ALK inhibitors. Melanoma patients with BRAF mutation responded well to specific and selective agents. Clinical studies of targeted agents with a pre-treatment genetic screening program are ongoing and have a great chance of success. Moreover, modern drug development techonologies allows the development of targeted agents with a higher degree of specificity and selectivity when compared to some of the approved targeted agents.
Although significant advances have been achieved in the field of targeted therapy, focus is needed across critical "gray areas". Biomarkers with the ability to predict targeted therapy benefit and/or resistance have been evaluated acrosss different phase I to III clinical studies, but not subsequently validated. Several mechanisms of resistance to different drugs have been described, but assessment of their prevalence and importance for the clinical setting is lacking. In order to circumvent this research gaps, it is fundamental to prioritize clinical trials (statiscally powered) to answer important translational research questions. Prospective collection of biospecimens including tumor biopsies must become a standard for the upcoming clinical studies. A genetic screening of tumors (e.g. for mutations, translocations, other key genetic abnormalities) will probably select better those which will benefit most from targeted therapy as single agent or combination. A comprehensive drug development plan in advanced as well in the neoadjuvant setting including translational research questions have the potential to identify the most promising targeted drugs to be used in the adjuvant setting in pre-defined patient subgroups where the chance of cure will be much higher.
As a conclusion and for the upcoming 20 years it is expected that the scientific achievements will be greater when compared to the last two decades. The lessons learnt up to now should bring the concept of "personalized anti-cancer treatment" closer to the reality. A close collaboration of basic scientists, chemists, clinical investigators and statisticians is of utmost important to achieve quickly the ultimate goal of personalized medicine and cure of patients.

Thursday, 18 November 2010 14:45–16:15

PLENARY SESSION 6

Proffered papers

2LB LATE BREAKING ORAL

Anti-tumor activity of anti-RON antibodies and biomarker of response

For full abstract, see p. 3.

252 ORAL

Polyclonal resistance to kinase inhibition in GIST: Mechanisms and therapeutic strategies

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Background: Clinical progression of metastatic GIST, during tyrosine kinase inhibitor (TKI) therapy, is often multifocal. However, TKI resistance mutations are assessed in only single, or few, progressing metastases per patient. We used high-throughput screens to evaluate TKI resistance mechanisms in up to 40 progressing GIST metastases per patient.
Methods: Clinically progressing *KIT*-mutant GISTs were from patients formerly responding to imatinib and/or sunitinib. *KIT* exons 8 through 18 were sequenced at 2000-fold coverage (454 pyrosequencing) and these analyses were confirmed and extended (dHPLC and Sanger sequencing) to additional metastases from the same patients. Drug-response studies were performed by expressing mutant constructs in a KIT-negative GIST model.
Results: 454 *KIT* sequencing was performed in progressing GISTs (N = 50), untreated GISTs (N = 32), and non-GIST sarcomas (N = 5). DNA dilution series showed that *KIT* mutations were detectable by 454 when present in $\geqslant$1% of the *KIT* DNA from a given GIST. Secondary *KIT* mutations (in addition to the known primary mutation) were demonstrated in 3 untreated GISTs (9%), but were rare events (<4% of KIT sequences) in 2 of these. Secondary *KIT* mutations were found in 40 progressing GIST metastases (80%), of which 5 metastases had 2 or more resistance mutations in the same <2 mm^3 sample. Combined dHPLC and 454 analyses revealed a maximum of 7 different predominant secondary *KIT* mutations (each mutation found in >25% of *KIT* alleles from at least one metastasis) among 40 geographically discrete progressing metastases, from one patient. Novel sunitinib resistance mutations, in pts with *KIT* exon 9 primary mutation, involved *KIT* ex 11 (del-ins), ex 13−14 (N655S, N680K and F681L), and ex 18 (S840N). All *KIT* secondary resistance mutations were on the same allele (cis) as the primary mutation, and novel resistance mutations conferred constitutive KIT phosphorylation or KIT-ligand hypersensitivity. Nilotinib and sorafenib inhibited a subset of these mutations but were ineffective against others. However, all resistance mutations were inhibited potently by a KIT switch pocket inhibitor (DP-3636; Deciphera Pharmaceuticals), and a second generation HSP90 inhibitor (STA-9090; Synta Pharmaceuticals).
Conclusions: Systematic genomic evaluations demonstrate up to 7 TKI resistance mutations per patient, in different progressing GIST metastases. These complex molecular resistance mechanisms can be inhibited, *in vitro*, by novel therapeutic strategies.

