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CLINICAL TRIAL REPORT

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A phase I, first in man study of OSI-7836 in patients with advanced refractory solid tumors: IND.147, a study of the Investigational New Drug Program of the National Cancer Institute of Canada Clinical Trials Group

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Abstract *Purpose*: To determine the maximum tolerated dose (MTD), recommended phase II dose (RP2D), safety, tolerability, toxicity profile, dose-limiting toxicities (DLTs), anti-tumor activity and pharmacokinetics of OSI-7836 given IV on day 1 and day 8 every 3 weeks in patients with advanced incurable cancer. *Methods*: Twenty-seven previously treated patients with advanced or metastatic solid tumors were enrolled in this phase I study conducted by the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG). OSI-7836 was administered IV on day 1 and day 8 every 3 weeks. The dose was initially escalated from 100 to 600 mg/m^2 and finally de-escalated to 200 mg/m^2 in seven cohorts of patients. Patients were evaluated every other cycle of treatment for radiological response. Pharmacokinetics were performed on day 1 and day 8 of cycle 1 for all patients. *Results*: Twenty-six patients were evaluable for toxicity. All patients experienced reversible Grade 3 lymphopenia beginning at cycle 1. The maximal delivered dose was 600 mg/m^2. MTD was reached at 400 mg/m^2. DLTs included fever, fatigue, rash, herpes simplex infection, nausea and vomiting. The RP2D was 200 mg/m^2. No objective responses were seen in 21 evaluable patients. Pharmacokinetics were dose proportional, with a mean half-life of 46.0 min and a clearance of 34 l/(h·m^2). *Conclusion*: OSI-7836 given at 200 mg/m^2 on day 1 and day 8 every 3 weekly is associated with manageable toxicity and is recommended for further study. While no objective responses were seen, the significant treatment related lymphopenia suggests that hematologic malignancies may warrant further investigation.

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Introduction

OSI-7836, 4′-thio-β-D-arabinofuranosylcytosine (4′-thio-araC) is a member of the nucleoside analog class of antineoplastic agents. This important class of oncology drugs is exemplified by the compounds cytarabine (ara C), fludarabine phosphate, cladribine and gemcitabine. OSI-7836 is a cytarabine analog with a sulfur substitution at the cyclic oxygen that arrests cells in the G2/M phase of the cell cycle [15, 18]. As with other nucleoside analogs, the proposed mechanism of action involves phosphorylation to the triphosphate form followed by incorporation into cellular DNA, leading to apoptosis [7, 12]. Although nucleoside analogs are generally used in hematological malignancies, the clinical utility of gemcitabine in solid tumors has spurred interest in the development of this class of agents against non-hematologic malignancies [9].

In preclinical models, OSI-7836 has a broad spectrum of activity in various solid tumor xenograft models including colon, lung, renal, breast, prostate and pancreatic cancer [16]. Schedule-dependency studies demonstrated similar efficacy of OSI-7836 with different schedules including more frequent (once daily×9; q4h×3, days 1–9) and less frequent schedules (q2days×5; days 1, 4, 7, 10; days 1 and 8) [16, 17]. However, prolonged

infusion duration was associated with decreased efficacy of OSI-7836 and increased toxicity [16]. OSI-7836 was equally effective by the intravenous and intraperitoneal routes of administration, with the oral route being less efficacious [17]. Cell cycling studies performed in xenograft tumors (Calu-6 and H460) supported the hypothesis that OSI-7836 cytotoxicity is dependent upon DNA synthesis [8]. A validated LC-MS/MS assay was used to show that OSI-7836 was incorporated in internal linkages in tumor DNA in a manner that was dose-independent at the doses tested and did not appear to accumulate during repeating dosing. These results suggest that if DNA incorporation is a toxic event, the relationships between administered dose, DNA incorporation, and toxicity are complex. Toxicology studies in mouse and beagle dog showed toxicity typical of compounds in this class with no evidence of cumulative toxicity [3]. These studies supported a starting dose of 100 mg/m^2/day of OSI-7836 via a 30 min infusion for a first in man phase I trial.

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) conducted a phase I study of OSI-7836 in a day 1 and 8 schedule every 3 weeks with the objectives of determining the maximum tolerated dose (MTD), the recommended Phase II dose (RP2D), the dose-limiting toxicities (DLTs), the safety and toxicity profile, the preliminary anti-tumor activity as well as the pharmacokinetics of OSI-7836.

