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

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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.

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

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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.

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

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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.

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

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