multicenter trials in breast and lung cancer. Furthermore, the regulatory documents have been made publicly available and the NCI has freely provided letters of reference to investigators to file their own INDs; many academic and commercial entities have done so.
New strategies are needed for clinical development of non-proprietary short-lived radiopharmaceuticals with low market potential. Even newer strategies may be needed for commercialization of such agents.

SP 108
Resistance to tyrosine kinase inhibitors in chronic myeloid leukemia

T. Lion. *CCRI, Austria*

In patients with chronic myeloid leukemia, targeted therapy with tyrosine kinase inhibitors (TKIs) has been the standard of treatment for a number of years. Despite the extraordinary success of this approach, the occurrence of resistant disease remains a clinically important problem. Point mutations within the BCR/ABL1 tyrosine kinase domain (TKD) are currently regarded as the most important mechanism of TKI resistance. The European LeukemiaNet (ELN) has therefore recently provided guidelines for mutation testing and the therapeutic implications (Soverini et al., Blood 2011).
In line with the ELN-recommendations, mutation screening is most commonly performed by direct sequencing of the entire BCR/ABL1 TKD following amplification by PCR. This approach does not reveal the presence of mutant subclones below the level of 10−20% of the entire leukemic cell pool.
Although more than 100 different mutations have been described in the BCR/ABL1 TKD, a subset of 15 common mutations are observed in the great majority (>85%) of instances. Patients harbouring BCR/ABL1 TKD point mutations were reported to have a progression-free survival inferior to patients without point mutations. By contrast, detection of mutant subclones, especially by highly sensitive technical approaches, did not necessarily imply impending onset of clinically resistant disease. A number of mutations may be biologically neutral with regard to TKI resistance ("bystander" or "passenger" mutations), while other mutations are frequently associated with the onset of resistant disease ("driver mutations"). However, even mutant subclones commonly associated with resistance to TKI treatment have been described to disappear spontaneously below the limit of detection and to remain undetectable. Hence, the detection of mutations may be difficult to interpret with regard to clinical relevance and therapeutic consequences. Our recent observations indicate that the surveillance of subclone evolution by quantitative monitoring of mutant cells during treatment with TKIs provides information on their actual responsiveness to therapy and the imminent onset of resistant disease.
Judicious implementation of quantitative diagnostic approaches in the surveillance of CML patients could therefore improve our current options for timely treatment decisions, and help optimizing disease management in patients displaying point mutations in the BCR-ABL1 TKD or other sites of potential relevance.

SP 131
MicroRNAs as prognostic and predictive markers in breast cancer

J. Martens. *Erasmus MC, The Netherlands*

MicroRNAs (miRNAs) are small ribonucleotides that use the endogenous RNA interference pathway to modulate mRNA expression and translation thereby contributing to cancer biology. Our aim was to determine in breast cancer which miRNAs are associated with time to disease metastasis (TDM) in estrogen receptor positive (ER+) and in triple negative (ER-, PgR- and Her-2-negative) breast cancer and with clinical benefit of (endocrine) therapy in ER+ disease. In silico and functional studies have been and are being performed to address in which biological pathways the significant miRNAs operate.
To discovery prognostic miRNAs genome-wide miRNAs panels were analyzed by qRT-PCR in ER+ and triple negative primary breast cancers with short and long TDM. All patients included were lymph node negative and none had been treated with adjuvant systemic therapy. Candidate prognostic miRNAs were confirmed in independent cohorts. To identify candidate predictive miRNAs, a panel of selected miRNAs was studied in a large cohort of ER-positive breast cancers treated first-line with tamoxifen for their metastatic disease. Cox and logistic regression was used to associate variables with TDM and clinical benefit, respectively. Co-expression analyses; database searches and functional studies were performed to identify biological pathways connected to the significant miRNAs.
Four microRNAs were in uni- and multivariate analysis associated with TDM in ER+ patients; these microRNAs were associated with VEGF signaling, cell cycle progression/chromosomal instability and cytokine signaling. Twenty candidate prognostic microRNAs were discovered in triple negative breast cancer; validation is currently on going in collaborationwith EORTC-PBG members. Several microRNAs predictive of clinical benefit of tamoxifen therapy were also identified. These were related growth factor/RAC signaling, apoptosis and polycomb remodeling.
Our work connects microRNAs and their associated biology to breast cancer disease progression and therapy resistance.

SP 115
Cancer stem cells

W. Matsui. *Johns Hopkins University School of Medicine, USA*

Emerging data suggest that cells within an individual tumor are both phenotypically and functionally heterogeneous despite their clonal origins. In many malignancies, most cells appear to lack significant replicative potential and instead arise from relatively rare populations of phenotypically distinct cancer stem cells. In both hematologic malignancies and solid tumors cancer stem cells have been prospectively identified based on their ability to give rise to differentiated progeny that recapitulates the original tumor in the ectopic setting. Additionally, these cells are capable of self-renewal and may be relatively resistant to various anti-cancer agents. These unique functional properties suggest that cancer stem cells play a central role in disease initiation, relapse, and progression and that the development of effective strategies inhibiting these cells may ultimately improve long-term clinical outcomes. We have studied multiple myeloma and found that the malignant plasma cells forming the tumor bulk and characterizing the disease arise from cancer stem cells phenotypically resembling normal memory B cells. Recently, we have translated these findings and initiated novel clinical trials explicitly designed to target myeloma stem cells. We will discuss the strategies we have used to identify novel cancer stem cell-targeting agents in the laboratory and develop biomarker strategies to monitor their efficacy in the clinical setting.

SP 117
Using genomic landscapes to map biomarkers of drug sensitivity

U. McDermott. *Wellcome Trust Sanger Institute, UK*

Clinical responses to anticancer therapies are often restricted to a subset of patients. In some cases, mutated cancer genes are potent biomarkers of response to targeted agents. To uncover new biomarkers of sensitivity and resistance to cancer therapeutics, we screened a panel of several hundred cancer cell lines, which represent much of the tissue-type and genetic diversity of human cancers, with 130 drugs under clinical and preclinical investigation. In aggregate, we found mutated cancer genes played an important role in determining cellular response to most currently available cancer drugs.
We assembled 639 human tumour cell lines, which were subjected to systematic genomic and transcriptional profiling, including sequencing of the full coding exons of 65 commonly mutated cancer genes, genome-wide analysis of copy number gain and loss using SNP6.0 arrays, and expression profiling of 14,500 genes using Affymetrix HT-U133A microarrays. Cells were treated with drugs for 72 hours and effects on cell viability were measured and a curve-fitting algorithm was applied to derive the half maximal inhibitory concentration (IC50) and the slope of the dose response curve. The drugs selected for analysis covered a wide range of molecular targets and processes implicated in cancer biology.
We first used a MANOVA to identify statistically significant associations between individual mutated cancer genes and drugs across the cell line panel, applying a Benjamini-Hochberg false discovery rate (FDR) cutoff of 0.2 ($P < 0.0099$) to correct for multiple hypothesis testing. This analysis revealed a large number of individual gene-drug associations, a subset of which (448/9039, 5%) were highly significant. Remarkably, most of the cancer genes analyzed (including gene fusions) were significantly associated with either sensitivity or resistance to at least one drug in our panel.
The scope of this work provides a unique perspective on the factors that modify drug response and the use of biomarkers for the clinical stratification of cancer patients. The emergent picture is of a complex network of biological factors that affect response to the majority of cancer drugs. The clinical utility of genome-based biomarkers is likely to increase in the coming years as the genomic characterization of cancers increasingly becomes routine practice and this is combined with clinical information about patient response to treatment.