

A first in human study of SB-743921, a kinesin spindle protein inhibitor, to determine pharmacokinetics, biologic effects and establish a recommended phase II dose

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Abstract

Purpose To determine the maximum-tolerated dose (MTD), dose-limiting toxicity (DLT), safety, pharmacokinetics, and pharmacodynamics of SB-743921 when administered as a 1-h infusion every 21 days to patients with advanced solid tumors or relapsed/refractory lymphoma.

Methods Patients who failed prior standard therapy or those without any standard options were eligible. Forty-four patients were enrolled using an initial accelerated dose-escalation phase followed by a standard dose-escalation phase. An additional 20 patients were enrolled at the recommended phase II dose to obtain additional safety and pharmacokinetic data. The doses evaluated ranged from 2 to 8 mg/m². The pharmacokinetics of SB-743921 was evaluated at 19 time-points over 48 h following during administration during cycle 1. Toxicity was assessed by the NCI Common Terminology Criteria version 3.0. Response evaluation was performed every 6 weeks.

Results The most common and consistent DLT was neutropenia. Other DLTs observed included hypophosphatemia, pulmonary emboli, SVC syndrome, transaminitis,

hyponatremia, and hyperbilirubinemia. The MTD of SB-743921 as a 1-h infusion every 21 days was established as 4 mg/m². The maximum plasma concentration and area under the plasma concentration time curve appeared to increase proportionally to dose. One durable objective response was seen in a patient with metastatic cholangiocarcinoma who was on treatment 11 months and 6 patients had stable disease for over four cycles.

Conclusions The recommended phase II dose of SB-743921 on this specific schedule of a 1-h infusion every 3 weeks is 4 mg/m². The promising efficacy and lack of severe toxicities in this study warrant the continued development of SB-743921.

Keywords SB-743921 · Phase I · Pharmacokinetics · Kinesin spindle protein · Mitosis · Safety

Introduction

Disruption of the mitotic spindle has been a target for antineoplastic therapies since the FDA approved an alkaloid derivative of *Catharanthus roseus*, vincristine, in 1963. These first generation anti-spindle agents targeted tubulin, the essential protein comprising the mitotic spindle, by either disassembly (the vinca alkaloids) or by polymerization stabilization (the taxanes). The clear disadvantage of anti-tubulin agents is that tubulin is also important in cellular maintenance of shape, motility, signal transmission, neuronal function, and intracellular transport [1, 2]. A more selective inhibitor of the mitotic spindle would prevent the associated toxicities of anti-tubulin agents, in particular neuropathy.

Kinesin motors are ATPases that produce directed mechanical force along the microtubule polymer. They

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are important motor proteins for a variety of cellular processes, including organelle and vesicular transport, cilia formation, and mitotic spindle function [3]. Mitotic kinesins are motor proteins specific to the mitotic spindle apparatus. They are most abundant in proliferating human tissues, correlate with a high proliferative index *in vitro*, are undetectable in post-mitotic neurons, and seem to be elevated in the majority of human cancers. Thus, an inhibitor of one of the specific mitotic kinesin proteins functioning in prometaphase would arrest cells in mitosis and spare other essential tubulin and kinesin family functions related to mitosis.

SB-743921 is a potent, small molecule inhibitor of the ATPase of kinesin spindle protein (KSP or Eg5), a mitotic-specific kinesin protein. SB-743921 has greater than 40,000 fold selectivity for KSP over other kinesins. SB-743921 has demonstrated promising anti-cancer activity in a variety of *in vivo* and *in vitro* human cancer models in preclinical studies. Furthermore, anti-cancer effect has been demonstrated in taxane-refractory malignancies with SB-743921. Toxicity studies demonstrated predictable neutropenias and gastrointestinal toxicities without clear evidence of neurotoxicity. We therefore conducted a first in human clinical trial to evaluate the toxicities, safety, pharmacokinetics and pharmacodynamics of SB-743921 in patients with refractory solid tumors and lymphoma.

