Issues such as sensitivity, specificity, reproducibility, and standardization are not on the typical patient's radar screen, nor should they need to be so long as the research community (academic, government, and commercial) does their jobs correctly.
Instead, issues of protection of privacy, non-discrimination, and affordability dominate the radar screens of the vast majority of patients.
The spelling of the words "hope" and "hype" differs by only one letter − "o" instead of "y". However, their definitions are vastly different, and in biomarker research the difference between hope and hype can be as wide or as narrow as the people conducting and interpreting the research. Timing is everything and patients depend on researchers for hope, not hype.
Molecular advancements that connect a patient's biomarker with an event such as a drug response are occurring and will continue to occur with greater frequency and reliability. With these emerging molecular methods comes great responsibility in educating health professionals, policy makers, and the general public about the potential use and misuse of the information these methods produce.

SP162
Clinical application of biomarkers: discovery, validation, and application

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Introduction: Biomarkers can function as diagnostic, prognostic, or predictive tools, and can also lead to new therapeutics. Alternatively, they can be applied for proof of concept for the mechanism of action of novel agents. The findings of EGFR and K-ras mutations in tumor tissue have had important implications in the treatment of lung and colon cancers and have led to pre-treatment patient selection based upon retrospective analyses. Key to development of new agents is application of pathway and function-related markers to tissue in order to validate the target of the agent. This approach will also yield important insight into the "why" and "why not" of outcomes.
Purpose: To demonstrate the value of tissue-based analyses of pathway and function-related markers in order to characterize and validate molecular treatment targets.
Main message: Clinical trials of single and multi-agent targeted therapies were designed to include at least a pair of biopsies. Biopsies were immediately frozen in OCT and later cut, pathology evaluated, and then cells collected for analysis. Proteomic approaches were optimized to allow reverse-phase protein array analysis of serially diluted proteins. Both total and phospho-protein quantity was measured and then analyzed against patient outcome, toxicity, and demographics. A new trial schema was designed to allow proof-of-concept measurements in combination therapy. We demonstrated on-target activity of imatinib and gefitinib in ovarian cancer patients; this on-target activity correlated with toxicity. Triplet biopsies obtained from patients treated with bevacizumab and sorafenib were analyzed to evaluate single and combination agent signal inhibition activity. Confirmation of target activity was demonstrated for both agents and inhibition of pathway activation was associated with clinical benefit.
Recommendations: Clinical trial design and execution should include objectives to confirm target presence, activation, modulation by therapeutic intervention, and association with outcome. This will expedite selection of patients as well as lead agents and should lead to faster and improved results.
Conclusions: Optimizing application of the new molecularly targeted agents requires knowledge and application of pertinent biomarkers. Prospective validation of target and biomarker will allow future controlled patient selection and would be expected to yield improved patient outcomes.

SP150
Pharmacogenomics in colon cancer

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Although the introduction of biologic agents and the development of associate molecular markers have shown promising results (K-ras, MSI, 18q del, TS, ERCC1), only a few of these biomarkers has been accepted into routine clinical practice. It is becoming increasingly apparent that complex pathways drive disease progression; analysis of one single marker is unlikely to predict efficacy and outcome. Tumors are being classified into specific tumor phenotypes based on molecular profiles. Two of these represent genetic instability classes. The majority of sporadic cases (85%) display chromosomal instability (CIN), defined as allelic imbalance (AI) at a number of chromosomal loci (including; chromosomes 5q, 8p, 17p, and 18q), chromosome amplification and translocation, which collectively contribute to tumor aneuploidy (Vogelstein, Fearon et al. 1988). In contrast, the remaining 15% of sporadic colon cancers demonstrate a high-frequency microsatellite instability phenotype (MSI-H), in which tumors display frameshift mutations and base pair substitutions commonly found in short tandemly repeated nucleotide sequences called microsatellites (Aaltonen, Peltomaki et al. 1993). The underlying genetic mechanism responsible for this phenotype is mutation and loss of function through gene silencing of DNA mismatch repair genes (MMR) (Kane, Loda et al. 1997). Recently the analysis of CpG island methylation as a mechanism of silencing genes in colon tumors has resulted in the identification of the CpG island methylator phenotype (CIMP). This phenotype appears to be complex and the overlap between this phenotype and MIN and CIN, and the subsequent prognostic significance in colon cancer patients has not been thoroughly investigated (Shen, Toyota et al. 2007). The design of new prospective trials must encompass a more comprehensive and disciplined approach with defined protocols, primary end points and increased statistical power. Follow-up studies are also required to identify the functional significance of the many mutations and polymorphic variants that exist in the patient population, such functional information will inevitably assist in unraveling the complex and multi-faceted mechanisms of drug metabolism and cytotoxicity. Markers of response to the novel therapeutic drugs including bevacizumab, cetuximab and panitumumab have been identified and need to validated so that the use of these agents can be targeted to those who will derive greatest benefit.

SP151
Current challenges in the design and conduct of pharmacogenetic and pharmacogenomic studies

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Introduction and Purpose: For many cancers, multiple regimens are active. Yet these different regimens produce a variable response to therapy and sometimes unpredictable toxicity. Some of these variations may be explained by tumour genomics or the patient's genetics. Eludication of the mechanisms behind such variations is a critical component of "personalized" or "individualized" medicine, allowing an intelligent choice of available therapies. Clinically, the primary goals of such studies are to maximize drug efficacy, select responsive patients, and avoid adverse drug reactions. These clinical goals can be accomplished through research goals that link either variation in genotype of the patients or the tumour to a phenotype (an observable characteristic or trait such as patient response, survival or drug toxicity), that determine mechanisms responsible for that link, and that translate that link into enhanced understanding, treatment and prevention of disease or toxicity. Well conducted studies are necessary to advance this field.
Main Message and Recommendations: Challenges in the design and conduct of such trials include: (i) phenotyping accuracy (e.g. toxicity or response to therapy) across prospective and retrospective study designs; (ii) treatment issues, including controlled and observational designs; (iii) sample size determinations, whether planned or convenient; (iv) control of Type 1 error (exploratory versus corrected); (v) inclusion or exclusion of known molecular and clinicoepidemiologic prognostic factors in multivariate analyses; (vi) DNA/RNA sample source, including formalin-fixed versus fresh tissues, blood versus saliva/buccal; and (vii) whether interventional or non-interventional trials by pharmacogenetic or pharmacogenomic markers are required for clinical adoption. In addition for genetic studies, additional challenges include gene selection (candidate, pathway or genome-wide) and variant selection, through either functional or tagging approaches. For genomic studies, additional challenges include reproducibility within and across platforms and cancer heterogeneity. Illustrations and examples of such design challenges are presented.
Conclusion: Tackling these challenges are key to successful pharmacogenetic and pharmacogenomic trials.

SP145
PET imaging in upper GI Cancer − past experience and current EORTC initiatives

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Introduction: Metabolic imaging and early response assessment by PET are gaining importance in guiding treatment of localised and metastatic cancer [Weber JNM 2009]. Consistent results have been obtained during neoadjuvant treatment of adenocarcinoma of the oesophagus and the oesophago-gastric junction.
Main messages: It was demonstrated that FDG-PET is highly accurate for identifying non-responding tumours within 2 weeks after the initiation of neoadjuvant chemotherapy when a quantitative threshold for metabolic response is used [Weber WA et al. JCO 2001; Ott K et al. JCO 2006]. In consecutive phase II studies we quantified the metabolic activity, defined by the standardised uptake (SUV) of 18-FDG before and during chemotherapy. We observed that after only two weeks of induction chemotherapy significant decreases of the SUV occurred. A drop of >35% measured