418 POSTER

Phase I, clinical, pharmacokinetic and schedule dependency study of the aurora kinase inhibitor AS703569 combined with gemcitabine in patients with solid tumors

E. Raymond[1], J. Alexandre[2], T. Besse-Hammer[3], S. Faivre[1], B. Longerey[4], N. Rejeb[5], A. Seithel[6], L. Trandafir[5], A. Awada[3]. [1]*Hopital Beaujon, Service Inter-Hospitalier de cancerologie Beaujon-Bichat, Clichy, France;* [2]*Université Paris-Descartes GH Cochin − Saint Vincent de Paul, Medical Oncology Unit, Paris, France;* [3]*Institut Jules Bordet, Medical Oncology, Bruxelles, Belgium;* [4]*Merck Serono SA, Global Biostatistics, Geneva, Switzerland;* [5]*Merck Serono SA, GEDU Oncology, Geneva, Switzerland;* [6]*Merck KGaA, Clinical Pharmacology and Pharmacokinetics Oncology, Darmstadt, Germany*

Background: AS703569 is an oral, ATP-competitive, small-molecule inhibitor of aurora kinases A, B, and C with *in vitro* and *in vivo* antitumor activity alone and in combination with gemcitabine (Gem), activity with Gem being schedule dependent. Phase I single-agent trials are ongoing.
Objective: To define the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), safety, pharmacokinetic (PK), and antitumor activity of two schedules (S) of dose-escalating AS703569 and fixed dose of Gem (1 g/m^2) in patients (pts) with advanced solid tumors.
Methods: Three-center, dose-escalation study with a 3 + 3 design, two S enrolling in parallel: S1: AS703569 d2 and 9, Gem d1 and 8; S2: AS703569 d1 and 8, Gem d2 and 9 of 21-d cycles. MTD definition: dose level (DL) below that at which >1/3 or >1/6 pts had DLT in cycle 1.
Results: 54 pts treated at 6 DLs: 10, 15, 21, 28, 37 and 49 mg/m^2/d. S1 (25 pts): mean age 61 (range 31−75) years (y); 18 (72%) men; most common tumors: colorectal (n = 6), pancreas (n = 4), lung (n = 4); 0−16 cycles per pt. S2 (29 pts): mean age 56 (20−80) y; 22 (76%) men; most common tumors: colorectal (n = 8), liver (n = 3), esophagus (n = 3); 0−11 cycles per pt. Most adverse events (AE) were hematologic with grade (G) 4 neutropenia in 1/3 of pts per S. Drug-related non-hematologic AEs (>15% of pts, mainly G1−2): diarrhea, vomiting, nausea, anorexia, asthenia, fatigue and headache; some G3−4, mainly asthenia (S1 4/25 pts; S2 2/29). The MTD was defined for both S as 37 mg/m^2/d. In S1, DLTs occurred at 37 (n = 1) and 49 mg/m^2/d (n = 2) and included G4 neutropenia $\geqslant$7 d and G3−4 thrombocytopenia. In S2, DLTs were G4 neutropenia and sepsis (n = 1, 10 mg/m^2/d), G3 performance status worsening and asthenia (n = 1, 15 mg/m^2/d), and G4 neutropenia $\geqslant$7 d (n = 1, 28 mg/m^2/d and n = 1, 37 mg/m^2/d). Preliminary PK (DL 10−37 mg/m^2/d): AS703569 T_{max} 2−4h (range 1−8 h). C_{max} and AUC_{last} increase proportionally with dose and the PK is similar to phase I single agent PK. Stable disease (SD$\geqslant$4 cycles) was reported in 16/54 heavily pretreated pts; in S2, 2 partial responses lasting 6 mos (NSCLC) and 3 mos (hepatocarcinoma) were reported.
Conclusion: AS703569 can be safely combined with standard-dose Gem regardless of schedule, DLTs being mainly reversible hematological toxicities. AS703569 PK in combination with Gem was similar to single agent PK. The MTD of AS703569 was 37 mg/m^2/d, similar to that of AS703569 single agent. Partial responses and long-lasting SD were observed in pretreated pts.

419 POSTER

Pharmacokinetic (PK) assessment of bosutinib (SKI-606) administered orally to patients with advanced solid tumors in a phase 1 study

R. Abbas-Borhan[1], J. Boni[1], P. Hsyu[2]. [1]*Pfizer Inc., Clinical Pharmacology, Collegeville, USA;* [2]*Pfizer Inc., Clinical Pharmacology, San Diego, USA*

