circulating tumor cells in the peripheral blood (CTC). Sequential peripheral blood analyses should be more acceptable than BM aspirations and many research groups are currently assessing in studies the clinical value of CTCs in primary and metastatic breast cancer. The purpose of this presentation is to give an overview of the clinical value of CTC.
Primary breast cancer: Depending on the detection technique used, CTC were revealed in 5−20% of patients with primary breast cancer. In contrast to metastatic breast cancer the role of CTC in primary breast cancer to predict prognosis is still under investigation and conclusive data have not yet be obtained. To monitor efficacy of therapy is of great clinical relevance especially in the adjuvant setting when no measurable tumor is present. In the SUCCESS-trial peripheral blood from 1,500 breast cancer patients before and after adjuvant taxane-based chemotherapy was examined for the presence of CTC. While the presence of CTC before systemic treatment did not show prognostic relevance, persistence of CTC after chemotherapy was a significant predictor for reduced disease free and overall survival. The aim of adjuvant therapy is to eliminate MRD reflected by CTC. Interestingly, the expression profile of therapeutic relevant markers differs between CTC and primary tumor indicating that adjuvant treatment strategies based on the expression profile of the primary tumor may not be efficient to eliminate minimal residual disease.
Metastatic breast cancer: The detection rates in metastatic breast cancer range from 40% to 80%. The prognostic significance of CTC in the metastatic setting has been clearly demonstrated by several large studies. Interestingly, CTC determinations seem to be superior over conventional imaging methods for therapy monitoring. In metastatic cancer the phenotype of metastatic disease is reflected by the phenotype of CTC. Therefore, characterization of CTCs may be useful to reassess therapeutic relevant markers (e.g. HER2, ER) particularly when a biopsy of the metastasis cannot be performed.
Conclusion: Based on current study results, circulating tumor cells have the potential to improve predicting prognosis, monitoring therapy and optimizing adjuvant treatment.

SP142
Molecular imaging

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Molecular Imaging (MI) using Positron Emission Tomography (PET) and tracers radiolabeled with positron emitting isotopes (Fluor-18, Gallium-68; Zirconium-89; Carbon-11; Copper-64, etc.) is increasingly studied as biomarkers in oncology. The strenght of the technology is based upon its unique nanomolar detection sensitivity (allowing a minimal amount of tracer to be administered, microdosing, without relevant pharmacologic effect) and by its capacity to perform rapid and semi-quantitative whole body imaging (allowing to quantitatively assess multiple lesions altogether in the same conditions, thus accounting for phenotypic heterogeneity), and to integrate molecular and structural information of cancer (hybrid PET-CT camera technology).
The PET biomarkers can be used for the selection of the patient for a specific drug (through the imaging of the expression of the molecular target, eg. HER2-neu receptor imaging, or physiologic state, eg. hypoxia), and for pharmacodynamic (PD) assessments (early changes of FDG uptake during therapy, or FLT, a surogate for proliferation, or apoptosis).
The lecture will deal with the rationale (how will MI contribute to a better cancer care), the technical principles (cameras and tracer) and the challenges (standardization and harmonization of MI in multicentric trials) of MI. Some ongoing multicentric clinical research projects incorporating MI will be discussed.

SP171
Prognostic and predictive signatures in breast cancer: update and future perspectives

