requiring a better selection of patients who should benefit from targeted therapies.
Methods: We evaluated the effects of the SRC tyrosine kinase inhibitor dasatinib (BMS-354825) on melanoma cell proliferation in relation with NRAS and BRAF mutation status and key proteins involved in melanoma signalling pathways.
Results: We examined 33 melanoma cell lines and found that 7 lines were highly sensitive to dasatinib (IC50 < 10^{-9}M), 13 were moderately sensitive (IC50 from 10^{-8} to 10^{-6}M) and 13 were resistant (IC50 > 10^{-5}M). All highly sensitive lines had no mutation on BRAF or NRAS, while 69% of the moderately sensitive and 69% of the resistant cell lines had activating mutations. All highly sensitive lines expressed high cKIT levels, whereas others had undetectable cKIT expression. Importantly, cKIT appeared as an effective target of dasatinib since the cell lines which were the most sensitive to dasatinib were also the most sensitive to the specific cKIT inhibitor ISCK03. Moreover, in all sensitive cell lines, dasatinib dramatically inhibited the phosphorylation of ERK and AKT, while it had not effects in the mutated lines, suggesting a selective effect on proliferation/survival of cKIT expressing cells, although NRAS/BRAF mutations are likely to render these cells much less dependant on cKIT signalling for their survival. We are currently evaluating this aspect as well as the effectiveness of dasatinib in combination with other agents in the case of tumor resistance.
Conclusions: We found that dasatinib was highly effective to inhibit cell proliferation in a subgroup of melanoma lines characterized by wild-type NRAS/BRAF and high cKIT expression, and this will be the basis of a clinical trial in a selected group of melanoma patients.

255 ORAL

Transcriptome sequencing of upper aerodigestive tract cancer cell lines to reveal potential therapeutic targets

J. Braegelmann[1], T. Stricker[2], C. Brown[2], M. El Dinali[1], X. Zou[1], E. Vokes[1], K. White[2], T. Seiwert[1]. *[1]Section of Hematology/Oncology, Dept. of Medicine, Chicago, USA; [2]Institute for Genomics and Systems Biology, Chicago, USA*

Background: We applied RNA-seq − a powerful technology that allows to obtain sequence and expression information simultaneously on a transcriptome-wide basis- to 30 upper aerodigestive tract cancer cell lines to conduct mutational profiling and enhance the knowledge of the underlying tumor biology.
Methods: RNA from 30 upper aerodigestive tract cancer cell lines was extracted and sequencing libraries constructed. Samples were analyzed using an Illumina Genome Analyzer with a paired end module (54 or 75 base read length). Raw data was processed with a proprietary data pipeline from the White Lab. Potential mutations were identified by subtracting common SNVs (e.g. dbSNP, population allele frequency), assessing evolutionary conservation, and evaluating ancestral alleles identified from multiple sequence alignments. These SNVs were then parsed via in house scripts to determine whether the SNVs were present in coding regions, 3′UTR, 5′UTR, or in splice acceptor/donor sites. The coding SNVs were further parsed to determine which SNVs result in non-synonymous changes. RNA-Seq expression data was analyzed using R scripts and Partek Genomics Suite. Pathway analysis was performed using GeneGO Metacore.
Results: 1 GB to 4 GB of data were obtained per sample. Between 700 and 3000 nsSNVs were identified, as well as a large number of alterations in the 3′ and 5′ untranslated regions. Genetic alterations in several commonly mutated genes were identified including TP53, ErbB2, and EGFR. Alterations were enriched in pathways commonly involved in cancer including cell cycle control, cytoskeleton, and receptor tyrosine kinases.
Conclusion: Cancer transcriptome sequencing is a promising approach for identifying mutations and obtaining expression analysis simultaneously. Transcriptome sequencing holds promise as a readily available platform for assessing potential treatment targets in a specific tumor.

3LB LATE BREAKING ORAL

MEDI-573, a dual IGF-1/-2 neutralizing antibody, blocks IGF-1R and IR-A signaling and maintains glucose homeostasis in a Phase 1 study for advanced solid tumors

For full abstract, see p. 4.

Thursday, 18 November 2010 16:30–18:30

PLENARY SESSION 7

Selected tumours as a niche for targeted therapies

256 INVITED

Emerging therapies in melanoma

A. Eggermont[1]. *[1]Erasmus University Medical Center Rotterdam, Daniel den Hoed Cancer Center/Department of Surgical Oncology, Rotterdam, The Netherlands*

The development of systemic therapies with and impact on overall survival in melanoma has been stagnant for decades. Both in the non-targeted as well as in the targeted therapy arena a number of new drugs with completely different mechanisms of action are active in melanoma with excellent chances to be approved in the nearby future. The imminent candidates are anti-CTLA4 antibody ipilimumab, which has recently been demonstrated to significantly improve survival in melanoma patients with advanced metastatic disease, and the highly selective BRAF-inhibitor PLX4032, which causes significant regression of metastatic lesions in 80% of patients with BRAF-mutated melanomas, and is currently being evaluated for its impact on overall survival. So on the one hand significant developments in the field of immunomodulation and on the other hand in mutation driven signaling pathway inhibitors. Moreover in each class various other molecules are under development with very good perspectives. The new discoveries will bring an avalanche of trials and rational combination approaches unlike anything seen before. It's a new world in melanoma and the key developments in creating that world will be presented.

257 INVITED

Recent advances in the treatment of refractory thyroid cancer: the use of kinase inhibitors

M. Schlumberger. *France*

Abstract not received

258 INVITED

Biology and treatment of thymoma

G. Giaccone. *USA*

Abstract not received

259 INVITED

Non small cell lung cancer molecular subtypes: therapeutic implications

J.-C. Soria[1]. *[1]Institut Gustave Roussy, Medical Oncology/Lung Unit, Villejuif, France*

NSCLC is currently being revisited on the basis of modern molecular portraits that allow the identification of new molecular subtypes.
Larges scale studies have identified frequent mutation mainly in TP53, RB1, CDKN2A, and STK11 tumor suppressor and in EGFR, KRAS and NRAS oncogenes. Many other molecular abnormalities have been reported at lower frequencies in genes such as PI3K, PTEN, AKT1, MDM2, APC, FGFR, HER2, KDR, MET, CTNNB1, ATM, BRAF, AKT1 and more recently ALK.
The most frequent kinase mutations were identified in EGFR receptor, a target of many recently developed molecules, in 10 to 20% of NSCLC. The majority of *EGFR* mutations occurred in exon 19 (small deletion) or in exon 21 (single point mutation, L858R). These activating mutations are associated to responsiveness to tyrosine kinase inhibitors. On the other hand, several mutations in exon 20 (T790M or small insertion) seem to confer resistance to such treatments. Patients harbouring EGFR mutation are highly sensitive to EGFR inhibitors, that have demonstrated a PFS advantage when compared to standard chemotherapy in the front-line setting.
Epidemiologic characterization of EML4-ALK translocations is ongoing but it seems to be a rare aberration, most common in non-smokers or light-smokers with the adenocarcinoma subtype of NSCLC (and signet ring features), forming a distinct subgroup from patients harbouring EGFR,