Thursday, 23 October 2008 14:30–16:00

PLENARY SESSION 6

Proffered paper session

1LB Late Breaking

First-in-Human study of the First-in-Class Hdm2 inhibitor JNJ-26854165

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Background: JNJ-26854165 is a potent inhibitor of the Human double minute (Hdm) ubiquitin ligase Hdm2. Hdm2 plays a key role in regulation of critical tumor suppressor genes such as p53 and Rb, and important transcription factors such as E2F-1. Therefore, Hdm2 represents an attractive target for anticancer therapy. JNJ-26854165 prevents degradation of p53 and inhibits tumor growth in p53 wild-type as well as mutant xenografts with broad activity from Cavg of 196 ng/ml onwards.
Methods: A classic 3+3 dose escalation trial in patients with advanced solid tumors refractory to standard therapies was initiated. The primary objective of this study is to determine the adverse event profile, the dose limiting toxicities (DLT) and the maximum tolerated dose (MTD) of JNJ-26854165. Secondary objectives include evaluation of pharmacokinetics (PK), drug-drug interaction (DDI) profile, food intake effect and pharmacodynamic (PD) activity. Sequential skin and tumor biopsies are taken, and evaluations for Hdm2, p53 and other pathway related markers are performed, including further molecular analyses for Hdm2 activity. Eligible patients have an ECOG PS 2 and adequate haematologic, renal and hepatic function. JNJ-26854165 is administered as an oral solution once daily continuous schedule (21 day cycle time). An accelerated titration design has been implemented, and intrapatient dose escalation is permitted. Samples for pharmacokinetic (PK) analyses have been collected on days 1, 10 and 21.
Results: 30 pts (14 m, 16 f) with a median age of 58 yrs (range 32−74) and a broad variety of solid tumors have been treated at dose levels of 4, 8, 20, 40, 60, 90, 150, 225 mg/d at the time of abstract submission. The median duration of treatment was 42 days (range 9–411). Pharmacokinetics were dose-proportional. After 225 mg mean steady state C_{max} and AUC were 1172 ng/mL and 20135 ng·h/ml, exceeding well preclinically effective dose levels. DDI testing at 40 mg did not indicate for major inhibition of CYP2C9, CYP2D6 or CYP3A4. Grade 3 and 4 adverse events observed include Grade 3 QT prolongation in 1 patient in cycle 2 at 225 mg. MTD has not been reached, yet. No clinical responses according to RECIST criteria have been observed so far, disease stabilization was seen in 1 patient with metastatic ependymoma. The trial continues with further dose escalation considered.
Conclusions: JNJ-26854165 is a novel, oral Hdm2 inhibitor entering the clinic as first-in-class molecule. JNJ-26854165 is well tolerated at doses well beyond preclinical minimum effective dose levels. Preliminary findings of this ongoing trial will be presented.

2LB Late Breaking

A phase II study of abiraterone acetate plus prednisone in patients with castration resistant prostate cancer (CRPC) and no prior therapy with ketoconazole

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Background: Abiraterone acetate (AA) is a potent inhibitor of CYP 17 (17α hydroxylase and C17,20-Lyase), a dual enzyme responsible for androgen synthesis. The mechanism of action of abiraterone is similar to ketoconazole (keto), which inhibits multiple adrenal CYP enzymes including CYP17, and is also used in CRPC. In this phase II study, keto naive CRPC patients were treated with AA.
Methods: Eligibility for this Phase II study required progressive metastatic CRPC by consensus criteria, normal organ function and no prior use of keto for CRPC. Treatment consisted of AA administered via daily oral dose of 1000 mg and concurrent use of Prednisone 5 mg po bid. Pts were evaluated monthly on therapy.
Results: Twelve pts have received 12 weeks or more of study therapy and are evaluable for response according to PSAWG criteria. The median age, PSA and Total Testosterone were 75.5 years (range 58−81) 43.7 ng/dL (range 7.1–1110) and 18.5 ng/mL (range <2−35), respectively. All patients had bony metastatic disease on radionuclide bone scan and three patients (25%) also had lymph node disease. The median number of cycles completed is 5.5. Disease progression has occurred in three patients at cycle 3, 5 and 8. Of the 12 evaluable patients, 11 (92%) have experienced a decline in PSA of 30% or greater. 10 of 12 patients experienced a greater than 30% decline in PSA during cycle 1. The median decline in PSA is 91%. Ten of 12 (83%) patients had a PSA decline of greater than 50% and sustained this through cycle 3. All 12 patients have continued therapy beyond 3 cycles of treatment and 6 have now been treated beyond 6 cycles without progression. Treatment related toxicities included hypertension (N = 1, grade 1), fatigue (N = 4, grade 1) and hot flashes (N = 3, Grade 1).
Conclusions: A high rate of response in this population of chemotherapy and keto naive patients has been observed in patients treated with abiraterone acetate. Studies of the endocrine effects of this agent are ongoing.

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BRAF V600E confers resistance to cetuximab or panitumumab in metastatic colorectal cancer

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Background: Cetuximab and panitumumab are effective in only 10−20% of patients with metastatic colorectal cancer (mCRC). The occurrence of KRAS mutations accounts for about 30−40% of the non-responsive cases. The serine-threonine kinase BRAF is the principal effector of KRAS. We hypothesized that, in the absence of KRAS mutations, resistance to anti-EGFR treatments could be caused by alterations occurring in BRAF.
Patients and Methods: We retrospectively analyzed the mutational status of KRAS in 114 tumors from cetuximab- or panitumumab-treated mCRC patients. Mutational analysis of BRAF exon 15 was carried out in samples that were wild type for KRAS. We further studied the effect of the BRAF V600E mutation on response to cetuximab and panitumumab using in vitro models of mCRC.
Results: KRAS mutations were present in 30% of the patients and were associated with resistance to cetuximab or panitumumab (P = 0.006). The BRAF V600E mutation was detected in 11 patients out of 80 who had wild type KRAS. None of the BRAF mutated patients responded to treatment, while none of the responders carried BRAF mutations (P = 0.028). Patients with BRAF mutated tumors had significantly shorter progression-free and overall survival than wild-type cases. In cellular models of CRCs, introduction of the oncogenic BRAF V600E allele dramatically impaired the therapeutic effect of cetuximab and panitumumab. Treatment with the BRAF inhibitor sorafenib restored sensitivity to anti EGFR antibodies of colorectal cancer cells carrying the V600E allele. The synergistic effect of cetuximab and sorafenib was associated with massive induction of caspase-mediated apoptosis in BRAF mutated cells.
Conclusions: These results show that BRAF wild type is required for response to anti-EGFR monoclonal antibody and could be useful as a biomarker to select patients eligible for treatment. They also strongly support 'double hit' therapies aimed at simultaneous inhibition of EGFR and BRAF in colorectal cancers carrying oncogenic activation of BRAF.

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Notch pathway: a potential new target for the treatment of paediatric ependymomas

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Background: Ependymoma are hardly sensitive to current chemotherapy and demand new therapeutic approaches. These tumours are rare and no specific pathway has been identified so far in their oncogenesis.
Material and Methods: CGH array analysis was performed on 59 ependymoma samples (33 at diagnosis and 26 at relapse). Genes