Phase I dose-escalation and pharmacokinetic study of ispinesib, a kinesin spindle protein inhibitor, administered on days 1 and 15 of a 28-day schedule in patients with no prior treatment for advanced breast cancer

Henry L. Gomez[a], Manuel Philco[b], Patricia Pimentel[b], Miriam Kiyan[c], Maria Laura Monsalvo[c], Maureen G. Conlan[d], Khalil G. Saikali[d], Michael M. Chen[d], Joseph J. Seroogy[d], Andrew A. Wolff[d] and Rafael D. Escandon[d]

The objective of the study was to evaluate the safety, pharmacokinetics, and antitumor activity of ispinesib, a kinesin spindle protein inhibitor. Patients with locally advanced or metastatic breast cancer who had received only prior neoadjuvant or adjuvant chemotherapy were treated with escalating doses of ispinesib administered as a 1-h infusion on days 1 and 15 every 28 days until toxicity or progression of disease. Doses were escalated until dose-limiting toxicity was observed in two out of six patients during cycle 1. A total of 16 patients were treated at three dose levels: 10 mg/m^2 ($n=3$), 12 mg/m^2 ($n=6$), and 14 mg/m^2 ($n=7$). Forty-four percent of the patients had locally advanced disease and 56% had metastatic disease; 50% were estrogen receptor positive, 44% were progesterone receptor positive, 25% human epidermal growth factor 2 were positive, and 31% triple (estrogen receptor, progesterone receptor, human epidermal growth factor 2) negative. Sixty-nine percent of patients were chemo-naive. The maximum tolerated dose was 12 mg/m^2 and dose-limiting toxicity was grade 3 increased aspartate aminotransferase and alanine aminotransferase. The most common toxicities included neutropenia (88%; 38% grade 3 and 44% grade 4), increased alanine aminotransferase (56%), anemia (38%), increased aspartate aminotransferase (31%), and diarrhea (31%). No neuropathy, mucositis, or alopecia was reported. Among the 15 patients evaluable for antitumor activity, there were three partial responses, one confirmed by the response evaluation criteria in solid tumors (7% response rate). Nine patients (60%) had stable disease lasting at least 42 days, with four (27%) lasting for at least 90 days. Disease stabilization (partial responses + stable disease) was observed in 11 (73.3%) patients. In conclusion, ispinesib was well tolerated when administered on days 1 and 15 every 28 days. Limited activity was observed with this schedule in patients with previously untreated advanced breast cancer. ***Anti-Cancer Drugs*** **23:335–341 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2012, **23**:335–341

Keywords: breast cancer, dose-limiting toxicity, ispinesib, kinesin spindle protein inhibitor, pharmacokinetics, phase I

[a]National Institute of Neoplastic Diseases (INEN), [b]Alberto Sabogal Solguren National Hospital, Lima, Peru, [c]I3 Research, Lima, Peru and Buenos Aires Argentina and [d]Cytokinetics Inc., South San Francisco, California, USA

Correspondence to Rafael Escandon, PhD, MPH, Cytokinetics Inc., 280 E Grand Ave, South San Francisco, California 94080, USA
Tel: +1 650 624 3000; fax: +1 650 624 3225; e-mail: Rafaele12@yahoo.com

Received 3 June 2011 **Revised form accepted** 23 October 2011

Introduction

Ispinesib (formerly SB-715992) is a kinesin spindle protein (KSP) inhibitor studied in more than 500 cancer patients to date. KSP, also known as Eg5, is a motor protein that functions exclusively during mitosis, translating energy from ATP hydrolysis into mechanical force for movement along microtubules [1]. This movement drives the organization of the mitotic spindle [2,3]. Unlike other antimitotic agents, such as the antitubulins that target the microtubule in both proliferating and nonproliferating cells, KSP inhibitors target the kinesin spindle, which is present only in proliferating cells. Therefore, some of the toxicity associated with antimitotics, such as neuropathy, can be eliminated. Ispinesib has demonstrated significant antitumor activity, including complete regressions, in several mouse syngeneic and xenograft tumor models, including models considered chemorefractory [4]. Intermittent dosing schedules provided the best efficacy in these models. In human breast cancer xenograft models, single agent ispinesib produced regressions in all models tested, including estrogen receptor (ER) positive, human epidermal growth factor 2 (HER2) positive, and triple negative models; activity was comparable with that observed for paclitaxel and ixabepilone [4]. Ispinesib enhanced the activity observed with other breast cancer standard of care therapies (doxorubicin, capecitabine, trastuzumab, and lapatinib).

