Speakers' Summaries

SP 116

Omics-based tests: What is the evidence and how to present it?

J. Bogaerts. *EORTC Headquarters, Belgium*

The methodology that is currently used to evaluate predictive "omics-like" tests is a mix of:
- Standard comparative clinical trials approach, describing effects in terms of hazard/odds ratios, time to event curves, multivariate regressions.
- The methods used in diagnostic tests, concentrating on specificity, sensitivity, positive and negative predictive value, receiver operating curve (ROC) and its area under the curve (AUC).

Both have their advantages and shortcomings in dealing with the specific problems associated with evaluating a predictive test.
In the setting of tests that aim to differentiate between those patients who will likely benefit from a treatment and those who will not, the following are key:
- What will be the intended use of the test? For example, it is a very different undertaking to develop a test to identify a sensitive subgroup (especially suited to receive a specific treatment), than to identify a low-risk subgroup (good prognosis, no need to treat), or a group that is unresponsive to a treatment.
- The statistical quantification of the merit of the test should focus on that intended use.
- Statistical tests that are standardly used in comparative clinical trials can very easily be misinterpreted when comparing treatment decision strategies. Conversely, the interpretation of ROC curves from a narrow diagnostic test perspective can be very unfair and completely miss the potential benefit of a new marker for long term prediction.

In addition, when trying to design trials to investigate the merit of a new treatment decision strategy, additional factors play:
- The existing method of treatment selection is not necessarily uniform across practitioners.
- Randomizations between the novel strategy and an existing treatment strategy must take into account the considerable overlap in assignment between the methods. These overlapping cases (that have the same assignment by both methods) add noise to any comparison.

The end of the talk will discuss decision analytic approaches. While this is not a simple method, merits include:
- Demanding expression and quantification of the negative value of treating when not needed. This is a difficult step for trialists.
- Potential to illustrate the relative improvement made in terms of patient benefit.
- Allowing several patterns of preference. These exist both among practitioners and patients.

Trialists need to learn to design and report marker results by means of relevant statistics.

SP 119

synthetic lethal approaches and biomarker discovery related to radiation sensitization in prostate cancer

R. Bristow. *Radiation Medicine Program, Princess Margaret Hospital and University of Toronto, Canada*

The profiling of DNA damage reponse (DDR) and DNA repair pathways within individual tumours may allow for personalized medicine in patients who are receiving precision radiotherapy for cure. These DDR-Repair signatures include information on genetic alteration, functional assays and the tumour microenvironment. Using these approaches, we have begun to create a molecular profile for sensitive and resistant prostate cancer radiotherapy patients. This may lead to new therapies based on synthetic lethality and molecular-targeted radiosensitization.
Our studies have utilized pre-clinical prostate cancer models (cell lines and xenografts) in isogenic systems to document response to combinations involving experimental radiotherapy and tyrosine kinase inhibitors, DNA repair inhibitors (e.g. PARP inhibition) and hypoxia-modifying agents. We have also utilized array comparative genomic hybridization (aCGH), whole genome sequencing (WGS) and tissue microarrays (TMAs) to correlate biomarkers to outcome in a cohort of intermediate-risk patients following image-guided radiotherapy (IGRT). Such approaches may be useful in determining the basis of tumour cell radioresistance and drive personalized cancer medicine.
Using pre-clinical prostate cancer cell lines and xenograft models, we have shown that MRE-11 deficiency and intratumoural hypoxia can alter DDR signaling and lead to a DNA repair-deficient phenotype in vitro and in vivo. These repair-deficient cells were more sensitive to experimntal radiotherapy, cisplatinum and PARP inhibition. Studies with pre-treatment biopsies/assays have shown that prostate cancer hypoxia and altered c-MYC, p53, PTEN and NKX3.1 status are all adverse prognostic indicators for patients undergoing IGRT. Strategies using whole geneome sequencing are underway and will be discussed.
A priori profiling of tumour genetics and the microenvironment is useful in delineating tumours which may be repair-deficient. This will lead to novel treatment strategies using synthetic lethality approaches or drugs which co-target DDR-Repair pathways. However, robust biomarkers which reflect functional DDR-Repair in solid tumours are urgently required to drive forward clinical trials in this area.

