544 POSTER

A phase I trial of the novel nucleoside analog osi-7836 given on days 1 and 8 every 3 weeks: ncic ctg ind.147

L.L. Siu[1], G.D. Goss[2], J. Powers[3], B. Waterfield[4], M. MacLean[5], L.M. Adams[6], D. Drolet[7], J. Rusk[8], L. Seymour[9]. *[1] NCIC-CTG IND Program, Kingston, Canada; [2] NCIC-CTG IND Program, Kingston, Canada; [3] NCIC-CTG IND Program, Kingston, Canada; [4] NCIC-CTG IND Program, Kingston, Canada; [5] NCIC-CTG IND Program, Kingston, Canada; [6] OSI Pharmaceuticals, Boulder, USA; [7] OSI Pharmaceuticals, Boulder, USA; [8] OSI Pharmaceuticals, Boulder, USA; [9] NCIC-CTG IND Program, Kingston, Canada*

Background: OSI-7836 (4'-thio-araC) is a nucleoside analog with a number of favorable characteristics. It is inactivated by dCyd deaminase at 6-fold slower rate than gemcitabine and has prolonged intracellular activity of the active triphosphate. Antitumour effects in xenograft models were generally greater than gemcitabine at equitoxic doses and OSI-7836 toxicity was consistent with other compounds of this class.

Methods: An accelerated phase I design was used with 1-2 patients (pts) entered at each dose level until ≥ grade 2 clinically relevant toxicity was encountered, after which 3-6 pts were entered. The starting dose was 100mg/m^2 given over 30 minutes by IV infusion. Determination of dose limiting toxicity (DLT) and recommended phase II dose (RPTD) followed standard criteria.

Results: Fifteen evaluable pts have been entered to five dose levels (100, 200, 400, 500 and 600 mg/m^2) and received a total of 29 cycles, median=2 (range 1-6) to date. Demographics are as follows: F:M = 8:7, median age = 56 (range 35-75), ECOG 0:1:2 = 2:10:3, primary tumour types = colorectal [6 pts], lung and unknown primary [2 pts each], and 5 pts had other primaries. All but 1 pt had prior chemotherapy. DLTs occurred at 600 mg/m^2 and 500 mg/m^2, consisting of grade 3 fever, rash and fatigue not ameliorated despite prophylactic use of steroids, antihistamine and acetaminophen, as well as the inability to administer the Day 8 dose. Other toxicities included grade 1-2 nausea and vomiting (with adequate antiemetics), diarrhea, herpes simplex reactivation and transaminase increases. No hematological toxicity has been observed to date other than lymphopenia at all dose levels, (median nadirs 0.06 to 0.2 x 10^9/L). Pharmacokinetic analyses were performed during the course of the first dose cycle. The mean (SD) plasma half-life of the major elimination phase was 46.4 (5.28) minutes. The mean (SD) plasma clearance on Day 1 and Day 8 was 36.4 (9.36) and 40.4 (14.6) L/(hr• m^2), respectively, indicating no significant difference. OSI-7836 plasma Cmax and AUC increased with increasing dose. No objective responses have been reported, but one pt with lymphoepithelioma of the thymus showed minor tumour shrinkage of thoracic lesions.

Conclusions: DLTs consist of fever, rash and fatigue at the higher doses. The trial is currently expanding at the 400 mg/m^2 dose level to determine if this will be the RPTD for this schedule.

545 POSTER

A randomized trial of a cd-rom educational intervention for advanced cancer patients (acp) enrolling in early phase trials

F. Hlubocky[1], N. Kass[2], L. Fogarty[3], J. Sugarman[4], C. Daugherty[5]. *[1] The University of Chicago Medical Center, Medicine, Section of Hematology/Oncology, Chicago, Illinois, USA; [2] Johns Hopkins School of Public Health, Health Policy and Managment and Bioethics Institute, Baltimore, Maryland, USA; [3] Johns Hopkins School of Public Health, Health Policy and Managment and Bioethics Institute, Baltimore, Maryland, USA; [4] Duke University, Center for the Study of Medical Ethics and Humanities, Durham, North Carolina, USA; [5] The University of Chicago Medical Center, Medicine, Section of Hematology/Oncology, Chicago, Illinois, USA*

Background: Prior informed consent research for phase I trials has substantiated concerns about acp understanding of both the research purposes of early phase trials and expectations of benefit. Furthermore, few studies have developed or evaluated interventions to enhance acp understanding.