Several dosing schedules of ispinesib have been explored in phase I clinical studies in adult patients with solid tumors: days 1, 8, and 15 every 28 days [5], days 1–3 every

0959-4973 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e32834e74d6

21 days [6], and an every 21-day schedule [7]. The day 1, 8, and 15 every 28-day schedule has also been explored in pediatric patients with solid tumors [8] and the daily X3 schedule has been explored in adult leukemia patients [9]. Several phase II studies in a variety of adult solid tumors have been conducted with ispinesib administered every 21 days [10]. The most promising activity was observed in metastatic breast cancer, where four out of 45 (9%) evaluable patients, all of whom had received at least one prior chemotherapy regimen for metastatic disease, had a response evaluation criteria in solid tumors (RECIST)-confirmed partial response [11,12]. In all studies, the dose-limiting toxicity (DLT) was neutropenia, with minimal gastrointestinal toxicity and little to no neurotoxicity. On the every 21-day schedule, neutrophil nadir was observed at day 7 with recovery by day 14, suggesting that an alternate schedule with dosing every 14 days might increase dose density without compromising safety.

On the basis of the above data, this study was designed to determine whether a higher dose density can be achieved without compromising safety by ispinesib administration every 14 days. A patient population in which activity had been observed previously (advanced breast cancer) was selected to optimize potential antitumor activity; this was further optimized by selecting patients with limited or no prior chemotherapy.

Methods

Eligibility

The protocol received internationally accredited Ethics Committee review and approval at all participating centers. Patients provided written, ethics committee approved, informed consent before study participation.

Female patients aged 18 years or older with histologically or cytologically confirmed, evaluable or measurable, locally advanced, or metastatic breast cancer were eligible. Patients must not have received prior cytotoxic chemotherapy for breast cancer other than one prior neoadjuvant or one prior adjuvant regimen (including taxanes) and a minimum of 1 year must have elapsed from such treatment. Prior hormonal therapy and targeted therapy were permitted. Patients had to have an Eastern Cooperative Oncology Group performance status of 0–1; absolute neutrophil count of at least 1.5×10^9/l; platelet count of at least 100×10^9/l; adequate hepatic organ function: alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase) less than $2 \times$ upper limit of normal (ULN) in the absence of liver metastases and less than $5 \times$ ULN in the presence of liver metastases, alkaline phosphatase less than $5 \times$ ULN, and total bilirubin less than $1.5 \times$ ULN; and adequate renal function (creatinine clearance < 40 ml/min). Women of child-bearing potential must have been practicing appropriate birth control methods. Patients were not permitted to have radiation therapy within the past 28 days; concurrent active malignancies; leptomeningeal or brain metastases; and uncontrolled coexisting medical conditions.