SP 127

Adapting treatment in metastatic and adjuvant phases to the nature of mutation: the example of GIST

M. Debiec-Rychter. *University of Leuven, Belgium*

Gastrointestinal stromal tumor (GIST) represents a morphological, immunophenotypical and molecular distinct entity, the recognition of which has profound therapeutic implications. The understanding of GIST biology has made this tumor a paradigm for molecularly targeted therapy in solid tumors. Approximately 85% of GISTs harbor activating mutations in KIT or the homologous receptor tyrosine kinase PDGFRA gene. Resulting oncoproteins serve as a target for the small molecule tyrosine kinase inhibitors imatinib and sunitinib, which were approved for treatment of metastatic and unresectable GISTs. Preclinical and clinical studies of imatinib and sunitinib in GIST patients have identified prognostic features that contribute to treatment failure. KIT or PDGFRA mutational status of the tumor is one of the strongest predictors of response to both drugs. Patients treated with imatinib whose tumors harbour KIT exon 11 mutations have better response rates, median progression-free survival, and overall survival compared to patients with other mutations. Patients with tumors carrying KIT exon 9 mutations might require higher dose of imatinib. Tumors bearing the most common PDGFRA mutation, D842V amino acid substitution, are primary resistant to imatinib. Furthermore, the common problem in management of GIST is resistance to imatinib, with two recognized clinical patterns: (1) primary or early resistance concerns ~10−15% of patients that progress within 3 months of starting imatinib; (2) patients with later progression are classified as having acquired resistance. Patients intolerant to imatinib (5%) and those who progress on imatinib are treated with sunitinib. The clinical benefit of sunitinib as second-line treatment is evidently better for patients whose tumors carry primary KIT exon 9 mutation (30% of which show primary imatinib resistance), and with KIT/PDGFRA wild-type genotype. The main mechanism of acquired resistance to imatinib and sunitinib is related to growth of heterogeneous clones with secondary mutations in KIT. Whereas surgical resection continues to be the standard of care for primary GIST, cautious and individualized use of adjuvant and neoadjuvant imatinib may enhance the potential for cure in GIST patients. The greatest benefit will derive from an individualized approach that among other factors considers also tumor mutational status to assess likelihood of benefit for each patient.

SP 128

KRAS mutations in colorectal cancer: lessons learned and future progress

S.G. Eckhardt. *University of Colorado School of Medicine Anschutz Medical Campus, USA*

Colorectal cancer (CRC) represents a major health burden, and is the 3rd leading cause of cancer deaths in the U.S. In the past decade, the median survival among patients with metastatic CRC (mCRC) has increased, primarily due to the introduction of irinotecan, oxaliplatin and signal transduction modulators targeting the vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) pathways. Studies in first, second and third-line CRC patient populations have demonstrated that approximately 40−50% of all patients with CRC have mutations in the KRAS gene that predicts for non-responsiveness to EGFR-targeted agents.

Unfortunately the lack of identification and utilization of this resistance marker in previous clinical trials led to the erroneous treatment of thousands of CRC patients with EGFR-targeted agents at the cost of considerable toxicity and no benefit. Although initially this resistance factor for EGFR-targeted therapy was thought to be relatively straightforward, subsequent studies using more robust analyses have revealed potentially important insights that may further refine the patient population selected for this class of agents. Furthermore, for those patients with KRAS mutations, treatment is restricted to first and second-line combinations of 5-FU/oxaliplatin/irinotecan/bevacizumab. No other options exist for this patient population, and although drug development is ongoing, preliminary results indicate that merely targeting putative resistance pathways may not be sufficient. Thus, there are numerous lessons learned and pathways forward in this disease, all of which rely upon the earlier development and integration of genomic technologies to refine patient selection and identify resistance pathways that may yield rational combination strategies.