Methods: In response, we developed an interactive cd-rom for acp eligible for phase I-II trial enrollment. Using a touch-screen monitor, the cd-rom contains phase I-II trial information and videos of acp and oncologists (MDs) talking about early phase trials. To test its efficacy, we randomized acp potentially eligible for phase I-II trials to either view the cd-rom or receive a NCI clinical trials pamphlet. After consulting with a MD about phase I-II trial enrollment, subjects were then interviewed about their understanding.

Results: To date, 199 subjects have been randomized; 109 have subsequently enrolled in phase I-II trials (58% women, 88% Caucasian, 51% with college degree, 34% income >80k/yr). There are trends for cd-rom users to have both a greater understanding of the research purpose of phase I trials (37% of cd-rom users vs. 21% of pamphlet users, p=.09) and lower perceptions of the unrealistic benefit of cure (13% vs. 24%). There is a trend for cd-rom users to more often strongly agree that they were upset by the cd-rom (as compared to the NCI pamphlet15% vs. 4%, p=.19). However, 63% of cd-rom users agree their MD thought trial enrollment was a good idea (vs. 37%, p=.02) and a larger number of cd-rom users agree that its use not only changed the way they made a decision to enter a trial (28% vs. 12%, p=.02), but that it also actually changed the decision itself (20% vs. 5%, p=.06). In a subset analysis, 71% of those who completed the cd-rom subsequently enrolled in a phase I-II trial, compared to 58% who received the NCI pamphlet.

Conclusion: While the cd-rom intervention may challenge acp decisions and produce some discomfort, it has the potential to improve consent outcomes, reduce unrealistic expectations of benefit, and improve phase I-II trial accrual.

546 POSTER

A Phase I dose-escalation trial of ZD6126 administered as 5 daily doses every 3 weeks to patients with cancer refractory to other treatments

G.T. Budd[1], J. Evelhoch[2], P. Langmuir[3], J. Veiero[1], K. Shepherdson[3], P. LoRusso[2]. *[1] Cleveland Cancer Foundation, Hematology/Oncology, Cleveland, OH, USA; [2] Karmanos Cancer Institute, Detroit, MI, USA; [3] AstraZeneca, Wilmington, DE, USA*

Background: ZD6126 is a novel vascular-targeting agent that causes disruption of the tubulin cytoskeleton of rapidly proliferating endothelial cells in tumour vasculature. In vivo, these changes have been shown to lead to tumour endothelial cell detachment, resulting in vessel occlusion and extensive tumour necrosis.

Methods: A Phase I, open-label, dose-escalation study in patients with solid tumours refractory to other treatments has been conducted to evaluate the safety and pharmacokinetics of ZD6126 administered as 5 consecutive daily doses every 3 weeks. Patients were required to have a WHO performance status of 0–2 and a life expectancy of ≥12 weeks; those with significant cardiac, haematopoietic, hepatic or renal dysfunction were excluded. Subjects received ZD6126 (1 or 4 mg/m2, given as a 10-minute infusion) daily for 5 days. Cycles were repeated every 21 days until an adverse event, disease progression or other criterion warranted withdrawal.