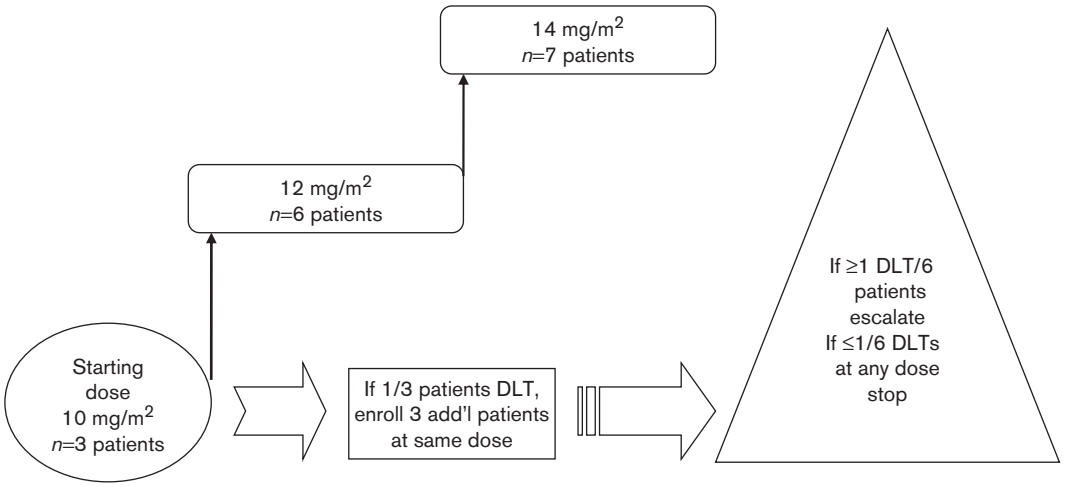
Study design

This was an open-label, nonrandomized, dose-escalation study of ispinesib that enrolled patients at two sites in Lima, Peru. Figure 1 illustrates the study design and enrollment by dose of the trial. The study was originally planned as a phase I–II study with further evaluation of the maximum tolerated dose (MTD) identified in the phase I portion of the study; however, the phase II portion of the study was not conducted. Ispinesib was supplied by Cytokinetics Inc., South San Francisco, California, USA, and was administered as a 1-h intravenous infusion on days 1 and 15 of a 28-day cycle. Dosing was continued until disease progression, intolerable toxicity, or patient withdrawal due to other reasons.

The study used a three-by-three design, with patients recruited in cohorts of three, at an initial dose of 10 mg/m^2 and with dose escalation occurring in 2 mg/m^2 increments once all patients in a cohort had completed the first 28-day cycle. If one DLT was observed in the initial three patients at any dose, the cohort was expanded to six patients. If no more than zero out of three or one out of six patients experienced DLT in cycle 1, the dose was escalated in a cohort of three new patients following agreement with investigators. MTD was defined as the dose at which no more than one out of six patients experienced DLT. A DLT was defined as any drug-related toxicity observed during the first 28 days (cycle 1) that included at least grade 3 nonhematological (excluding nausea/vomiting and alopecia); grade 3 nausea/vomiting/diarrhea lasting more than 10 days despite treatment; grade 4 neutropenia lasting at least 5 days without hematopoietic growth factor support or febrile grade 3 neutropenia (absolute neutrophil count $< 1.0 \times 10^9$/l with a fever $\geq 38.5^\circ$C); grade 4 thrombocytopenia (platelet count $< 25 \times 10^9$/l); grade 4 anemia (hemoglobin < 6.5 g/dl) lasting more than 7 days and not due to hemorrhage or diffuse bone marrow infiltration; at least grade 2 nonhematologic toxicity persisting beyond cycle 1 that the investigator considered dose limiting; or grade 2 toxicity that the investigator and the sponsor considered to be dose limiting. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3 [13]. Investigators were instructed by the protocol to conduct an examination of strength and sensation if patients reported neurotoxicities (sensory or motor neuropathies) that were not present before baseline.

Laboratory evaluations (hematology, clinical chemistry), ECGs, and physical examination including vital signs and neurological assessment were performed at baseline and before each cycle. Hematology and chemistry laboratory

Fig. 1



Enrollment by dose. DLT, dose-limiting toxicity.

assessments were also performed after each dose of ispinesib. Response was assessed by investigators using RECIST [12]. Imaging was performed at baseline, after completion of cycle 1, and after every two cycles of treatment and at discontinuation. Responses were confirmed no less than 28 days after the initial response. The assessment after cycle 1 was included to identify early disease progression and to allow early initiation of alternative treatment in any patient showing signs of early progression.

Pharmacokinetic methods and analysis

Limited pharmacokinetic (PK) sampling was performed. Results by ispinesib dose are presented in Table 4. PK blood samples (6 ml per sample) were drawn before and following dosing on days 1 and 15 of cycle 1 at the following time points: baseline, completion of infusion (1 h), 2–4 h after infusion, and 24–36 h after infusion. PK parameters were summarized by dose level using descriptive statistics (mean, standard deviation, minimum, median, maximum, and percent coefficient of variation). Samples were collected in potassium-EDTA tubes and centrifuged at 2500*g* for 10 min at 5°C. Plasma was frozen at −20°C until analysis. Ispinesib (molecular weight, 517.1) quantification was performed using a high-pressure liquid chromatography–mass spectrometry assay validated (Cedra Corporation, Austin, Texas, USA) over a range of 0.1–100 ng/ml (~0.19–193 nmol/l). Ispinesib was harvested from 0.2 ml human plasma by liquid–liquid extraction, using 2.1 ml (total volume) of 1 : 1 acetonitrile: distilled H_2O, 1.0 mol/l sodium carbonate, and methyl tert-butyl ether containing 10 ng of an isotopically labeled internal standard, ispinesib-D4. Following centrifugation, the upper organic layer was removed and evaporated. The sample was then reconstituted in the mobile phase (acetonitrile:distilled H_2O:formic acid:ammonium hydroxide; 900 : 100 : 1.00 : 0.25) and an aliquot was analyzed using Sciex API 4000 (Foster City, California, USA) HPLC-MS-MS equipped with a TurboIonSpray interface along with quality control samples (0.30, 20.0, and 80.0 ng/ml). The peak area of the mass-to-charge ratio (m/z) 517→247 of ispinesib product ion was measured against the peak area of the m/z 521→251 of the ispinesib-D4 internal standard product ion. Quantification was performed using a weighted ($1/x^2$) linear least squares regression analysis generated from calibration standards prepared immediately before each run. PK analysis was performed using WinNonlin Enterprise Edition version 4.0 (PharSight Corporation, St Louis, Missouri, USA) noncompartmental methods. Concentration–time data that were below the limit of quantification (0.100 ng/ml) were treated as zero (0.00 ng/ml) in the data summarization and descriptive statistics. Nominal protocol sample times were used for all PK and statistical analyses. The following PK parameters were calculated: C_{max}, T_{max}, C_{last}, T_{last}, $T_{1/2}$, area under the curve (AUC), AUC_{last} AUC_{inf}, AUC_{Extrap} (%), λz, clearance, mean residence time, V_z, and V_{ss}.

