1208 POSTER

Phase I and Pharmacokinetic Study of the Angiogenesis Inhibitor TSU-68 Combined With Carboplatin Plus Paclitaxel in Patients (pts) With Advanced Non-small-cell Lung Cancer (NSCLC)

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Background: TSU-68 is an oral, angiokinase inhibitor targeting the vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor β, and fibroblast growth factors receptor 1. This study was conducted to evaluate drug safety and pharmacokinetics as well as tumour response of TSU-68 in combination with carboplatin and paclitaxel in pts with advanced NSCLC.
Materials and Methods: Chemotherapy-naïve pts with advanced stage (IIIB/ IV) received TSU-68 twice daily (bid) continuously at either 200 mg or 400 mg, combined with carboplatin (AUC 6 mg/ml/min) plus paclitaxel (200 mg/m^2) on day 1 every 21 days. The primary endpoint was feasibility at the recommended dose (RD), which was defined as the proportion of pts who received more than 50% of the planned dose of TSU-68 within first three cycles. The sample size at the RD was determined to be 30 with a one-sided alpha of 0.025 and a power of 0.9; the expected and threshold value were 66.7% and 33.3%. Pharmacokinetics (PK) of all drugs were performed, and tumour response was assessed by RECIST.
Results: No dose-limiting toxicities (DLTs) was observed at the 200 mg bid dose level in the first three pts. Six pts were treated at the 400 mg bid dose level; one pt experienced a DLT (grade 3 anorexia) during the first cycle. Cmax and AUC of TSU-68 were dose-dependently increased from 200 to 400 mg/dose, and PK of carboplatin and paclitaxel were not appreciably different between the two dose levels of TSU-68. The 400 mg bid dose level was determined to be RD and expanded. Of the 34 pts treated at the RD, 32 pts (94.1%) achieved defined criteria of TSU-68 administration for treatment feasibility. At the RD, the objective response rate was 38.2% (95% CI, 22.2% to 56.4%). The median progression-free survival was 5.6 months (95% CI, 3.6 to 7.2 months), whereas median overall survival was 16.6 months (95% CI, 14.3 to NR).
Conclusions: TSU-68 can be combined with standard doses of carboplatin/paclitaxel and this combination therapy had encouraging antitumour activity and was not associated with relevant pharmacokinetic interaction in advanced NSCLC pts.

1209 POSTER

ONX 0912, a Novel Oral Proteasome Inhibitor (PI), in Patients (pts) With Advanced Refractory or Recurrent Solid Tumours: a Phase 1, Open-label, Dose Escalation Study

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Background: ONX 0912, a structural analog of carfilzomib (CFZ), is a potent, irreversible, orally bioavailable tripeptide epoxyketone PI. In preclinical assessments, ONX 0912 demonstrated antitumour activity in human hematologic and solid tumour models, similar to that observed with CFZ. This first-in-human phase 1 single agent dose escalation study was conducted to assess the safety, tolerability, pharmacokinetics /pharmacodynamics of ONX 0912.
Patients and Methods: Adult pts with advanced refractory or recurrent solid tumours are eligible to enroll in this open-label, multicenter study (clinicaltrials.gov NCT01129349). The primary outcome measures of the study are the safety (including assessing the maximum tolerated dose [MTD]), tolerability, and pharmacokinetic/pharmacodynamic properties of ONX 0912. Responses will be assessed according to RECIST. ONX 0912 is administered orally once daily for 5 days followed by 9 days rest on a 14-day cycle (C). Beginning with 30 mg/d, ONX 0912 doses are escalated in 30-mg increments in groups of 3 pts; if a dose-limiting toxicity (DLT) is observed, the group is expanded to 6 pts.
Results: As of a data cut-off of 16 Mar 2011, 21 pts received ONX 0912 in 6 cohorts (doses from 30–180 mg). The most frequent treatment-related AEs were similar to toxicities observed in animal studies, and included nausea (91%) and vomiting (76%). Two DLTs occurred at 180 mg dose (N = 6): one Grade (G) 3 vomiting and dehydration and one G3 transient asymptomatic hypophosphatemia. The 150 mg dose cohort was expanded (N = 7) and no DLTs were observed.
ONX 0912 has shown dose dependent exposure through the 180 mg dose level with maximum plasma concentrations of up to 4.2 μM, exceeding the IC_{50} for proteasome inhibition by >50-fold. Proteasome inhibition in whole blood and peripheral blood mononuclear cells was ⩾80% in 13 of 21 pts receiving 90–180 mg doses, comparable to inhibition achieved with CFZ. Stable disease of >6 mo duration has been observed in 3 pts (1 each with prostate cancer, liposarcoma, and non-small cell lung cancer).
Conclusions: ONX 0912, an orally bioavailable PI, has an acceptable safety profile and effectively inhibits the proteasome when given daily for 5 consecutive days every 2 weeks in pts with advanced solid tumours. Onyx plans to initiate a Phase 1 trial in hematologic malignancies in 2011.

