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."