Statistical methods

The primary objectives of the phase I portion of the study were to determine the DLT and MTD of ispinesib administered as a 1-h intravenous infusion on days 1 and 15 of a 28-day cycle and to assess the overall safety and tolerability of this regimen. The safety population consisted of all patients receiving at least one dose of ispinesib. The efficacy evaluable population consisted of all participants who received at least one dose of study medication and for whom baseline and at least one posttreatment efficacy evaluation were available.

Results

Disposition and demographics

Between 21 November 2007 and 4 July 2008, 16 patients were enrolled at two study sites in Lima, Peru, into one of three dose levels: 10 mg/m^2 ($n = 3$), 12 mg/m^2 ($n = 6$), and 14 mg/m^2 ($n = 7$). The median number of treatment cycles was 3 (range, 1–20). All 16 patients discontinued study treatment. The reasons for discontinuation included progressive disease (PD) ($n = 5$), investigator decision ($n = 4$), symptomatic deterioration ($n = 3$), withdrawal of consent by the patient ($n = 3$), and pregnancy ($n = 1$).

Table 1 summarizes patient demographics and baseline cancer characteristics. All patients were Mestizo or Hispanic women. The median age was 50 ± 14 years. The median time since the initial diagnosis was only 1.5 months (range of 0–65 months). At study entry, 44% of patients had locally advanced disease and 56% had metastatic disease. Half the patients were ER positive, 44% were progesterone receptor (PR) positive, and 25% were HER2 positive. Five patients (31%) were triple (ER, PR, and HER2) negative. Sites of metastases at study entry included the lymph nodes ($n = 15$, 93.8%), lung ($n = 6$, 38%), liver and bone ($n = 3$ each, 19%), pleura ($n = 2$, 13%), and adrenal gland ($n = 1$, 6%). All patients had measurable disease per RECIST at baseline, except for one, who had evaluable disease only (bone lesions and a small solitary pulmonary nodule).

Table 1 Patient disposition and demographics

	N (%)
Age (years)	
Median (±SD)	50 ± 14
Range	26–82
Race/ethnicity	
Hispanic	10 (62.5)
Mestizo	6 (37.5)
Menopausal status	
Postmenopausal	6 (37.5)
Histology	
Ductal	15 (93.8)
Medullary	1 (6.3)
Time since diagnosis (months)	
Median	1.5
Range	0–65
Cancer stage at study entry	
Stage IIIb	6 (37.5)
Stage IIIc	1 (6.3)
Stage IV	9 (56.3)
Sites of metastases	
Lymph nodes	15 (93.9)
Lung	6 (37.5)
Liver	3 (18.8)
Bone	3 (18.8)
Pleura	2 (12.5)
Adrenal gland	1 (6.3)
Receptor status	
ER+	8 (50.0)
PR+	7 (43.8)
HER2+	4 (25.0)
ER−/PR−/HER2−	5 (31.3)
ECOG performance status	
0	9 (56.3)
1	7 (43.8)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER, human epidermal growth factor 2; PR+, progesterone receptor positive; SD, standard deviation.