Methods

Patient selection

Patients were selected based on the following criteria: refractory advanced and/or metastatic solid tumors, clinical or radiological evidence of disease (tumor marker elevations alone were not eligible), age ≥18 years, ECOG performance status of 0–2. Twenty-one days must have elapsed since prior anti-cancer therapy (28 and 42 days for carboplatin and nitrosoureas/mitomycin, respectively) and patients must have recovered from treatment-related toxicities. Previous surgery was permitted provided that wound healing had occurred. All patients had neutrophil counts $\geq 1.5\times10^9$ l^{-1}, platelets $\geq 100\times10^9$ l^{-1}, bilirubin $\leq$ 1.25×UNL, AST or ALT $\leq$ 2.5×UNL ($\leq$ 5×UNL if documented liver metastases), serum creatinine $\leq$ 1.25×UNL, and PT/INR, PTT and ECG within normal limits. Female patients of childbearing age must have had a baseline negative pregnancy test and be using adequate birth control measures.

Patients were excluded if they: (1) were pregnant or lactating,(2) had untreated brain or meningeal metastases, (3) had untreated and/or uncontrolled cardiovascular conditions, (4) had active or uncontrolled infections or other serious medical conditions or would receive concurrent treatment with other experimental drugs or anti-cancer therapy.

Study treatment was to begin within 2 working days of patient registration. All patients gave written informed consent. The study was approved by the institutional ethics review boards of each participating center.

Trial design

This was a two-center, open-label, dose-seeking phase I study of OSI-7836 in patients with advanced incurable cancer and was carried out by the NCIC CTG. The study was supported in part by OSI Pharmaceuticals.

Dose escalation and endpoints

Dose-limiting toxicities was defined as follows: absolute granulocyte count $<0.5\times10^9$ l^{-1} for ≥7 days, febrile neutropenia, grade 3 or 4 clinically or microbiologically documented infection with grade 3 or 4 absolute granulocyte count, platelets $<25\times10^9$ l^{-1} or thrombocytopenic bleeding, any grade 3 non-hematologic toxicity (excluding unpremedicated nausea and vomiting and alopecia), grade 2 persistent (≥7 days) clinically relevant neurotoxicity or cardiac toxicity, or toxicity that resulted in either the omission of day 8 or a ≥14 day delay before the second cycle.

An accelerated titration design without intrapatient dose escalation was performed to increase trial efficiency [11]. Initially, 1–2 evaluable patients were entered at each dose level until ≥grade 2 drug-related toxicity was seen. Thereafter, at least three evaluable patients were entered at each dose level until the MTD was reached. If only one-third of the patients experienced a DLT, an additional three patients were enrolled for a total of six patients. Escalation to the next dose level occurred if fewer than two-sixth of the patients experienced DLT. If ≥2/3 or ≥2/6 patients experienced a DLT on a dose level, then that dose was declared the MTD. The next lower dose was to be the RP2D, provided this dose level was well tolerated in an expanded cohort including an additional four to seven patients (up to ten patients in total).

Starting dose, dosing and drug administration

A day 1 and 8 schedule was selected based on the preclinical data, as well as experience with similar agents such as gemcitabine. For gemcitabine, One-twentieth of the rodent LD10 was used as starting phase I dose. For OSI-7836, the mouse was the most sensitive of the rodent species with an LD10 value in excess of 4,800 mg/m^2. One-twentieth of the LD10 in mice is in excess of 240 mg/m^2. In the dog, the toxic dose low (TDL) was 224 mg/m^2. The starting dose for this study was thus selected as 100 mg/m^2/day. OSI-7836 was administered IV through peripheral or central line as a 30 min infusion.

Patients were not initially routinely premedicated for nausea. Hematopoietic growth factors could not be used as a substitute for a scheduled dose reduction; however, they could be used in the management of acute toxicity or when clinically indicated at the discretion of the investigator. Patients could receive ongoing supportive and palliative care including palliative radiation therapy.