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In primary breast cancer, tumor-biology-based prognostic and predictive factors are urgently needed to optimize treatment decisions. The uPA/PAI-1 protein test and multigene assays, e.g. the Amsterdam 70-gene, the Rotterdam 76-gene or the 21-gene (recurrence score) signatures have been shown in retrospective studies to reliably predict patient outcome. Other promising factors include methlylation-based markers (e.g. PTIX2) or disseminated tumor cells in bone marrow or blood. Among prognostic factors, only uPA/PAI-1 has been validated by a prospective clinical trial at LOE I. For recurrence score and the 70-gene signature, large international trials are currently recruiting. The only tumor-biological predictive factors routinely used are HER2-status (trastuzumab) and hormone receptor status (endocrine therapy); but no factor can reliably identify the optimal chemotherapy. HER2 status has been suggested as a marker for anthracycline response yet high response rates with anthracycline and taxane containing neoadjuvant chemotherapy are seen in triple-negative disease. For topoisomerase 2, neither the biological role in anthracycline response nor the best determination method have been clarified. For endocrine therapy, CYP 2D6 mutation status has been suggested as a predictive factor based on decreased tamoxifen metabolism in mutation carriers. However, the lack of consistent predictive marker data is partly explained by hypothesis-generating data from small retrospective analyses lacking power for appropriate interaction and validation analyses. Individualizing adjuvant therapy decisions in primary breast cancer is already possible by protein or molecular markers. The challenge is to make these assays robust, quality-controlled, and applicable for clinical routine. Assays aimed at sparing patients from unnecessary therapy need to be thoroughly technically and clinically validated. Beside HER2 and hormone receptor status, no clinically validated biological predictive markers are currently available. We need assays that can help select chemotherapeutic and endocrine options that optimize therapeutic benefit and minimize side effects. Prognostic and predictive factors can only be prospectively validated in appropriately sized clinical trials with translational research programs. Pharmaco-economic data need to be generated to ensure appropriate pricing and benefit from these assays independent of the strength of national health budgets.

SP160
Targeted therapies directed against EML4-ALK translocations and BRAF mutations in patients with lung cancer

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Introduction: Prospective clinical trials have now shown non-small cell lung cancer NSCLC) patients with sensitizing mutations of the epidermal growth factor receptor EGFR) have 2 to 3 fold prolongation of progression-free survival when treated with gefitinib compared to those treated with chemotherapy. This led to the European Commission granting marketing authorization for gefitinib in patients with mutations in the EGFR in July of 2009.
Purpose: This presentation provides information on other potential genomic abnormalities that can be targeted with novel agents.
Main message: EML4-ALK translocations: Investigators discovered a chromosomal translocation in adenocarcinomas of the lung which could transform NIH 3T3 cells. The transforming gene was a fusion of the ALK gene with echinoderm microtubule-associated protein-like 4 (EML4) in Japanese NSCLCs. Further studies show the EML4-ALK translocation is present in NSCLCs arising in about 3% of patients from the United States and Europe. The translocated gene can now be detected by using fluorescence in situ hybridization in histologic sections of the tumor. The drugs directed against the ALK tyrosine kinase include TAE684 and PF2341066. PF2341066 has shown antitumor activity with a 50% response rate in phase I trials for NSCLC patients with the EML4-ALK translocation. A randomized phase III trial for patients with relapsed NSCLC and EM4-ALK translocation is planned.
BRAF mutations: Investigators have documented that BRAF mutations are common in melanoma and clinical trials have been developed for patients with melanoma where treatment is determined by the patients' BRAF mutations status. BRAF mutations are present in approximately 3% of patients with NSCLC. Trials have now been designed that include patients with NSCLC and BRAF mutations who are treated with MEK inhibitors.
Recommendations: Patients with advanced NSCLC should undergo genomic characterization for mutations in EGFR so they can initially be treated with gefitinib or erlotinib. The characterization of genomic changes should include additional genes so they can be allocated to appropriate genomically directed trials.
Conclusions: There are now two examples where genomic characterization of NSCLCs can lead to encouraging therapeutic outcomes (EGFR mutations and EML4-ALK translocation). Consistent characterization of other genomic changes will allow assessment of other targeted therapies in genomically defined NSCLC patient subsets.

SP164
Biomarker research: the patient perspective

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Biomarkers and biospecimens hold the promise of helping patients and their healthcare teams improve in their goals of preventing, managing, treating, and curing disease.
Patients focus primarily on the opportunities and end products of biomarker research − translation: "How will this help me or my loved ones?"
Patients are not concerned with the challenges researchers face in arriving at the end products of biomarker research − translation: "Hurry up and figure this out so you can help me/us."

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