SP 122

Debate on access to tissue specimens from clinical trials: when is the preliminary data strong enough to invest in highly annotated biospecimens?

J. Hall. *EORTC Headquarters, Belgium*

Panelists: J. Gastier-Foster, M. Hegi, S. Hilsenbeck, and JY. Blay. Access to well-annotated quality biospecimens is critical for tumor characterization and biomarker development and validation. Tissue specimens from clinical trials are often seen as a unique tissue resource that should mainly be used for the late stages of biomarker validation where considerable preliminary data already exists. Given that clinical trial tissue specimens are limited, how do we decide on the best use of samples? Should the trial specimens be saved for biomarker validation or could they also be used for large coordinated multidimensional -omics profiling? How to prioritize specimen use? Who decides on the scientific merit of proposed research and when are highly annotated trial specimens needed? The objective of the session is to explore the decision making processes behind the access to and feasibility of use of clinical trial specimens in multiple platforms and large scale genomic studies. Two short case studies on use of trial specimens in large-scale genomic studies from COG pediatric acute lymphoblastic leukemia (US) and glioblstoma trials (EU) will be presented followed by an open discussion on the topic by a multidisciplinary panel (biobanker, translational scientist, statistician and clinical oncologist).

SP 132

IDH1/IDH2 mutations predict survival in glioma and AML

M. Hegi. *CHUV, Switzerland*

Mutations in the isocitrate dehydrogenase family genes 1 or 2 (IDH1/2) have been discovered by high through put sequencing approaches in glioma and acute myeloid leukemia (AML) and related myeloproliferative neoplasms. In both diseases, the discovery of IDH mutations has identified a prognostically new subtype with distinct pathogenetic evolution. In gliomas mutations are mostly found in IDH1 (>90%). They are infrequent in primary glioblastoma (GBM) (<10%), but common in secondary GBM that evolve from lower grade glioma (60−90%). Mutations in IDH1 precede p53 mutations or 1p/19q co-deletions in sporadic low grade glioma, hence are an early evant. Co-deletions of 1p/19q, characteristic for oligodenroglioma, are highly associated with IDH1/2 mutations, while they are mutually exclusive with EGFR amplifications, a hall mark of primary GBM. IDH1 or 2 mutations are associated with younger patient age, but absent in childhood gliomas, and have a better prognosis that seems to be consistent in grade II through IV gliomas. In myeloid malignancies mutations are more likely in IDH2 and are found in de novo and secondary AML (12−18%) and pre-leukemic clonal malignancies (5% chronic; 20% transformed). IDH1/2 mutations are strongly associated with NPM1 mutations that are found in 30% of novo cytogenetically normal AML. In CN-AML with mutated NPM1, without FLT3 internal tandem duplication (ITD) IDH mutations constitute an adverse prognostic factor. Mutations in the metabolic enzymes IDH1 or 2 result in a neomorphic reaction, generating high levels of the metabolite 2-hydroxyglutarate (2-HG). IDH mutations are mutually exclusive with TET2 mutations in myeloid malignancies that led to the discovery that high levels of 2-HG inhibit the a-KG dependent dioxygenase TET2. TET2 is involved in epigenetic regulation and mediates demethylation of DNA. This mechanism is in accordance with the association of a methylator phenotype with loss of function of TET2 by mutation or indirectly by mutation of IDH1/2 in myeloid malignancies and gliomas, respectively.

Metabolism meets Epigenetics. These discoveries will have important clinical implications: IDH1/2 mutants may serve as unique targets for therapy. Further, the high concentrations of the onco-metabolite 2-HG generated by IDH1/2 mutants, may serve as biomarker in the serum of patients with myeloid malignancies and may be amenable by magnetic resonance spectroscopy in glioma patients.

