assigned number that is generated by the honest broker so the file is anonymized and neither the investigator nor the NSABP can identify any particular participant. Since 2003, 54 projects have been approved, including the development and initial validation of the Oncotype DX® 21 Gene Assay. The approach described here provides access to the specimens and the clinical data while allowing participant consent limitations to be respected, assuring that the privacy and confidentiality of the patients will be maintained, and that the trial data sets will be accurately interpreted.