Results: A total of thirteen patients (7 male, 6 female; mean age 52.5 years) have received ZD6126 therapy in this study (1 mg/m2, N = 7; 4 mg/m2, N = 6). Maximum concentrations of the active species (ZD6126 phenol) were observed 10–20 minutes from the start of infusion, and decayed in a bi-exponential manner with a relatively short half-life (1.01–4.26 hours on day 1; 0.78–2.45 hours on day 5). Cmax and AUC increased with dose, with no evidence of differences between exposure on day 1 and day 5. The most common adverse events were fatigue (N=7), nausea and vomiting (N=7), fever (N=5), dyspnoea (N=5), constipation (N=4), and headache (N=4). Three CTC grade 3 events were seen in patients receiving 1 mg/m2 (1 case each of hyponatraemia, peripheral motor neuropathy [not considered to be treatment-related] and intestinal obstruction, in 3 separate patients). One CTC grade 3 event (increased liver enzymes) was seen in the 4 mg/m2 group. Dose-limiting toxicities were seen in 2 patients receiving ZD6126 4 mg/m2 (1 case of increased aspartate aminotransferase and 1 case of prolonged QTc interval, although this patient also received 2 other treatments known to be associated with QT prolongation during the trial).

Conclusions: This study has provided preliminary pharmacokinetic and safety data and constitutes one of three Phase I studies designed to identify the optimal administration schedule and dose of ZD6126 for future clinical assessment.

547 POSTER

KOS-862 (Epothilone D): Phase 1 dose escalating and pharmacokinetic (PK) study in patients (Pts) with Advanced malignancies

D.R. Spriggs[1], J. Dupont[1], S. Pezzulli[1], J. Larkin[1], G. Cropp[2], Y. Zhou[2], M. Sherrill[2], R. Johnson, Jr.[2], A.L. Hannah[2]. *[1] Memorial Sloan-Kettering, Developmental Chemotherapy Service, New York, NY, USA; [2] Kosan Biosciences, Inc., Medical Affairs, Hayward, CA, USA*

Background: KOS-862 (Epothilone D; 12,13 desoxyepothilone B) is a naturally occurring cytotoxic macrolide that stabilizes microtubules and induces

mitotic arrest. Preclinical data suggest that KOS-862 has comparable activity to paclitaxel, but retains efficacy in MDR overexpressing cells (Chou et al, *PNAS* 2001). Previous Phase 1 schedules showed drug-related toxicities recovering within 7 days following an IV infusion. Objective of this protocol was to investigate a more dose intense schedule of KOS-862, administering the drug for 3 out of every 4 weeks to pts with advanced malignancies.

Materials and Methods. Groups of 3 pts were treated at escalating doses of KOS-862. Toxicity was assessed in 4-week cycles. PK sampling occurred after the 1st, 3rd and 4th doses; PD after the 1st and 3rd doses at doses ≥ 100 mg/m^2. Drug concentrations were analyzed using LC/MS/MS (LLQ 2 ng/mL) and analyzed using non-compartmental methods; PD was assessed by percentage tubulin polymerization in PBMCs evaluated by IHC.

Results: (n=21; 5 dose levels: 16-120 mg/m^2). Baseline demographics include median age 58 (38-76); median KPS 80 (70-100); 9 male; diagnoses: 7 ovarian, 5 colorectal, 3 NSCLC; 6 other. Dose limiting toxicity (consisting of one episode each of NVD/dehydration and brief visual hallucination) was observed at the highest dose. The cohort at 100 mg/m^2 is being expanded to 12 patients. Drug-related toxicities (all mild-to-moderate severity) included: fatigue (n=13), sensory neuropathy (n=8) and N/V (n=3). Sensory neurological toxicities were not cumulative but persisted throughout the cycle. Other than the 2 pts with DLT, there were no withdrawals for drug-related toxicities. PK data (n=16 pts; 16-100 mg/m^2; 38 sampling days) showed mean increases in C_{max} (626, 1624, 2215 and 3768 ng/mL) and AUC_{total} (3088, 4610, 7752 and 10812 ng*h/mL) that were linear across the dose levels. At the 100 mg/m^2 dose, there was no significant change in AUC comparing the 3 sampling days (84.3% ± 6.6%) nor accumulation. Compartment independent PK analysis (mean±SD): half-life= 8.5 ± 2.7 hours; Vz = 117 ± 57 L/m^2; CL = 9.9 ± 4.4 L/h/m^2; no dose dependency was observed. Compared to the previous less dose intense schedule, PK on this schedule maintains the systemic exposure with a slightly higher C_{max}; other parameters are similar (although clearance showed a trend towards higher values on this schedule). Data regarding tubulin polymerization in PBMCs (including a comparison between the two schedules) will be presented. Stable disease (≥ 3 months) was seen in renal, ovarian and mesothelioma; tumor marker declines (colorectal, ovarian) were observed.