Patients and methods

Patient selection

All patients were required to have a cytologically or histologically confirmed solid organ malignancy refractory to standard therapy or for which no standard therapy exists. Patients with a diagnosis of B- or T-cell lymphoma were also included, as long as they had relapsed or refractory disease after prior chemotherapy or radiotherapy or for which salvage chemotherapy, radiotherapy, or bone marrow transplantation was not indicated or had been refused by the patient. There was no limit on the number of prior therapies allowed. All patients met standard organ function limits, had an ECOG performance status of 0–2, and had no unstable major medical problems that would interfere with the study treatment. At least 4 weeks had to have elapsed between the start of protocol treatment and last chemotherapy (6 weeks for nitrosoureas and mitomycin) and radiotherapy. Patients with treated stable brain metastases were allowed.

The study protocol was approved by the institutional review boards of the participating institutions and all

patients gave written informed consent. The study was conducted according to the Declaration of Helsinki.

Drug administration

SB-743921 was administered intravenously as a 1-h infusion once every 3 weeks. The starting dose was 2 mg/m². Dosing was repeated for up to six cycles or more, until disease progression or withdrawal from treatment due to an unacceptable toxicity or withdrawal of consent.

Acceleration design

The accelerated titration design was utilized for the study. At least two patients were entered at the starting dose and monitored for toxicity. Dose escalation to subsequent dose levels did not occur until all patients in the previous cohort reached at least day 21 of their first cycle. The decision to dose escalate was based on toxicity encountered during the first cycle of treatment only. In the accelerated phase, doses were escalated by 100% until grade 2 toxicities were observed in two patients, a non-dose limiting grade 3 or 4 toxicity was observed in one patient, or a dose-limiting toxicity (DLT) was observed in one patient within a given dose-cohort. Thereafter, the modified escalation phase began, with doses escalated at 50% if grade 2 toxicities were observed or 33% if grade 3 or 4 toxicities were observed. A minimum of three patients per cohort were treated during the modified escalation phase. If a DLT was noted, additional patients were enrolled for a total of six evaluable patients. If only one of six patients experienced a DLT, the escalation continued at 33% of the prior dose. If two or more patients experienced a DLT, then the next lower dose was further evaluated with additional patients to a total of six. The MTD was defined as the highest dose at which less than two of six patients experience a DLT. DLTs were defined using standard criteria and included the following: (1) grade 3 or 4 non-hematologic toxicity, (2) 5 or more days of grade 4 neutropenia, (3) febrile neutropenia, (4) grade 4 thrombocytopenia, or (5) any grade 2 toxicity that was thought to be severe enough to be considered a DLT or caused a 2 week or more delay in the start of cycle 2. Any subject with nausea, vomiting, or diarrhea met DLT criteria only if the symptom was grade 3 or greater and the treating physician had made adequate attempts at treating the symptom with supportive medications.

Patients were enrolled simultaneously in each cohort group. Patients who were removed from the study before completion of cycle 1, for reasons other than safety, were replaced. A maximum of 20 additional patients were treated at the MTD to obtain additional safety and pharmacokinetic

data. Prophylactic use of colony-stimulating factors was not allowed.

Evaluation

The baseline evaluation consisted of a history and physical examination, assessment of performance status (ECOG scale), chest X-ray, electrocardiogram (ECG), complete blood count (CBC), pregnancy test when applicable, hemoglobin, reticulocyte count, blood smear, alpha-1-acid glycoprotein (AAG), albumin, serum chemistries, serum tumor markers, and documentation of measurable disease by computed tomography scan or magnetic resonance imaging. Serum chemistries and CBC were obtained weekly. Physical examination, assessment of performance status, CBC, and serum chemistries were obtained at the start of each treatment cycle. Response was assessed according to RECIST criteria every 6 weeks. Non-measurable lesions were evaluated by the same methods as measurable lesions and reported as “present” or “absent.”

Pharmacokinetics

Pharmacokinetic disposition of SB-743921 was studied in all patients. Serial blood samples (3 mL/sample) were collected during Cycle 1 at: predose, 15 min, 30 min, 45 min, 1 h (immediately at the end of the infusion), 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, and 48 h. Intra-patient dose escalation was allowed; for these patients, the above PK sampling was performed at the higher dose.

