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.