Table 2 Prior anticancer treatments, *N* (%)

Prior mastectomy	4 (25.0%)
Prior radiation therapy	4 (25.0%)
Prior hormonal therapy	2 (12.5%)
Prior chemotherapy	
Any	5 (31.2%)
Neoadjuvant	3 (18.8%)
Adjuvant	3 (18.8%)
Anthracycline	5 (35.7%)
Taxane	4 (28.6%)

Prior treatments are summarized in Table 2. The majority of the patients (69%) had not received any prior systemic anticancer therapy, either chemotherapy, targeted therapy, or hormonal therapy. Of the five patients who had received prior chemotherapy, three (60%) had two prior regimens and two (40%) had one prior regimen. Neoadjuvant and adjuvant chemotherapy were each provided in three (19%) patients. Two patients had received prior hormonal therapies, both as adjuvant treatment. Five (31%) patients had prior anthracycline and four (25%) had prior taxane.

Determination of maximum tolerated dose and safety results

Two DLTs, both transient grade 3 aspartate aminotransferase (AST) and ALT increases, were observed at 14 mg/m^2. Both patients remained in the study without dose reduction without further toxicity. These were the only two DLTs reported in the study. The MTD was determined to be 12 mg/m^2.

Table 3 summarizes AEs reported in one or more patients during the study. The most common AEs, reported in at least three patients, included neutropenia ($n = 14$, 87.5%), increased ALT ($n = 9$, 56.3%), anemia ($n = 6$, 37.5%), increased AST and diarrhea ($n = 5$, 31.3%), increased alkaline phosphatase ($n = 4$, 25.0%), and leukopenia, thrombocythemia, nausea, vomiting, headache, and breast pain ($n = 3$, 18.8%). No AEs of neuropathy, mucositis, or alopecia were reported.

The only grade 3 and grade 4 AEs reported were neutropenia (grade 3, $n = 6$, 37.5%; grade 4, $n = 7$, 43.8%), ALT and AST increased (grade 3, $n = 2$, 12.5%), and febrile neutropenia (grade 3), thrombocytopenia (grade 4; likely a laboratory error), pleural effusion (grade 3), and spontaneous abortion (grade 4), each $n = 1$, 6.3%. The spontaneous abortion occurred in a patient who had a negative pregnancy test at study entry but was found to be pregnant following the completion of cycle 1 dosing. Because of the pregnancy, post-treatment imaging was not performed and the patient was excluded from the study. There were no grade 5 AEs. No notable changes in ECG measurements, including Bazett's corrected Q–T interval, vital signs, or physical exam including neurological assessments, were observed.

Table 3 Adverse events reported in three or more patients in cycle 1 only (*N*, %)

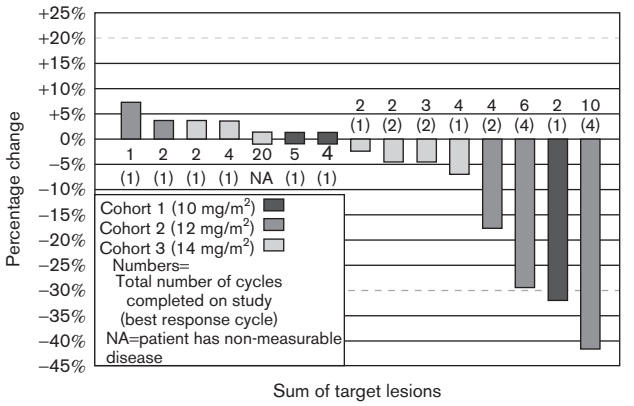
	Dose (mg/m^2)							
	10 (*N*=3)		12 (*N*=6)		14 (*N*=7)		Total (*N*=16)	
Adverse event	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Neutropenia	2 (67%)	1 (33%)	5 (83%)	4 (67%)	7 (100%)	7 (100%)	14 (88%)	12 (75%)
ALT increased	0	0	4 (67%)	0	5 (71%)	2 (29%)	9 (56%)	2 (13%)
AST increased	0	0	2 (33%)	0	3 (43%)	2 (29%)	5 (31%)	2 (13%)
Anemia	0	0	3 (50%)	0	4 (57%)	0	7 (44%)	0
Diarrhea	1 (33%)	0	1 (17%)	0	2 (29%)	0	4 (25%)	0
Alk. Phos. increased	0	0	0	0	3 (43%)	0	3 (19%)	0
Nausea	2 (67%)	0	1 (17%)	0	0	0	3 (19%)	0

ALT, alanine aminotransferase; Alk. Phos., alkaline phosphatase; AST, aspartate aminotransferase.