The planned dose-escalation strategy is outlined in Table 1. Intra-patient dose escalation was not permitted. Day 1 for any cycle was delayed for neutrophil count $<1.5\times10^9\ l^{-1}$ or platelets $<100\times10^9\ l^{-1}$, unresolved ≥grade 2 neuro or cardiac toxicity, or grade 3 toxicity. Day 1 doses were adjusted for any toxicity meeting the definition of DLT, or if day 8 doses were reduced for 2 successive cycles. Day 8 doses were reduced by one dose level if neutrophils were <1.0–$0.75\times10^9\ l^{-1}$ or platelets 50–$99\times10^9,l^{-1}$, and omitted with neutrophils $<0.75\times10^9\ l^{-1}$, platelets $<50\times10^9\ l^{-1}$ or for grade 3/4 non-hematologic toxicity. Treatment was discontinued permanently for grade 4 non-hematologic toxicity.

Treatment was discontinued for disease progression, unacceptable toxicity, withdrawal of consent, or at the investigators discretion. Up to six cycles were planned, but patients experiencing clinical benefit could receive additional cycles at the discretion of the investigator.

Pharmacokinetics

Pharmacokinetics was performed in all patients during the first cycle of treatment. Venous blood sample of 3 ml were collected into an EDTA vacutainer, containing 30 μg tetrahydrouridine (supplied by OSI Pharmaceuticals). Samples were centrifuged within 30 min of collection and stored at −20°C until analysis. Cycle 1 plasma (day 1 and day 8) and urine (day 1) samples were evaluated for OSI-7836 and its deaminated metabolite, 4′-thio-AraU, using validated LC-MS/MS method (Cedra Corporation, Austin, TX, USA) [13]. Plasma concentration–time data for OSI-7836 and 4′-thio-araU were analyzed by non-compartmental methods using WinNonlin® version 4.1 (Pharsight Corporation, Mountain View, CA, USA).

Table 1 Planned dose escalation The starting dose of OSI-7836 was 100 mg/m^2

Worst grade of toxicity[a] in previous dose level/cohort	Minimum % dose escalation	Maximum % dose escalation
1	50	100
2	30	49
3 or 4	0	29

Dose was escalated between cohorts according to the dose escalation scheme outlined above. There was no intrapatient dose-escalation

[a]Toxicity believed related to study drug; excludes nausea and vomiting unless uncontrolled by standard measures

Assessments

Pretreatment evaluation included (a) history and physical exam, (b) hematology, biochemistry and coagulation studies, (c) urinalysis, (d) ECG, (e) pregnancy test and imaging studies to document disease. Toxicity was graded using the Common Toxicity Criteria version 2.0. Hematology was performed twice weekly on cycles 1 and 2 then weekly thereafter while biochemistry was done weekly on cycle 1 and 2 and on day 1 of each cycle thereafter. Imaging studies were repeated every 6 weeks.

Response criteria

All patients with measurable disease at baseline, who received one cycle of therapy and were re-evaluated were evaluable for response assessed by the RECIST (Response Evaluation Criteria in Solid Tumors) criteria [14].

Statistical analysis

The primary objective of this study was to establish the MTD and RP2D of OSI-7836 when given IV on day 1 and day 8 every 3 weeks. The sample size was based on the number of patients needed to determine the RP2D and the MTD. For the PK assessment, repeated measures ANOVA on log dose-normalized AUC and C_{max} were performed to test for differences between genders and days. For analyses of half-lives, two-way repeated measures ANOVA on the ranks of the half-lives were performed.

Results

Twenty-seven patients were initially enrolled onto the study. However,one patient died prior to receiving treatment. Therefore, 26 patients were evaluable for non-hematologic and hematologic toxicity. Of these 26 patients, 2 patients had no measurable disease and 3 patients did not have their disease reassessed leaving 21 patients evaluable for response. Patients' characteristics are presented in Table 2. The majority of enrolled patients had a performance status of 0–1. The most common tumor types were colorectal and head and neck cancer (7 and 6 patients, respectively) and NSCLC (4 patients). One patient had no prior chemotherapy while 15 had 1 or 2 prior regimens and 10 had 3 or more prior regimens.