Conclusions: KOS-862 is a promising new agent; a dose of either 100 or 120mg/m^2 will be the recommended Phase 2 dose, depending on toxicity seen in expanded cohorts. Phase 2 single-agent trials and combination studies using this schedule are planned.

548 POSTER

CERA (Continuous Erythropoiesis Receptor Activator) is an innovative erythropoietic agent with an extended serum half-life: studies of mode of action, pharmacokinetics and erythropoietic activity

A. Haselbeck[1], B. Reigner[2], P. Jordan[2], A. Pannier[2], J. Glaspy[3]. [1] *F. Hoffmann-La Roche, Penzberg, Germany;* [2] *F. Hoffmann-La Roche, Basel, Switzerland;* [3] *UCLA Medical School, Los Angeles, CA, USA*

Background: CERA is an innovative erythropoietic agent developed for the treatment of anaemia. Using a combination of *in vivo* and *in vitro* studies, the mode of action, pharmacokinetic properties and erythropoietic activity of CERA were investigated.

Materials and methods: Binding of CERA and epoetin to the erythropoietin (EPO) receptor were compared *in vitro* using a soluble EPO receptor-binding assay. Pharmacokinetic properties of CERA were investigated in dogs and in human volunteers. In dogs, single intravenous (IV) and subcutaneous (SC) doses of CERA (3-10 μg/kg) and epoetin (2.5 μg/kg) were compared. Two randomised, placebo-controlled studies in healthy volunteers were also conducted, where single doses of CERA 0.4-3.2 or 0.1-3.2 μg/kg were administered IV or SC, respectively. Erythropoietic activity of CERA and epoetin were compared *in vivo* using a normocythaemic mouse model and *in vitro* using a UT-7 (human myeloid leukaemia cell line) proliferation assay.

Results: Notable differences between CERA and epoetin were observed in both the association and dissociation rates in the soluble EPO receptor-binding assay. The median serum half-life ($t_{1/2}$) for CERA in dogs was 49.0 h versus 6.4 h for epoetin following IV injection, i.e. a 7-fold increase. In humans, mean $t_{1/2}$ for CERA ranged from 70-122 h after IV and from 102-216 h after SC administration, depending on dose. The increase in area under the curve (AUC) and maximum concentration (Cmax) with dose was more than proportional. In the normocythaemic mouse model, *in vivo* comparison of identical amounts of protein across the dose range 60-1000 ng protein/animal revealed that CERA had greater erythropoietic activity than epoetin, with greater bone marrow cell stimulation and reticulocyte counts. However, CERA stimulated less proliferation of UT-7 cells than epoetin in the *in vitro* assay across the dose range 0.003-3 U/ml.

Conclusions: These findings suggest an innovative mechanism of action for CERA. The combination of its different binding characteristics to epoetin, and its extended half-life, may enable an enhanced and sustained stimulation of erythropoiesis with CERA compared with epoetin. This may lead to less frequent dosing and help to optimise patient outcomes.