Antitumor activity

Fifteen patients (93.8%) were efficacy evaluable; one patient became pregnant during the study, was excluded, and did not have post-treatment imaging performed. According to the investigators' assessments, there were three responses: no complete responses and three partial responses (20%); only one partial response was confirmed by RECIST, for an overall response rate of 6.7%. As can be seen, when data are summarized as a waterfall plot (Fig. 2), additional patients showed significant reductions in the sum of target lesions, not quite reaching the 30% reduction required for partial response by RECIST. Nine patients (60%) had stable disease (SD) lasting at least 42 days and four (27%) for at least 90 days. Disease stabilization (partial response + SD) was observed in 11 (73.3%) patients. Three patients (20%) had the best response of PD.

Fig. 2



Waterfall plot of response.

The confirmed partial response was in a 57-year-old woman with ER positive, PR positive, and HER2 positive metastatic breast cancer treated at 12 mg/m^2. She had received prior adjuvant chemotherapy (without a taxane) and hormonal therapy. Partial response was observed after four cycles of ispinesib and confirmed after the fifth cycle, with a significant reduction in liver metastases. The maximum reduction in sum of target lesions was 45% and the duration of partial response was 17 weeks. The two unconfirmed partial responses were at 10 and 12 mg/m^2, respectively, with a maximum reduction in the sum of target lesions of 31 and 30%, respectively; PD was observed within 4 weeks. In addition, one patient with nonmeasurable disease (small solitary pulmonary nodule and bone lesions), treated at the highest dose (14 mg/m^2), experienced SD for greater than 20 cycles.

Pharmacokinetic results

Descriptive PK parameters were calculated using non-compartmental methods. Because of a sparse sampling scheme, the full PKs of ispinesib cannot be completely described. Available PK data (Table 4) suggest that systemic exposure of ispinesib was not dose proportional over the dose range of 10–14 mg/m^2. The mean C_{max} ($C^{1\,h}$/end of infusion) and AUC_{last} on day 1 were 349 ± 107 ng/ml (10 mg/m^2), 223 ± 48.5 ng/ml (12 mg/m^2), and 213 ± 109 ng/ml (14 mg/m^2). On day 15, the mean C_{max} and AUC_{last} were 396 ± 129 ng/ml (10 mg/m^2), 248 ± 136 ng/ml (12 mg/m^2), and 230 ± 68.7 ng/ml (14 mg/m^2). There was no significant difference in drug exposure between days 1 and 15.

Discussion

This phase I study was designed to explore a new dosing schedule of ispinesib in a patient population in whom antitumor activity had been observed before. The goal was to increase dose density in anticipation of increased antitumor activity, without compromising safety. Prior studies with alternate dosing schedules had demonstrated that neutropenia was dose-limiting, with an MTD of 18 mg/m^2 (dose density = 0.86 mg/m^2/d) on the most studied every 21-day schedule. On the every 14-day schedule explored in this study, neutropenia was significant but not dose limiting. Instead, hepatic toxicity appeared to be dose limiting, with two patients experiencing transient grade 3 increases in hepatic transaminases, with smaller increases in alkaline phosphatase and bilirubin. No other significant toxicity was observed. Of interest, no neuropathy, mucositis, or alopecia was reported, which are all associated with

Table 4 Mean day 1 ispinesib concentration–time data

	10 mg/m^2				12 mg/m^2				14 mg/m^2			
Time (h)	*n*	Mean (ng/ml)	SD (ng/ml)	CV (%)	*n*	Mean (ng/ml)	SD (ng/ml)	CV (%)	*n*	Mean (ng/ml)	SD (ng/ml)	CV (%)
0	3	0	0	0	6	4.75	11.6	244.9	7	0.02	0.06	264.6
1	3	349	107	30.6	6	223	48.5	21.7	7	213	109	51.1
3	3	95.1	38.8	40.8	6	98.5	26.7	27.1	7	106	27.8	26.3
25	3	35.4	5.0	14.1	6	33.2	5.7	17.3	6	38.2	13.8	36.2

Plasma samples analyzed using a method with a validated range of 0.100–100 ng/ml.
CV, coefficient of variation; SD, standard deviation.