Drug delivery

A total of 73 (3 week) cycles of OSI-7836 were delivered at 5 dose levels (7 cohorts). The starting dose was 100 mg/m^2 and was escalated to 200, 400, 600 mg/m^2

Table 2 Patients characteristics ($N = 26$)

	No. of patients
Median age [54 years (range 32–75 years)]	
Gender	
Female	13
Male	13
Performance status (ECOG)	
0	5
1	18
2	3
Malignancy	
Breast	1
Colorectal	7
Gall bladder	1
Head and neck	6
Liver	1
Mesothelioma	2
Non-small cell lung cancer	4
Other malignancy/unknown primary	2/2
Measurable disease	
No	2
Yes	24
Prior therapy	
Adjuvant chemotherapy	8
Chemotherapy for metastatic disease	24
Adjuvant hormonal therapy	0
Hormones for metastatic disease	1
Immunotherapy	0
Radiotherapy	14
Other therapy	3
No. prior chemotherapy regimens	
0	1
1	3
2	12
≥3	10
Sites of disease	
Peritoneal disease	10
Adrenal	3
Head and neck	3
Bone	6
Liver	11
Nodes	13
Lung	31
Others	9
No. sites of disease	
1	3
2	7
3	7
4 or more	9

and then de-escalated back to 500, 400 and finally 200 mg/m^2. The number of cycles given at each dose level ranged from 1 to 33, with the highest number of cycles being given at the 200 mg/m^2 dose level. The median number of (3-week) cycles given per patient was 2 (range 1–8).

Toxicity

Twenty-six patients were evaluable for hematological and non-hematological toxicity. No significant neutropenia was observed and only grade 1 or 2 thrombocytopenia was documented at doses ≥400 mg/m^2. Interestingly, all 26 patients experienced non-dose dependent grade 3 lymphopenia beginning as early as day 2 of cycle 1 (Table 3). Lymphopenia was generally reversible, though not all patients were followed to full recovery once off treatment.

The main non-hematologic toxicities (Table 4) were grade 2 or 3 fever, fatigue, skin rash, herpes infection and grade 1 or 2 nausea and vomiting. Grade 1 or 2 herpetic stomatitis of short duration was observed in 13 patients at all doses ≥200 mg/m^2; 7 cases were considered to be related to OSI-7836. A maculopapular rash, thought to be drug related, was reported in 14 patients. Biochemical toxicity was encountered at the higher dose levels and was mainly grade 1 or 2 elevations in AST, bilirubin and alkaline phosphatase. No clinically significant grade 3 or 4 liver toxicity was seen.

Dose-limiting toxicities are summarized in Table 5. No DLTs were observed in the first 2 cohorts (100, 200 mg/m^2). However, the initial two patients treated at the 200 mg/m^2 level experienced some drug related grade 1 and 2 nausea and vomiting, so premedication with non-5HT3 anti-emetics was introduced for the third dose level of 400 mg/m^2. At the 400 mg/m^2 dose level the first two patients experienced grade 2 nausea and vomiting despite premedication with non-5HT3 antiemetics. This cohort was further expanded by two patients who were premedicated with steroids and 5HT3 antiemetics, with improved emesis control. The dose was then escalated by 50% to 600 mg/m^2. Both of the two patients accrued experienced DLT (one patient had grade 3 fatigue and one patient had grade 3 fatigue, rash and seizures and grade 2 fever, confusion and dysphagia), which resulted in dose de-escalation to 500 mg/m^2 for the next cohort. At the 500 mg/m^2 dose level, fatigue and fever appeared to be dose limiting. It was decided to expand this cohort, giving the patients a pre-medication cocktail consisting of a steroid, an antiemetic, an antihistamine and acetaminophen in an attempt to alleviate

Table 3 Lymphocytes count nadir and recovery from baseline value ($N = 26$)

Dose level (mg/m^2)	No. of patients	Baseline median (range)	Nadir median (range)	Day to nadir median (range)	Last value median (range)	Day to last value median (range)
100	1	0.5	0.2	2	0.3	25
200	8	0.9 (0.2–1.4)	0.05 (0.0–0.1)	20 (8–64)	0.5 (0.1–2.2)	108 (42–153)
400	11	1.1 (0.7–1.5)	0.0 (0.0–0.2)	12 (3–163)	0.7 (0.0–2.6)	56 (14–234)
500	4	1.15 (0.9–1.2)	0.05 (0.0–0.1)	8 (5–78)	0.7 (0.3–1.8)	58 (26–91)
600	2	1.15 (1.1–1.2)	0.15 (0.1–0.2)	10 (7–12)	1.09 (0.9–1.3)	63 (27–98)

Table 4 Main non hematologic adverse events considered related to OSI-7836 according to NCI Common Toxicity Criteria version 2.0 ($N=26$)