All SB-743921 samples were collected in potassium EDTA tubes and centrifuged at 2,500g at 5°C for 10 min. Plasma was then frozen at −20°C until analysis for SB-743921 levels using a validated LC/MS method by the GlaxoSmithKline Division of Drug Metabolism and Pharmacokinetics. The method for the determination of SB-743921 concentration in human plasma has been validated over the range 0.5–500 ng/mL using HPLC–MS/MS. SB-743921 was extracted from 50 µL of human plasma by protein precipitation using 75/25 acetonitrile/10 mM ammonium formate (pH 3) containing an isotopically labeled internal standard ($^{13}\text{C}_7$)-SB-743921). Extracts were analyzed by HPLC–MS/MS using a TurboIonSprayTM interface and multiple reaction monitoring. (GlaxoSmithKline document CD2004/00286/00).

Pharmacokinetic analysis

Pharmacokinetic endpoints included AUC, C_{max}, Cl, V_d, and $t_{1/2}$. Dose proportionality of AUC for SB-743921 (KSP) solution was assessed using the power model as described below and evaluated visually in graphical form.

$$\log(\text{PK parameter}) = a + b \times \log(\text{dose})$$

where a is the intercept and b is the slope.

The power model was fitted by the maximum likelihood (ML) using SAS Proc GLM. The mean slope was estimated from the power model and the corresponding 90% confidence interval was calculated. Pharmacokinetic analyses of plasma SB-743921 concentrations were conducted with standard non-compartmental methods using WinNonlin Professional software (Pharsight Corporation, Mountain View, CA, USA).

Results

Patient characteristics and dosing

A total of 44 subjects were enrolled in the study; 19 men and 25 women. The median age was 61 (range 32–80) and all subjects were Caucasian (Table 1). The most common diagnoses were colon and rectal cancer (12), non-small cell lung cancer (5), biliary tumors (5), and ovarian cancer (5), pancreas cancer (4), esophageal cancer (4) and hepatocellular cancer (2). There was one subject with each of the following cancers: mesothelioma, paraganglioma, melanoma, appendiceal tumor, bladder cancer, neuroendocrine tumor (islet cell cancer), and lymphoma. Nearly all patients

Table 1 Baseline patient characteristics ($N = 44$)

Characteristic	Patients	
	Number	Percentage (%)
Sex		
Male	19	43
Female	25	57
Age, years		
Median	61	
Range	32–80	
ECOG performance score		
0	8	18
1	34	77
2	1	2
Unk	1	2
Prior treatment, in number of regimens	Median 4 (0–10)	
0	1	2
1	2	5
2	4	19
3	11	25
4 or more	26	59

ECOG eastern cooperative oncology group

(98%) had received prior chemotherapy, and 93% of patients had received at least two prior chemotherapy regimens. Five different doses of SB-743921 were evaluated: 2, 4, 5, 6, and 8 mg/m². Patients received a median of two cycles (range, 1–16 cycles).

Escalation

No DLTs were noted at the first level (2 mg/m²) or in the first three patients treated at the second level (4 mg/m²). At the next higher dose level (8 mg/m²), four of six patients experienced DLTs. Therefore, the next cohort of three patients was treated at an intermediate dose level of 6 mg/m². Since two of three patients had a DLT at this dose level, the next six patients were treated at a new dose level of 5 mg/m². Two of the six patients had a DLT at 5 mg/m², and therefore three additional patients were treated at 4 mg/m². Only one of six subjects had a DLT at this dose level. This level was then expanded with an additional 21 patients to further characterize the toxicities at this dose. In total, there were three DLTs in 27 patients treated at 4 mg/m². Therefore, 4 mg/m² was deemed as the MTD for this agent.

Toxicity

The most common toxicities noted were hematologic and gastrointestinal in nature, consistent with predicted toxicities from both the preclinical data and the mechanism of action of SB-743921. Common toxicities included nausea, neutropenia, diarrhea, abdominal pain, fatigue, pyrexia, vomiting, dizziness, headache, leucopenia, AST elevations, and constipation, summarized in Table 2. Alopecia, mucositis, and neuropathy were not observed.