antitubulin agents such as paclitaxel and ixabepilone. The laboratory abnormalities noted above met the protocol definition for DLT, and therefore, MTD was determined to be 12 mg/m^2. This is the same dose density as that achieved with the every 21-day schedule. Although DLT was reached on the basis of the protocol definition, the protocol did not take into account that many patients with metastatic breast cancer have hepatic metastases that may compromise liver function and that transient hepatic enzyme increases may reflect antitumor activity as well as toxicity. Both of the patients with grade 3 increases in hepatic transaminases had resolution to grade 1 levels with a temporary interruption of dosing. When dosing was resumed without dose reduction, there was no recurrence of toxicity. Therefore, it is questionable as to whether DLT was actually reached or whether the definition of DLT should have allowed for a more liberal assessment of hepatic transaminase increases in the presence of hepatic metastases. Other studies with ispinesib administered on other dosing schedules have been associated with only mild (grade 1–2) increases in hepatic enzymes in 15–20% of patients [3–10]. However, in the studies in adult leukemia patients treated daily X3 every 21 days and in the pediatric solid tumor study with a day 1, 8, and 15 every 28-day schedule [8], hepatic toxicity was dose limiting. It is unclear from the current study whether hepatic toxicity is truly dose limiting on an every 14-day schedule. Further evaluation may be warranted, either in patients without hepatic metastases or with a DLT definition that addresses the issue of hepatic metastases.

One patient achieved RECIST-confirmed partial response in this study for a confirmed response rate of approximately 7%, similar to the 9% response rate reported in a more heavily pretreated metastatic breast cancer population treated at the same dose density on an every 21-day schedule [11]. This response rate is disappointing, given that 69% of the patients enrolled in this study had no prior chemotherapy or targeted therapy for their disease, with the remaining having only prior neoadjuvant or adjuvant chemotherapy. However, it should be noted that the patients enrolled included a large proportion of patients without distant metastases, as well as patients who were HER2 positive or triple negative. This study was conducted in Peru, where the initial presentation of disease is somewhat different from other countries and access to early diagnostic resources is more limited. Hence, many patients with extensive locally advanced disease were enrolled in the study. Perhaps this population does not respond as well to systemic chemotherapy when the local disease has not been surgically reduced or irradiated. Also, HER2-positive patients may benefit from anti-HER2-targeted therapy first, followed by ispinesib, or a combination approach. Other KSP inhibitors in development such as SB-743921 have demonstrated that dosing regimens that included concomitant granulocyte-colony stimulating factor support mitigate hematologic toxicities (i.e. high-grade neutropenia) similar to those observed at or near the MTDs determined in the ispinesib development program [14]. Preclinical studies with ispinesib have also shown clear and significant synergistic activity of ispinesib with trastuzumab and lapatinib [4].

Despite the low response rate, the waterfall plot (Fig. 2) does show significant activity of ispinesib in aggregate, in this population. Many patients showed clearly measurable reductions in the sum of their target lesions that approached but did not meet the RECIST criteria for partial response. It should also be noted that three patients were excluded from the study due to 'symptomatic deterioration', predominantly breast pain or enlargement, again suggesting that perhaps locally advanced disease without optimized local management may not respond as well to systemic therapy with ispinesib.

Other sponsors considering similar clinical trials in similar regions where access to worldwide-best standard of care is limited or unavailable should note that this protocol's safety and ethical strategies of mandatory early disease assessments, rapid discontinuation of an ineffective agent, and making the worldwide best-known treatments available to the investigator for prescription to their patients according to their own clinical judgment were, in the opinions of the investigators, sponsor, ethical committees, and ministry of health, the only acceptable approach to explore the questions of whether a more dose-dense regimen or prior treatments affected the efficacy of ispinesib in a breast cancer population that would hypothetically be less resistant to primary chemotherapy.

Conclusion

Antimitotic agents are among the mainstays of therapy for advanced breast cancer. Unfortunately, they are associated with significant neurotoxicity that can be disabling as well

as alopecia, fatigue, and gastrointestinal disturbances that affect quality of life. The availability of an antimitotic that maintains the efficacy of existing antimitotics while reducing neurotoxicity, with minimal or absent alopecia and gastrointestinal disturbances, would be welcome in the treatment armamentarium. To date, ispinesib has met this latter goal but has not yet achieved the former. Additional studies may be warranted with the every 14-day or other schedules, either with a modified DLT definition or a slightly different patient population with less potentially complicating metastatic disease.