SP 134

Predictive and pharmacodynamic markers of susceptibility for targeting IGF-1R receptor

F.R. Hirsch. *University of Colorado, USA*

Numerous human tumors have been shown to overexpress IGF-1R or have increased IGF-1R kinase activity resulting in enhanced proliferation, protection from apoptosis, stimulation of migration and invasion and stimulation of angiogenesis. Targeted therapies, including insulin-like growth factor (IGF) binding proteins, human monoclonal antibodies and small-molecule tyrosine kinase inhibitors, against IGF-1R, have been developed and show promise for therapeutic use in both in vitro and in vivo experiments. Several clinical studies with IGF-1R inhibitors are performed or currently on-going. In non-small cell lung cancer (NSCLC) most advanced in clinical development was studies with the monoclonal antibody, Figitinumab (Pfizer), which in randomized phase II study showed encouraging effect in combination with chemotherapy. However, large randomized phase III study in 1st line therapy was prematurely stopped due to futility and toxicity. None of the IGF-1R inhibitors studies was based on biomarker selection related to the IGF-1R pathway. The "negative" experience in patients with NSCLC have put clinical development of IGF-1R inhibitors on hold and calls for a better understanding of mechanisms development of predictive biomarkers. Retrospective analysis of the specimens from the figitumumab studies demonstrated significant association between plasma IGF and response and outcome. These findings have not yet been validated prospectively. However, several tissue assays might also be potential predictive assays which need to be validated. We demonstrated that many NSCLC tumors express IGF-1R protein by IHC and increased IGF-1R gene copy number occurs in many tumors, which represents potential tools for predictive assays. IGF-1R protein expression by AQUA-technology (HistoRx, USA) was in a retrospective analysis from the figitumumab studies also demonstrated to be associated with response. We recently demonstrated that IGF-1R activation might play a role as intrinsic resistant mechanisms for EGFR TKI therapy in patients with NSCLC, even in patients with tumors harboring activating EGFR-mutations, which raises a potential for use of IGF-1R inhibitors in combination with EGFR TKIs in order to overcome resistance to EGFR TKIs. In conclusion, while IGF-1R seems to play a role in tumor genesis of many cancer and use of IGF-1R targeted therapies in some early studies have demonstrated encouraging results, much focus have yet to be put into the development of predictive biomarkers. This needs to be done in preclinical studies and through retrospective analysis of specimens from the existing clinical trials.

SP 113

Translating molecular imaging agents into phase 3 trials

P. Jacobs. *National Cancer Institute, United States*

Drugs that have not been approved by regulatory authorities for marketing, including imaging agents, must be studied clinically under an Investigational New Drug (IND) exemption in the US or a Clinical Trial Authorization (CTA) in Europe or Canada. Many molecular imaging probes are short-lived radiopharmaceuticals with no intellectual property protection and relatively small market potential. Most commercial entities correctly view development of such discoveries as high risk (high cost, low potential revenue) that cannot be justified. Pre-investigational new drug application (IND) and early feasibility studies that are essential to moving drugs to the clinical investigational stage cannot generally be funded through the typical grant mechanisms because they are considered neither original research nor novel nor will they be funded by industry because of the lack of intellectual property. Multicenter trials with such agents present unique logistical, quality, and regulatory issues.

A few years ago, the Cancer Imaging Program at the National Cancer Institute began an effort to open multicenter trials with a few non-proprietary PET molecular imaging probes and encountered a number of hurdles. One was assuring that the radiopharmaceuticals used at each site were chemically equivalent. A second was the logistical barrier to supplying sites without cyclotrons and synthesis resources. The third was dealing with regulatory issues.

The strategies, failures, and successes of this effort will be discussed. An attempt to establish identical preparations of 18F-fluorothymidine at four academic sites with identical synthesis boxes was a failure. Commercial suppliers were then engaged to establish manufacturing to the identical specifications and to file Drug Master Files with FDA. These companies have gradually increased the number of sites preparing the agent to around 20 and can now supply most of the US. Under IND, the NCI is performing