The major dose-limiting toxicity was neutropenia, observed in two of six subjects (33%) at the 8 mg/m² dose level. There was one dose-limiting neutropenia DLT at 6 mg/m², 2 at 5 mg/m², but only 1 of 27 had a grade 4 neutropenia at the MTD (4 mg/m²). This subject's neutrophil count recovered within 5 days and therefore did not meet criteria for a DLT. Other DLTs observed included: grade 3 hypophosphatemia (1), grade 5 pulmonary embolus (1), grade 3 superior vena cava (SVC) syndrome (1), grade 3 hyponatremia and grade 3 hyperbilirubinemia (1), and grade 3 transaminase elevation (1). The DLTs and the corresponding dose levels are listed in Table 3.

Myelosuppression

Fifteen patients (34%) of the 44 treated had at least one episode of neutropenia. This included 8 of 27 patients (30%) treated at the MTD (4 mg/m²), 2 of the 6 patients (33%) treated at 5 mg/m², 2 of 3 patients (67%) treated at 6 mg/m², and 3 of 6 patients (50%) treated at 8 mg/m².

Most of these occurrences were not considered clinically relevant with only 5 of the 15 patients meeting criteria for DLT (neutropenia accompanied by fever or of duration less than 5 days). Neutropenia nadir occurred at approximately 8 days after the infusion of SB-743921 and was of a short duration (3 days).

Gastrointestinal toxicities

Nausea was the most common reported gastrointestinal complaint (41% of patients), occurring in 17 patients across 4, 6, and 8 mg/m² cohorts. Diarrhea, all grade 2 or less, occurred in 11 patients. Abdominal pain (nine patients), vomiting (eight patients), and constipation (five patients) were the three other more common gastrointestinal toxicities. Abdominal pain was reported in nine patients in total, seven in the 4 mg/m² cohort and two in the 8 mg/m² cohort.

Hepatobiliary toxicities

Elevations in AST and ALT were noted in six and three patients, respectively at doses ≥ 4 mg/m². These were notable given that in most cases the levels were normal at baseline and seven were grade 3. Other hepatobiliary toxicities included increased alkaline phosphatase (five patients, one DLT), and increased bilirubin level (four patients, three DLTs).

Deaths

A 45-year-old woman with a metastatic adenocarcinoma of the appendix treated at the 4 mg/m² dose level died while on study. She had sudden onset dizziness and shortness of breath 11 days after administration of her first dose of SB-743921. She was diagnosed with a massive pulmonary embolism in the emergency room and died that same day despite aggressive cardiopulmonary resuscitation. The investigator considered that there was a reasonable possibility that the pulmonary embolism was caused by SB-743921.

Pharmacokinetics

There were pharmacokinetic data for at least one cycle of SB-743921 from the 44 patients who enrolled in the study. The median maximum observed plasma concentration (C_{max}) and area under the plasma drug concentration–time curve from predose to 48 h (AUC(0–48)) increased as the SB-743921 dose was increased in all cohorts. See Fig. 1. Exposures did not appear to increase in a dose-dependent manner, however. There was a dramatic intersubject variability in clearance values. Occasionally, patients at the same dose level would have a clearance that was a 14-fold