253 ORAL

Screening for PIK3CA, RAS, and RAF mutations in trials with PI3K/AKT/mTOR signaling pathway inhibitors

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Background: Activating mutations of the p110α subunit of PI3K (*PIK3CA*) have been identified in many malignancies. Preclinical data suggest that these mutations may predict response to PI3K/AKT/mTOR inhibitors, but that concomitant *RAS* or *RAF* mutations may mediate resistance.
Methods: Patients with diverse cancers referred to the Phase I Program for targeted therapy from October 2008 to May 2010 were analyzed for *PIK3CA*, *RAS* (*KRAS*, *NRAS*), and *RAF* (*BRAF*) mutations using PCR-based DNA sequencing. Consecutive patients with any tumor type and *PIK3CA* mutations were treated whenever possible with agents targeting the PI3K/AKT/mTOR signaling pathway.
Results: Overall, 504 patients were tested and 54 (11%) had *PIK3CA* mutations (exon 9, n = 28; exon 20, n = 26). Patients with *PIK3CA* mutations in comparison to patients with wild-type *PIK3CA* had more frequently simultaneous *KRAS* mutations (38% vs. 16%; p = 0.001). *PIK3CA* mutations were most frequent in squamous cell cervical cancers (36%, 5/9 patients), endometrial cancers (24%, 7/29), breast cancers (21%, 6/29), colorectal cancers (17%, 17/103), squamous cell head and neck cancers (15%, 5/34), and ovarian cancers (12%, 7/60). Of the 54 patients with *PIK3CA* mutations, 40 (median number of prior therapies, 3) were treated on a protocol that included a PI3K/AKT/mTOR pathway inhibitor. Of these 40 patients, 8 (20%) achieved a partial response (PR) (2/5 squamous cell cervical cancers; 2/6 endometrial cancers; 1/3 squamous cell head and neck cancers; 2/7 ovarian cancers; 1/5 breast cancers) and 7 (17%) had stable disease (SD) for $\geqslant$4 months. Of the 40 treated patients, 17 (42%) had coexisting *RAS* and/or *RAF* mutations. Of these 17 patients (colorectal cancers, 10; ovarian cancers, 5; endometrial cancers, 2), only 2 patients with ovarian cancers had a PR.
Conclusion: *PIK3CA* mutations were detected in 11% of patients with various solid tumors. Fifteen (37%) patients had a PR (20%) or SD $\geqslant$4 months (17%). These preliminary results with PI3K/AKT/mTOR axis inhibitors are encouraging and although the number of patients is small, they suggest that coexisting *RAS* and/or *RAF* mutations may be associated with resistance to PI3K/AKT/mTOR axis inhibitors in colorectal and endometrial cancers, but not in ovarian cancer.

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cKIT overexpression and wild-type NRAS/BRAF predict response to the tyrosine kinase inhibitor dasatinib in melanoma cell lines

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Background: Patients with advanced melanoma have limited effective therapy. Thus, there is an urgent need to evaluate new targeted drugs. On the other hand, NRAS and BRAF mutations are described in about 25% and 50% of melanoma tumors, respectively, and are mainly responsible of the constitutive activation of the MAPK pathway independently of any growth factor-mediated tyrosine kinase receptor stimulation. Of note, both mutations are mutually exclusive. We hypothesised that the presence of these activating mutations should interfere with the efficacy of drugs,