Acknowledgements

The authors would like to express their gratitude to the patients who volunteered for treatment in this trial as well as their families. In addition, special thanks are due to all members of the study staff who were diligent and dedicated to the conduct of the study.

This clinical trial was sponsored by Cytokinetics Inc., South San Francisco, California 94080, USA. The nonsponsor authors have no disclosures. Cytokinetics employees and consultants are paid directly by the sponsor and may be company shareholders.

Conflicts of interest

There are no conflicts of interest.

References

1 Blangy A, Lane HA, d'Hérin P, Harper M, Kress M, Nigg EA, *et al*. Phosphorylation by p34cdc2 regulates spindle association of human Eg5, a kinesin-related motor essential for bipolar spindle formation in vivo. *Cell* 1995; **83**:1159–1169.

2 Marcus AI, Peters U, Thomas SL, Garrett S, Zelnak A, Kapoor TM, Giannakakou P. Mitotic kinesin inhibitors induce mitotic arrest and cell death in Taxol-resistant and sensitive cancer cells. *J Biol Chem* 2005; **280**:11569–11577.

3 Lad L, Carson JD, Dhanak D, Jackson JR, Huang PS, Lee Y, *et al*. Mechanism of inhibition of human KSP by ispinesib. *Biochemistry* 2008; **47**:3576–3585.

4 Purcell JW, Reddy M, Davis J, Martin S, Samayoa K, Vo H, *et al*. *Ispinesib* (SB-715992) a kinesin spindle protein (KSP) inhibitor has single agent activity and enhances the efficacy of standard-of-care. In: *Therapies in Pre-Clinical Models of Breast Cancer. 31st Annual San Antonio Breast Cancer Symposium (SABCS)*. San Antonio, TX. December 2008. Poster presentation.

5 Burris HA, Lorusso P, Jones S, Guthrie TM, Orr JB, Williams DD, *et al*. Phase I trial of novel kinesin spindle protein (KSP) inhibitor SB-715992 IV days 1, 8, 15 q 28 days. ASCO Meeting Abstracts 2004; 22.

6 Heath EI, Alousi A, Eder JP, Valdivieso M, Vasist LS, Appleman L, *et al*. A phase I dose escalation trial of ispinesib (SB-715992) administered days 1-3 of a 21-day cycle in patients with advanced solid tumors. American Society of Clinical Oncology (ASCO), June, 2006.

7 Chu QS, Holen KD, Rowinsky EK, Wilding G, Volkman JL, Orr JB, *et al*. Phase I trial of novel kinesin spindle protein (KSP) inhibitor SB-715992 IV Q 21 days. ASCO Meeting Abstracts 2004; 22:2078.

8 Souid A-K, Dubowy RL, Ingle AM, Conlan MG, Sun J, Blaney SM, Adamson PC. A pediatric phase 1 study of ispinesib: a children's oncology group phase 1 consortium study. *Pediatr Blood Cancer* 2010; **55**:1323–1328.

9 LoRusso P, Jones JB, Gadgeel1 S, Willcutt N, Helmke1 W, Orr J, *et al*. A phase I study to determine the safety and pharmacokinetics of intravenous administration of SB-715992, a novel kinesin spindle protein (KSP) inhibitor, on a once weekly for three consecutive weeks schedule in patients with refractory solid tumors. European CanCer Organization (ECCO) Annual Meeting; 2003.

10 Chu Q, Holen KD, Rowinsky EK, Alberti DB, Monroe P, Volkam JL, *et al*. A phase I study to determine the safety and pharmacokinetics of IV administered SB-715992, a novel kinesin spindle protein (KSP) inhibitor, in patients with solid tumors. ASCO Meeting Abstracts 2003; 22: Abstract 525.

11 Data on File. GSK 20001 Ispinesib in Locally Advanced and Metastatic Breast Cancer Study Report.

12 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al*. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; **92**:205–216.

13 Common Terminology Criteria for Adverse Events CTCAE (v 3.0). National Cancer Institute. Available at *http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf*. [Accessed 29 May 2011].

14 O'Connor OA, Gerecitano J, Van Deventer H, Afanasyev B, Hainsworth J, Chen MM, *et al*. A Phase I/II Trial of the Kinesin Spindle Protein (KSP) Inhibitor SB-743921 Dosed Q14D without and with Prophylactic G-CSF in Non-Hodgkin Lymphoma (NHL) or Hodgkin Lymphoma (HL). American Society of Hematology, 51st Annual Meeting and Exposition. December 2009. Poster presentation.