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	% Patients
Fever	9	4	2			15	57.7
Fatigue	6	7	8			21	80.8
Anorexia	5	4				9	34.6
Nausea	6	7	1			14	53.8
Stomatitis	6	1				7	26.9
Vomiting	6	6	1			13	50.0
Herpes simplex	2	10	1			13	50.0
Neuropathy/sensory	1		2			3	11.5
Seizure (s)			1			1	3.8
Hypoxia			1			1	3.8
Dyspnea		1	1			2	7.7
Dry skin	4	1				5	19.2
Pruritus	1		1			2	7.7
Rash/desquamation	5	4	5			14	53.8

the fatigue and fever. One patient was accrued to this expanded cohort and had grade 3 fever requiring hospitalization. At this point, a decision was made to further re-explore the 400 mg/m^2 dose level by expanding this initial cohort of four patients by two additional patients. Neither experienced a DLT and a further five patients were entered for a total of ten evaluable patients at this dose level (one patient came off study for progression after receiving only one dose and was not considered evaluable). Four of these additional five patients experienced DLT, including two patients who did not receive day 8 of their treatment. A further dose de-escalation to 200 mg/m^2 was made by expanding the initial cohort of two patients by two patients initially then a further four patients. Since no DLT was observed in a total of eight patients,200 mg/m^2 was considered the RP2D.

Five patients discontinued treatment with OSI-7836 because of toxicity, usually combinations of rash, vomiting, fatigue and or herpes; one patient had pneumonitis. Twenty-three treatment modifications were required in 11 patients. Seven patients had dose reductions, nine patients missed treatment doses and seven patients had treatment delays mainly due to grade 3 fever, fatigue, nausea or rash as well as grade 2 herpes.

Hospitalization and death

There were seven admissions to hospital, four for drug related and three for unrelated adverse events. Among the four serious adverse events considered related to study treatment, one patient was hospitalized for grade 3 rash and CNS symptoms including confusion, tremors, dysphagia and seizures of uncertain etiology. This patient had no documented brain metastases or prior history of seizures. Investigation, which included magnetic resonance imaging (MRI) of the head and cerebrospinal fluid examination following lumbar puncture were all negative. The second patient was hospitalized for dehydration resulting from grade 3 vomiting, dyspnea and hypoxia. This patient had an adenocarcinoma of unknown origin with peritoneal invasion, ascites and effusions at baseline evaluation. The hypoxia started on day 2 of cycle 1. Patient was given oxygen and chest imaging demonstrated a large pleural effusion, which

Table 5 Cycles administered and dose limiting toxicities (DLT) per cohort of patients ($N=26$)

Dose level (mg/m^2)	Total no. of patients	Total no. of cycles	No. of cycles	No. of patients	No. of patients with DLT/total	Type of DLT per patient
100	1	1	1	1	0/1	None
200	2	8	2	1	0/2	None
			6	1		
400	4	7	1	1	0/4	None
			2	3		
600	2	4	1	1	2/2	1. Grade 3 fatigue, rash,seizure;
			3	1		grade 2 fever, confusion, dysphagia;
						2. Grade 3 fatigue
500	4	9	1	1	3/4	1. Grade 3 fatigue; grade 2 rash
			2	2		2. Grade 3 fever; grade 2 herpes
			4	1		3. Grade 3 fatigue
400	7	19	1	3	4/7	1. Grade 3 fatigue
			2	2		2. Grade 3 rash
			4	1		3. Grade 3 fever; grade 2 fatigue, herpes, rash
			8	1		4. Grade 3 rash
200	6	25	2	1	0/6	None
			4	4		
			7	1		

was drained. The same patient was hospitalized in second time with grade 3 vomiting and found to have a bowel obstruction—thought to be related to disease. The third and fourth patients developed grade 3 and grade 2 fever, respectively, and were admitted to hospital for investigation and treatment. Three cases of serious adverse events unrelated to study treatment were also reported. Two deaths occurred on study, considered related to disease progression.

Pharmacokinetics

Plasma pharmacokinetic data were obtained from 25 patients (13 males and 12 females) following the first OSI-7836 dose (Table 6). The median (range) half-life of elimination across all dose groups was 46.0 (35.0–58.3) min. A statistically significant ($P < 0.0001$), but not clinically relevant difference in elimination half-life was observed between males [48.3 (43.2, 58.3) min] and females [42.6 (35.0, 49.3) min]. No significant gender effect was observed for $AUC_{0\rightarrow\infty}$ ($P = 0.1136$) or C_{max} ($P = 0.1555$) and both parameters increased proportionately with dose. Thus, plasma clearance was independent of dose over the range tested with a representative plasma concentration–time plot at the recommended phase II dose (200 mg/m^2).