Table 2 Summary of frequent (more than two patients) toxicities all grades

Toxicity	Grade	# of patients (% Total <i>N</i>)
Hematology disorders		
Neutropenia	2	2 (5)
	3	4 (9)
	4	9 (20)
Leukopenia	2	1 (2)
	3	5 (11)
Anemia	2	3 (7)
	3	1 (2)
Gastrointestinal disorders		
Nausea	1	15 (34)
	2	3 (7)
Diarrhea	1	8 (18)
	2	3 (7)
Abdominal pain	1	4 (9)
	2	1 (2)
	3	4 (9)
Vomiting	1	4 (9)
	2	2 (5)
	3	1 (2)
Constipation	1	4 (9)
	2	1 (2)
General disorders		
Fatigue	1	9 (20)
	2	1 (2)
	3	1 (2)
Pyrexia	1	5 (11)
	2	2 (5)
Chills	1	5 (11)
	2	1 (2)
Peripheral edema	1	3 (7)
	2	1 (2)
Hepatobiliary disorders		
Hyperbilirubinemia	1	1 (2)
	3	2 (5)
	4	1 (2)
AST elevation	2	2 (5)
	3	4 (9)
ALT elevation	2	1 (2)
	3	2 (5)
Blood alkaline phosphatase	2	2 (5)
	3	3 (7)
Musculoskeletal disorders		
Arthralgia	1	4 (9)
Back pain	1	2 (5)
	2	2 (5)
Nervous system disorders		
Dizziness	1	7 (16)
Headache	1	6 (14)
	2	1 (2)

Table 2 continued

Toxicity	Grade	# of patients (% Total <i>N</i>)
Respiratory disorders		
Cough	1	5 (11)
	2	1 (2)
Dyspnea	1	1 (2)
	2	1 (2)
	3	2 (5)

Table 3 Summary of DLTs

Dose level (mg/m ²)	Patients treated	Toxicities
2	3	No DLTs
4 ^a	27	Grade 3 hypophosphatemia
		Grade 5 pulmonary embolism
		Grade 3 SVC syndrome
5	6	Grade 4 neutropenia, febrile
		Grade 4 neutropenia, febrile
6	3	Grade 3 hyponatremia
		Grade 4 neutropenia, ≥ 5 days
8	6	Grade 4 neutropenia, ≥ 5 days
		Grade 4 neutropenia, ≥ 5 days
		Grade 3 hypertransaminase
		Grade 4 hyperbilirubinemia

DLT dose-limiting toxicity, *SVC* superior vena cave syndrome

^a Defined as the maximum-tolerated dose (MTD)

difference. At the MTD (4 mg/m²), the median half life was 29 h (range 19–64 h). See Table 4.

Response

Efficacy data were available for 41 of the 44 subjects enrolled in this study. Six patients had prolonged stable disease on study, defined as stable disease for at least four cycles. These patients had colon cancer (1), ovarian cancer (2), hepatocellular cancer (1), non-small cell lung cancer (1) or a neuroendocrine tumor (1). Two of these patients were on study with stable disease for 10 cycles; one with ovarian cancer and another with a neuroendocrine tumor. One patient with cholangiocarcinoma was treated at the MTD for a total of 16 cycles. The patient's tumor met criteria for a confirmed partial response 7 months from the time of treatment initiation and she remained on study until disease progression after nearly 12 months on study.

Discussion

This phase I study documents the safety of SB-743921 in patients with advanced solid tumors and has provided a

Table 4 Summary of median (range) pharmacokinetic parameters for SB-743921 following a single intravenous infusion in cancer subjects (SB-743921/001)

Dose (mg/m ²)	C _{max} (ng/mL)	AUC (0–48) (ng h/mL)	AUC (0) (ng h/mL)	CL (mL/h)	t _{1/2} (h)	C _{min} (ng/mL)
2 (n = 2)	233 (233 and 233)	1,706 (1602 and 1811)	2,516 (2,087 and 2,946)	1,596 (1,366 and 1,827)	31.1 (23 and 39)	17.4 (14.9 and 19.9)
4 (n = 26)	489 (268–771)	3,776 (1,620–11,639)	5,156 (2,233–12,508)	1,487 (595–3,934)	28.0 (16.4–64.0)	35.5 (16.4–498)
5 (n = 6)	607 (427–820)	5,378 (3,327–9,713)	8,959 (5,146–16,167)	1,229 (527–1,920)	36.8 (32.9–50.1)	64.2 (36.2–115.4)
6 (n = 3)	817 (704–1,209)	5,421 (4,535–9,433)	8,151 (5,473–14,600)	1,413 (676–1635)	33.7 (19.6–34.6)	56.1 (33.2–103)
8 (n = 6)	803 (622–1,228)	7,264 (3,439–8,286)	10,357 (4,676–13,256)	1,388 (283–3,480)	30.3 (20.7–36.0)	67.0 (29.7–96.4)

