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Phase 1 First-in-Human Trial of the Vascular Disrupting Agent Plinabulin (NPI-2358) in Patients with Solid Tumors or Lymphomas

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Abstract

Purpose: Plinabulin (NPI-2358) is a vascular disrupting agent that elicits tumor vascular endothelial architectural destabilization leading to selective collapse of established tumor vasculature. Preclinical data indicated plinabulin has favorable safety and antitumor activity profiles, leading to initiation of this clinical trial to determine the recommended phase 2 dose (RP2D) and assess the safety, pharmacokinetics, and biologic activity of plinabulin in patients with advanced malignancies.

Experimental Design: Patients received a weekly infusion of plinabulin for 3 of every 4 weeks. A dynamic accelerated dose titration method was used to escalate the dose from 2 mg/m² to the RP2D, followed by enrollment of an RP2D cohort. Safety, pharmacokinetic, and cardiovascular assessments were conducted, and Dynamic contrast-enhanced MRI (DCE-MRI) scans were performed to estimate changes in tumor blood flow.

Results: Thirty-eight patients were enrolled. A dose of 30 mg/m² was selected as the RP2D based on the adverse events of nausea, vomiting, fatigue, fever, tumor pain, and transient blood pressure elevations, with DCE-MRI indicating decreases in tumor blood flow (Ktrans) from 13.5 mg/m² (defining a biologically effective dose) with a 16% to 82% decrease in patients evaluated at 30 mg/m². Half-life was 6.06 ± 3.03 hours, clearance was 30.50 ± 22.88 L/h, and distributive volume was 211 ± 67.9 L.

Conclusions: At the RP2D of 30 mg/m², plinabulin showed a favorable safety profile, while eliciting biological effects as evidenced by decreases in tumor blood flow, tumor pain, and other mechanistically relevant adverse events. On the basis of these results additional clinical trials were initiated with plinabulin in combination with standard chemotherapy agents. *Clin Cancer Res; 16(23); 5892–99. ©2010 AACR.*

Vascular disrupting agents (VDA) such as plinabulin are a rapidly advancing class of oncology therapeutics that elicit antitumor activity by selectively disrupting established tumor vasculature. The differences between tumor neovasculature and normal vasculature have been recognized for over 20 years, and a number of drugs targeting the growth of the tumor vasculature (e.g., sunitinib and bevacizumab) have become standard of care validating this approach (1, 2). These agents principally target the vascular endothelial growth factor (VEGF) pathway to inhibit tumor angiogenesis. Because VDAs target the existing tumor vasculature through a different set of molecular targets by exploiting the lack of structural support and dependence on proliferating vascular endothelial cells, there is an *a priori* expectation, supported by preclinical and clinical data that the efficacy and toxicity profiles of VDAs will be different from, and complementary to, the VEGF targeted agents and standard cytotoxic agents (3–6). In particular, the principal toxicities of VDAs have been neurologic, cardiac, transient hypertension, and tumor pain as opposed to events such as myelosuppression, mucositis, prolonged hypertension, and bleeding events. This lends strong support to not only develop this new class of oncology agents, but to do so in combination with cytotoxic and VEGF targeted agents, and clinical trials are ongoing combining standard agents with VDAs, in at least 1 case with a regimen that includes bevacizumab (6). The strongest support for VDAs has come from the marked improvement in overall survival seen in a randomized phase 2 study comparing carboplatin–paclitaxel with carboplatin–paclitaxel–DMXAA (5,6-dimethylxanthenone-4-acetic acid) in patients with advanced non–small

Translational Relevance

This article describes the first evaluation of the novel vascular disrupting agentplinabulin (NPI-2358) in humans. As the chemical structure of plinabulin is novel, being a synthetic analogue of a marine microorganism product, preclinical evaluation indicated properties that were different from other members of the class, including efficacy and toxicity profiles. This clinical trial determined the recommended phase 2 dose, biologic effect dose, pharmacokinetic, pharmacodynamic, and safety profiles of plinabulin in patients, confirming the preclinical findings, and led to the continued clinical assessment in combination with standard of care cancer therapies.

cell lung carcinoma (NSCLC) (5,6-dimethylxanthenone-4-acetic acid), leading to the initiation of a phase 3 study (National Institutes of Health: ASA404 or placebo in combination with paclitaxel and carboplatin as first-line treatment for stage IIIb/IV non–small cell lung cancer, http://www.clinicaltrials.gov/ct2/show/NCT00662597; refs. 7, 8). Particular advantage can be envisioned for VDAs in NSCLC compared with other classes of drugs in terms of the apparent lack of relevance of squamous cell carcinoma histology and bleeding risk with VDAs (8).Plinabulin is a VDA of novel structure, being derived as a synthetic analogue of a marine microbial product, that binds the colchicine binding site of β-tubulin preventing polymerization, thus disrupting the cytoplasmic microtubule network resulting in loss of morphology and cytoxicity in rapidly proliferating immature tumor neovascular endothelial cells (9, 10). The tumor neovasculature is particularly susceptible to these effects given the lack of supporting structures found in normal vasculature and dependence on proliferating endothelial cells. Plinabulin was shown to produce antitumor activity in animal models alone and synergistically with chemotherapy agents including taxanes, without worsening, and even improving chemotherapy tolerability in some cases (11, 12). Overall, preclinical studies indicated plinabulin had a favorable safety and activity profile leading to the initiation of this single agent phase 1 first-in-human trial, with the objective of determining the recommended phase 2 dose (RP2D) of plinabulin, and defining the pharmacokinetic, pharmacodynamic, and safety profiles.