Background: Bosutinib, a dual inhibitor of Src and Abl tyrosine kinases, is being developed for the treatment of patients with Ph$^+$ leukemias and of patients with solid malignant tumors, such as breast cancer. This study evaluated the PK of bosutinib following oral administrations of a single dose and once-daily multiple doses to patients with advanced solid tumors in a phase 1 dose-escalation study of safety and tolerability of bosutinib.
Material and Methods: This was a 2-part, open-label study. In part 1, patients received bosutinib 50, 100, 200, 300, 400, 500, or 600 mg with food. In part 2, patients were treated at the maximum tolerated dose (MTD) that was determined in part 1. Plasma samples, collected at predose and at selected time-points following bosutinib administrations on day 1 and day 15, were analyzed by using a liquid chromatography/tandem mass spectrometry assay for bosutinib concentrations. PK analyses were performed using noncompartmental methods.
Results: A total of 151 subjects were enrolled (83 females, 68 males; median age [range] 60 [19−83] y, 85% White). MTD was confirmed at 400 mg once daily. Plasma samples for 98 patients from all 7 dose cohorts were available for PK analysis. On day 1, mean C_{max} and mean AUC for the 50 to 600 mg doses ranged from 4.89 ng/mL (CV% = 75; n = 4) to 206 ng/mL (CV% = 92; n = 10) and 129 ng h/mL (CV% = 102; n = 4) to 4,300 ng h/mL (CV% = 77; n = 10), respectively. For the same doses on day 15, steady-state mean C_{max} and AUC (AUC_{ss}) ranged from 6.92 ng/mL (CV% = 44; n = 3) to 304 ng/mL (CV% = 57; n = 2) and 114 ng h/mL (CV% = 29; n = 3) to 4,220 ng h/mL (CV% = 36; n = 2), respectively. Multiple-dose exposure was 1.9 to 3.0-fold greater than single-dose exposure (mean accumulation ratio, AUC_{ss}/AUC_{0-24h}) for the 50 to 600 mg dose range. Absorption of bosutinib following single or multiple doses was relatively slow with a median t_{max} of 4 to 6 h, and both C_{max} and AUC increased with increasing dose and appeared linear for the 300 to 600 mg dose range. Mean half-life ($t_{1/2}$) for a single dose on day 1 ranged from 13 to 22 h (CV% = 26 to 57), apparent mean volume of distribution was large and ranged from 6,000 to 11,100 L (CV% = 34 to 133), and mean clearance ranged from 207 to 721 L/h (CV% = 21 to 123).
Conclusions: Bosutinib exposures increased with increasing dose (50 to 600 mg) and the relationship of bosutinib exposures to dose appeared to be linear for the 300 to 600 mg dose range. Bosutinib $t_{1/2}$ supports a once-daily dosing regimen.

420 POSTER

Population pharmacokinetic and pharmacodynamic modelling of E7820 in patients with solid tumor

B. Mistry[1], O. Majid[2], C. Farrell[3], D. Rossignol[4], C. Okereke[4], J. Fan[1], Z. Hussein[2], A. El-Khoueiry[5], M. Sawyer[6], C. Rocha-Lima[7]. [1]*Eisai Inc., Oncology PCU, Woodcliff Lake, USA;* [2]*Eisai Ltd., Modeling and Simulation, Hatfield, United Kingdom;* [3]*ICON Development Solution, Modeling and Simulation, Marlow, United Kingdom;* [4]*Eisai Inc., Frontier PCU, Woodcliff Lake, USA;* [5]*University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, USA;* [6]*Cross Cancer Institute, Cancer Medicine, Edmonton, Canada;* [7]*University Of Miami, Sylvester Comprehensive Cancer Center, Miami, USA*

Introduction: E7820 inhibits angiogenesis by inhibiting mRNA expression of α2-integrin and induces tumor remission in preclinical models. Aim of the pharmacokinetic (PK) and pharmacodynamic (PD) modelling was to derive a relationship between plasma E7820 concentrations and plasma α2-integrin levels on circulating platelets from Phase 1 and 2 trials.
Method: Nonlinear mixed effect modelling (NONMEM) with FOCEI was performed on 1757 E7820 plasma concentrations and 596 α2-integrin measurements from 77 patients. Exponential error models were used for inter-individual variability and a combined proportional/additive model was used for residual error. Patient age, body weight, body surface area, race, creatinine clearance, alanine aminotransferase level and dose were assessed for their effects on clearance (CL) and volume of distribution (Vd). An indirect response model for inhibition of cell-surface expression of α_2-integrin by E7820 was fitted to the observed PD data. Model parameters estimated were: baseline α_2-integrin (α_2-int_{BASE}, MESF), rate of formation (α_2-int_{KIN} MESF/hr), rate of loss (α_2-int_{KOUT}, 1/hr) (estimated indirectly) and the slope of the E7820 concentration − α_2-int_{KOUT} relationship (α_2-int_{EFF} mL/μg).
Result: A one compartment model with first-order absorption (Ka) and elimination with lag time best fit E7820 plasma concentration-time profiles. Inter-individual variability for CL and Vd ranged between 34 and 47% and was 93% for Ka. Co-variance for CL and Vd was 30%. Vd significantly increased with dose according to a power model (V-Dose). Proportional residual variability was estimated to be 36%. Final parameter estimates for the PK/PD model were (RSE): α_2-int_{BASE}, 8470 MESF (5.28 %), α_2-int_{KIN}, 17.2 MESF/hr (23.5 %), α_2-int_{KOUT}, 0.002031 1/hr and α_2-int_{EFF}, 0.291 mL/μg (23.8 %). 95% confidence intervals for α_2-int_{EFF} were 0.155 to 0.427, indicating a positive relationship between increased inhibition of α_2-integrin expression and E7820 concentration. From α_2-int_{KOUT} the half-life for α2-integrin was determined to be 340 h. Inter-individual variability in PK/PD model parameters ranged from 40 % for α_2-int_{BASE} to 73% for α_2-int_{EFF}. Residual variability was estimated to be 17%. None of the covariates tested showed any effect on change in α_2-integrin levels ($p > 0.01$).
Conclusion: An indirect PK/PD model showed dose dependency of Vd and a increase in E7820 concentration correlated with increase inhibition of α2-integrin expression.