characterization of the pharmacokinetic properties of this novel agent. We have also noted encouraging anti-cancer activity in a subset of patients that provide the rationale for continued development of SB-743921. The expansion of the number of patients at the phase II recommended dose to 21 is one of the strengths of this study since it has facilitated a more detailed assessment of the safety profile. The study also documents the ability to administer this agent for multiple cycles without evidence of cumulative toxicity. Consistent with animal studies, we did not notice neuropathy with this agent. Neutropenia, the main dose-limiting toxicity, was dose-dependent and was not accompanied by thrombocytopenia or anemia. Other toxicities such as nausea and emesis were manageable with appropriate supportive care measures.

One of the goals of the design of this anti-mitotic agent was to improve the therapeutic window; limiting the potentially debilitating side effects of taxanes and vinca alkaloids, most significantly neurotoxicity, as well as to improve upon the efficacy and overcome any resistance to anti-tubulin agents. Certainly, in vitro data suggest that paclitaxel-resistant cell lines are susceptible to SB-743921 and preclinical data also appear that SB-743921 has a favorable toxicity profile. It remains, unclear, however, in this limited population of patients to determine if this goal has been accomplished.

An analysis of this and other studies of kinesin spindle protein inhibitors have shown neutropenia as the major dose-limiting side effect [4, 5]. However, more grade 3/4 neutropenia (94%) was noted with the first KSP inhibitor in the clinic, ispensib (SB-715992), compared to SB-743921 (29%). The neutropenia is consistent enough as to be proposed as a possible biomarker of activity with kinesin spindle protein inhibitors. We would hesitate to use neutropenia, however, as such, given the vast and various factors that also can significantly alter white blood cell populations. Alternatively, the changes seen in phosphohistone H3 and PCNA with other KSP inhibitors may provide a better glimpse into the ability of SB-743921 to affect mitosis, particularly in the cells where it matters most, the tumor cells [4, 5].

As mentioned earlier, marrow suppression, in particular neutropenia, seems to be a class effect of kinesin spindle protein inhibitors. Other agents with a similar mechanism of action, namely AZD4877 and MK0731, have striking similar toxicity profiles. MK0731 demonstrated prolonged neutropenia, defined as grade 4 neutropenia lasting greater than 5 days, as the major dose-limiting toxicity [6]. Similarly, AZD4877 in both weekly and twice weekly schedules, was again limited to further dose escalation by prolonged neutropenia, in this case defined as grade 4 neutropenia lasting >4 days [7, 8].

