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