Following the cycle 1, day 8 dose, pharmacokinetic data were obtained from 18 patients at the following dose levels; 100 ($n = 1$), 200 ($n = 8$), 400 ($n = 6$), 500 ($n = 2$), and 600 ($n = 1$) mg/m^2 (data not shown). No effect on elimination half-life ($P = 0.7286$), C_{max} ($P = 0.8372$) or $AUC_{0\rightarrow\infty}$ ($P = 0.5520$) due to dosing day was observed. Across all dose cohorts, the median plasma clearance on day 8 was 36.5 l/(h·m^2) compared to 34.0 l/(h·m^2) on day 1.

The plasma $AUC_{0\rightarrow\infty}$ of the inactive metabolite,4′-thio-araU, was much greater than that of OSI-7836 and also increased proportionally with dose (data not shown). Across all day 1 doses, the 4′-thio-araU $AUC_{0\rightarrow\infty}$ was 9.06 ± 2.51-fold (mean ± SD) greater than the OSI-7836 $AUC_{0\rightarrow\infty}$. After the initial dose of OSI-7836, the median (range) terminal half-life of 4′-thio-araU was 4.59 (1.51–6.41) h.

Complete 24-h urine data were obtained from 14 patients. The median fraction of the total dose recovered in urine was 86.7%, with the majority recovered as 4′-thio-araU. The mean recovery was 91.0% with a 95% confidence interval of 76.6–105%.

Response

Of 27 patients accrued to this study, 21 were evaluable for response. Complete or partial responses were not documented. Nine patients had a best response of stable disease for a median duration of 4.3 months (1.8–6.4 months). Among these, one patient with lymphoepithelioma of the thymus treated at the first dose level had shrinkage in non-measurable pleural disease. Twelve patients had progressive disease as their best response.

Exploratory analysis: interaction between pharmacokinetics parameters and toxicity

Since no treatment response was observed in any patients, C_{max} and $AUC_{0\rightarrow\infty}$ on cycle 1 day 1 ($n = 25$ patients) and day 8 ($n = 18$ patients) were only correlated to the main experienced toxicities including lymphopenia, fever, rash, herpes simplex, nausea and vomiting. Worst grade of skin rash, fever and herpes simplex were significantly associated with $AUC_{0\rightarrow\infty}$ on cycle 1 day 1 ($P = 0.0079$, 0.0459, 0.0384, respectively) in a correlation analysis unadjusted for multiple tests. The significant unadjusted correlation between skin rash and $AUC_{0\rightarrow\infty}$ persisted on cycle 1 day 8 ($P = 0.0019$). Skin rash was also significantly associated with C_{max} on day 1 and day 8 (respective unadjusted P values, 0.0561 and 0.0140).

Discussion

We have described the phase I results of a study evaluating the nucleoside analog OSI-7836 given IV on day 1 and day 8 every 3 weeks in a group of patients with incurable solid tumors. Twenty-six patients were treated with IV OSI-7836 at five dose levels in seven cohorts. The starting dose was 100 mg/m^2 and was escalated to 200, 400, 600 mg/m^2 and then de-escalated back to 500, 400 and 200 mg/m^2. The highest administered dose was 600 mg/m^2/day. The MTD was reached at doses of ≥400 mg/m^2; at 400 mg/m^2, 4 out of 11 patients experienced DLT. The recommended phase II dose of

Table 6 OSI-7836 median (range) plasma pharmacokinetic parameters following the cycle 1, day 1 dose

Dose (mg/m^2)	100	200	400	500	600
n	1	8	10	4	2
C_{max} (μg/ml)	2.93	7.99 (6.08–12.2)	12.8 (9.38–27.2)	18.4 (13.8–19.0)	24.0 (17.4–30.6)
$AUC_{0\rightarrow\infty}$ (μg·h/ml)	2.70	6.43 (5.25–7.73)	10.9 (6.85–17.9)	14.0 (13.1–16.6)	17.7 (16.0–19.3)
CL (l/(h·m^2))	37.0	30.8 (25.9–38.1)	36.9 (22.2–58.6)	35.9 (30.1–38.1)	34.4 (31.1–37.6)
$t_{1/2elimination}$(min)	39.6	45.5 (35.0–52.6)	47.3 (38.0–56.0)	44.3 (43.2–58.3)	49.6 (47.1–52.0)
V_{ss} (l/m^2)	31.9	25.2 (21.2–34.5)	34.6 (16.8–48.7)	30.6 (29.0–44.1)	35.6 (26.9–44.3)