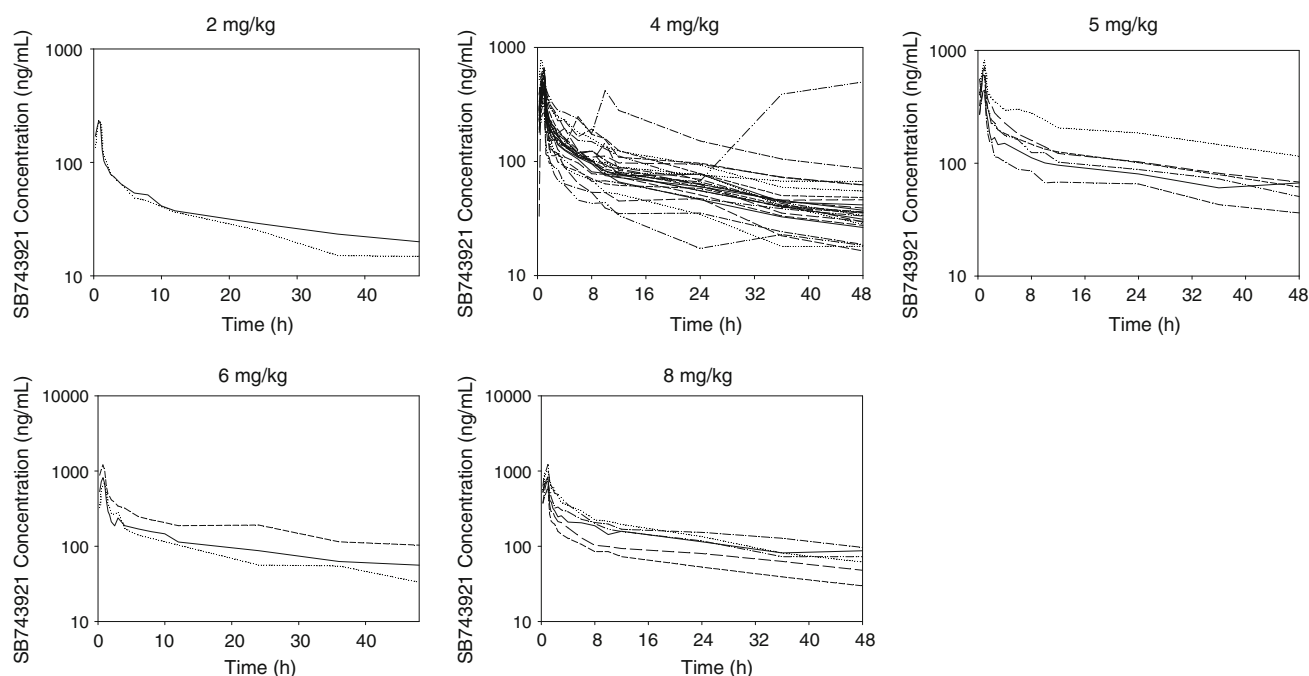


Fig. 1 Concentration versus time plots for the five cohorts analyzed, at 2, 4, 5, 6, and 8 mg/kg

Gastrointestinal toxicities were reported with some consistency. Most severe were grade 3 and 4 laboratory abnormalities (AST/ALT, bilirubin, and alkaline phosphatase increases). These were not clinically significant and were reversible. Nausea and vomiting, although noted at all dose levels, were manageable and never dose-limiting. Similarly, diarrhea, when it occurred, was only grade 2 or less.

In regard to efficacy, it is impossible to demonstrate an improvement over other anti-mitotic agents in a phase I study as efficacy was not the primary endpoint. Although one partial response was noted and there were a significant number of patients with stable disease, many patients had fairly low doses, many had tumors where anti-mitotic agents are unlikely to have efficacy, and many had substantial prior treatment. The partial response is notable, however, in that it was a disease not thought to be particularly responsive to anti-mitotic agents (cholangiocarcinoma) and the patient had multiple prior therapies (gemcitabine, fluoropyrimidine, and oxaliplatin). Of note, some of the patients with prolonged stable disease had a history of prior taxane treatment (the patients with ovarian cancer and the non-small cell lung cancer patients). The other patients were taxane-naïve; however, each had a history of multiple prior treatments. We have also compared the exposures of those with stable disease versus those who progressed on therapy and there is no clear relationship across similar dose levels.

The exposures following SB-743921 dosing increased in a dose-dependent manner and were at levels that were roughly comparable to achieve on-target effects in the animal models. There was high intersubject variability in clearance values, approximating a 14-fold range. This could be, in part, attributed to intersubject variability inherent to CYP3A enzyme activity. A review of the concomitant medications for those with toxicities and have not noted any medications that would have significantly affected CYP isoenzymes. We have also compared the SB743921 exposures among those with grade 3 and above toxicities with those who did not have toxicities and given the limited data set and interpatient variability; we were not able to demonstrate a trend toward higher exposures and toxicity. There was no clear correlation between exposures and observed toxicities in this subject population.

In sum, the recommended phase II dose for SB-743921 as a 1-h infusion every 21 days is 4 mg/m². The pharmacokinetics was predictable with the maximum plasma concentration and area under the plasma concentration time curve increasing proportionally to dose. This mechanism of kinesin spindle protein inhibition is being explored in multiple phase I and phase II studies to provide further clarification on the benefits of inhibiting mitosis without directly affecting microtubules. The results of these studies are anticipated with interest.

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