1210 POSTER

Phase 1 Study of MLN9708, an Investigational Proteasome Inhibitor, in Advanced Nonhematologic Malignancies- Updated Results

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Background: The investigational drug MLN9708 is a potent, reversible and specific 20S proteasome inhibitor. Both IV and oral formulations are in clinical development. Here we report the updated results of a phase 1 trial in patients with nonhematologic malignancies to assess safety, maximum tolerated dose (MTD), pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumour activity.
Methods: Patients received IV MLN9708 on Days 1, 4, 8, and 11 of 21-day cycles for up to 12 cycles. The starting dose of 0.125 mg/m^2 was doubled (1 patient/dose) until 1.0 mg/m^2 then escalated by 33% based on occurrence of dose limiting toxicity (DLT) in cycle 1. Adverse events (AEs) were graded by NCI-CTCAE v3. Response was assessed by RECIST. Blood based PK/PD data were collected after the first and last dose of MLN9708 in cycle 1 and analyzed using noncompartmental methods (WinNonlin v 5.2).
Results: To date, 87 pts have been enrolled in the dose escalation (n = 23) or MTD expansion (n = 64) cohorts. Patients received a median of 2 cycles (range 1−10). There were 5 patients with DLTs: grade 3 rash at 1.0 and 1.76 mg/m^2; grade 3 and 4 thrombocytopenia at 2.34 mg/m^2 and grade 3 renal failure at 2.34 mg/m^2. The MTD was established as 1.76 mg/m^2. MTD expansion cohorts include patients with prostate cancer (n = 7), NSCLC (n = 15), head and neck carcinoma (n = 12), sarcoma (n = 20), and a tumour biopsy cohort (all solid tumours; pre- and post-dose biopsies were taken; n = 10). Common AEs included fatigue (56%), thrombocytopenia (40%), rash (40%), vomiting (39%), and nausea (38%). Grade ⩾3 drug-related AEs included thrombocytopenia (21%), skin disorders (10%), nausea and vomiting (4%), and peripheral neuropathy (2%). One patient with head and neck carcinoma treated at MTD had a partial response after 4 cycles, and two patients with renal cell carcinoma treated at 2.34 mg/m^2 had measurable tumour shrinkage of 14 and 22%. Preliminary PK data showed multi-exponential plasma disposition and a terminal half-life of approximately 5−8 days post Day 11 dose. Exposure increased proportionally with dose from 0.5 to 2.34 mg/m^2. At MTD, E_{max} for 20S proteasome inhibition was approximately 60% at 0.08 hr. Whole blood PD effect was immediate and dose dependent.
Conclusions: At the MTD of 1.76 mg/m^2 MLN9708 has a manageable safety profile; PD measures indicate inhibition of proteasome activity. MLN9708 may have early signs of clinical efficacy. This study is ongoing.
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