Abbreviations: C_{max} maximum concentration, *AUC* area under the curve, *CL* clearance, $t_{1/2}$ half-life, V_{ss} distribution volume at steady state

200 mg/m^2 was tested in an expanded cohort of 8 patients.

The dose escalations and de-escalations encountered in this study are consistent with reported phase I trial experiences of other antimetabolites in which toxicity appeared to be incompletely predicted by dose alone [10]. This complex relationship between administered dose and toxicity was also suggested by previously mentioned preclinical data [8].

The accelerated titration design is usually more efficient than other dose escalation schema by reducing the number of study patients, limiting the number of patients treated with subtherapeutic doses and, providing more information with regard to interpatient variability and steepness of the dose toxicity curve. The pattern of interpatient variability in toxicity observed in this phase I trial and reported in most published phase I trials with antimetabolites suggests that current accelerated escalation trial designs enrolling a single patient per dose level may not be appropriate. Therefore, this accelerated titration design was not the optimal design to evaluate this drug as evidenced by the necessity to escalate and then de-escalate study drug dose. In future, this study design should not be used in evaluating nucleoside analogs.

The major toxicities documented were grade 3 lymphopenia, fatigue, fever and rash. According to the exploratory analysis of the interaction between pharmacokinetic parameters and toxicity, the rash consistently and significantly correlated to both peak concentration (C_{max}) and overall drug exposure ($AUC_{0\rightarrow\infty}$). The lymphopenia was generally reversible and non-dose dependent. It was difficult to differentiate the etiology of fever. Despite routine investigations, bacterial infection as a cause of fever was not demonstrated in any of the patients. Overall, half of the patients experiencing DLT had missed day 8 of cycle 1 dosing of OSI-7836. No objective response was reported.

The European group De Jonge et al. [4] reported similar results in a concurrent phase I trial assessing a different dosing schedule of OSI-7836 administered on day 1 of every 21-day cycle. Nine patients were given a 60-min infusion and 16 patients received a 5-min bolus of OSI-7836 for a total of 25 treated patients. The shorter infusion had been explored in an attempt to modulate toxicity, especially fatigue. The recommended phase II doses were respectively 200 and 300 mg/m^2 for the 60-min infusion and the 5-min bolus. The major toxicities were similar to the toxicities seen in our study vis-à-vis fatigue, fever, rash, nausea/vomiting and herpes simplex reactivation. Lymphopenia was the only significant hematologic toxicity and occurred as early as cycle one. The pharmacokinetic profile and antitumor activity were also comparable to our experience. Plasma C_{max} and AUC appeared to increase linearly with dose and no objective responses were documented.

The significant activity observed with the gemcitabine analog OSI-7836 in preclinical solid tumor models did not translate into tumor response in any solid tumor type. Although no responses were observed, this was a small phase I study in heavily pretreated patients including tumor types with variable documented responses to gemcitabine. A previous phase I study evaluating gemcitabine in pretreated patients with solid tumors reported only one response [1]. Furthermore, patients with colorectal cancer, a tumor type not expected to respond to gemcitabine, represented 27% of the study population. In phase II trials assessing gemcitabine in patient with colorectal cancer, low response rates of 0–4% were reported [5, 6]. Nevertheless, it is difficult to recommend the solid tumor type in which phase II studies of OSI-7836 should be conducted. The main toxicity profile of OSI-7836 characterized by lymphopenia, fever, rash, and myalgia was very similar to the ones of fludarabine and cladribine, agents used in the treatment of hematologic malignancies. Lymphopenia and flu-like symptoms, including fever and myalgia, are expected common adverse events of fludarabine and cladribine. Fever may occur in 46–60% of cases treated with these nucleoside analogs. Although uncommonly reported with fludarabine, rash may occur in 5–27% of cases treated with cladribine [2]. Finally, the observation of significant lymphopenia in this study suggests that further exploration of the role of OSI-7836 in lymphoid malignancies may be reasonable.

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