549 POSTER

Liver toxicity: a predictable and manageable toxicity for kahalalide F (KF)

J.H.M. Schellens[1], L. Paz-Ares[2], J.M. Trigo[3], B. Pardo[4], A. Ruiz-Casado[5], E. Ciruelos[2], M. García[3], J. Beijnen[1], M.A. Izquierdo[5]. [1] *The Netherlands Cancer Institute, Medical Oncology, Amsterdam, The Netherlands;* [2] *Doce de Octubre, Medical Oncology, Madrid, Spain;* [3] *Vall d Hebron, Medical Oncology, Barcelona, Spain;* [4] *Institut Catalá d Oncologia, Medical Oncology, Barcelona, Spain;* [5] *PharmaMAr, Medical Oncology, Madrid, Spain*

Background: KF is a new marine cytotoxic currently under phase II evaluation. Acute (4 to 6 hours after infusion) and reversible grade 4 aminotransferases increase (AI) was the dose limiting toxicity (DLT) in two phase I clinical trials with KF. The following features will be described: a) patients (pts) with grade (g) 3-4 ALT, AST, Bilirubin (Bb), Alkaline phosphatase (AP) and GGT elevation, b) patients with both grade 4 AI and LDH increase, c) duration of aminotransferases increase, d) patients with ALT/AP (times x ULN) ratio >5 (a marker for hepatocellular damage), e) patients with concomitant g3-4 AI and bilirubin or AP elevation, e) patients with encephalopathy, ascites or jaundice, f) dose/toxicity relationship, g) cumulative toxicity: pts treated for more than 4 months (m)

Results: G3/g4 *AST* and *ALT* elevation: 11.7/15% and 11.7/18.3% of pts, respectively. G3 *Bb* elevation: 1.7% of pts (g4, 0%). G3 and g4 *GGT* elevation: 26.7% and 6.7% of pts (6 patients ñout of 20- had normal basal GGT). G3 and g4 *AP* elevation: 11.7 and 1.7% of pts (all these patients had baseline abnormalities).

G4 AI with concomitant LDH elevation: 20% of pts. Only 1 (out of 13) patient with g4 AI showed normal LDH.

Median *time to recovery* from grade 3-4 AI to grade 1 was 6 days [2-10] for AST and 10 d [4-19] for ALT

ALT/AP ratio >5: 25% of patients.

10% of pts had *concomitant g3-4 AI and any Bb deviation*, 38.3% had concomitant g3-4 AI and AP deviation

There were no patients with encephalopathy, jaundice or ascites related to the drug. No significant deviations of prothrombin activity have been reported.

For pts treated with doses lower than 600 μ g/m^2: g4 ALT, AST and GGT was 3.8, 0 and 7.7%, respectively. For pts treated with doses between 600 and 700 μ g/m^2 (recommended dose ñRD-) g4 ALT, AST and GGT was 11.1, 11.1 and 0%. For pts treated with doses higher than 700 μ g/m^2 (above RD) g4 ALT, AST and GGT was 50, 43.8, and 12.5%.

8 pts received KF for more than 4 m. 3 pts showed grade 4 AI and continued to receive treatment without any dose reduction. No evidence of cumulative toxicity was reported and after some cycles, toxicity was even lower.

Conclusions: G4 AI has consistently been DLT for KF administered over one hour. It usually goes with LDH elevation and ALT/AP ratio >5 indicating hepatocellular damage. It is spontaneously reversible and dose-dependent.

Liver toxicity was not clinically significant and features related to cholestasis seemed to be more related to the tumor than to the drug.

550 POSTER

Antitumour efficacy of MEN4901/T-0128, a new camptothecin derivative-carboxymethyldextran conjugate, in a panel of human gastrointestinal tumours xenografted in nude mice

M. Bigioni[1], F. Animati[1], M. Kakushima[2], T. Kawaguchi[2], C.A. Maggi[1], S. Manzini[1], C. Goso[1]. [1] *Menarini Ricerche S.p.A., Pomezia (Rome), Italy;* [2] *Tanabe Seiyaku Co., Ltd., Discovery Research Laboratories, Saitama, Japan*

Gastrointestinal tumours comprise various histological types including pancreas, oesophageal, stomach, and colon cancers and are among the most unresponsive cancers to the chemotherapy. Recently some camptothecin derivatives like Irinotecan (CPT-11) have been shown to exert a significant antitumour activity against some of these tumour histotypes (colon). How-