Materials and Methods

Patient selection

Patients with advanced solid tumors or lymphomas who were not candidates for further standard therapy and ages 18 years or more were eligible. Patients were required to have Eastern Cooperative Oncology Group performance status 2 or less and adequate hematopoietic, electrolyte, hepatic, renal, coagulation, and cardiac laboratory results. Patients were excluded if they had chemo, biologic, immune or radiotherapies or major surgery within 3 to 6 weeks, significant cardiac history, anticoagulant, anticonvulsant, or QTc prolonging medication use, history of VDA therapy, seizure disorder, brain metastases, gastrointestinal bleeding disorders, vascular disorders, chronic obstructive pulmonary disease (COPD), central chest tumors, whole abdomen or perioperative pelvic radiotherapy or residual gastrointestinal/neurologic/pulmonary symptoms from radiation therapy, pregnant, breast feeding, or experiencing a significant active infection or second malignancy. On the basis of greater understanding of the relevant safety profile from the data that had been accrued during the escalation portion of the protocol, during the RP2D Cohort restrictions based on the calcium and magnesium levels, anticoagulant use, central chest tumors, and COPD were removed, whereas those relevant to cardiac function, hemoglobin, platelets (hemoglobin $\geq$ 9 g/dL, platelet count $\geq$ 100 $\times$ 10^9/L, troponin I within normal limits, brain natriuretic peptide (BNP) within normal limits, QTcF $\geq$ 450 ms and left ventricular ejection fraction (LVEF) $\geq$ 60% changed to hemoglobin $\geq$ 8.5 g/dL, platelet count $\geq$ 75 $\times$ 10^9/L, QTcF $\geq$ 475 ms and LVEF $\geq$ 50%), and prior radiation therapy (to excluding only prior whole abdomen radiation therapy) were reduced. The study was conducted in accordance with the Declaration of Helsinki Ethics committee approval and informed consent was obtained prior to participation.

Study design and drug treatment

Plinabulin was administered via intravenous (IV) infusion over 15 or 30 minutes depending on infusate volume on days 1, 8, and 15 of 4-week cycles. A dynamic accelerated dose titration dose escalation design described later in the text was used with a starting dose of 2 mg/m^2. Escalations were initially made in approximately 100% increments, until grade 2 or more toxicity was observed in cycle 1, then escalations were made in increments of 50% or less. Dose level cohorts enrolled 1 patient per cohort until a grade 2 adverse event was observed in cycle 1. Thereafter, at least 3 patients were enrolled per cohort. If, during a subsequent 3 patient cohort, no grade 2 or more adverse event was observed in cycle 1, the following cohort could again consist of a single patient. Dose limiting toxicity (DLT) was defined by cycle 1 grade 4 hematologic toxicity, grade 3 nonhematologic toxicity (excluding alopecia, anorexia, fatigue, and nausea, vomiting or diarrhea controlled with optimal supportive care and/or prophylaxis), QTc prolongation (QTcF $\geq$ 500 or 60 ms increase from baseline), troponin elevation (levels consistent with unstable angina per each manufacturer's assay specifications) or LVEF decrease (>15% to less than 50%). If 1 patient experienced a DLT, then the cohort was increased to 6 patients. If no further patients experienced a DLT, then the next dose level could be evaluated. If 2 or more patients in a cohort experienced DLT, then the previous dose level was considered the maximum tolerated dose (MTD). Any dose level at or below an MTD could be selected as the RP2D based on safety, pharmacokinetic, and/or pharmacody-

namic data. Up to 12 additional patients could be enrolled at the RP2D dose level. Patients who were not evaluable (not having received 3 infusions in cycle 1 without having been withdrawn secondary to DLT) were replaced. Treatment was continued in individual patients until progressive disease, toxicity of DLT-level, or requiring a 14-day treatment delay in spite of a dose reduction, or withdraw from study by patient or investigator decision. Intrapatient dose escalations to the next highest dose tested were allowed for individual patients, provided the higher dose level had been determined to be below the MTD.

Study drug

Plinabulin {NPI-2358: 2,5-piperazinedione, 3-[[5-(1,1-dimethylethyl)-1H-imidazol-4-yl]methylene]-6-(phenyl-methylene)-, (3Z,6Z)} is a yellow to orange solid supplied as a solution in 40% Solutol HS-15/60% propylene glycol in amber vials containing 80 mg of drug in 20 mL (4 mg/mL). Plinabulin is stored at 15°C to 30°C and protected from light at all times. The drug is diluted in dextrose 5% in water at a dilution between 1:20 and 1:200 and administered IV with an in-line filter within 6 hours. The starting dose of 2.0 mg/m^2 was based on repeated dose toxicology studies, as approximately 1/10 the STD$_{10}$ (severely toxic dose 10%) in the rodent and 1/6 the HNSTD (highest nonseverely toxic dose) in the dog (the single dose MTD was approximately 50 mg/m^2).

Study assessments

Physical exam, performance status, CBC, serum chemistry, troponin I, BNP, and coagulation parameters were assessed weekly. Vital signs were taken before, after, 30, 60, and 120 minutes and ~2–4 hours after infusion. Electrocardiograms (ECG), echocardiograms, and urinalysis were obtained before and after infusion on days 1 and 15 in cycle 1, then on day 15 in subsequent cycles. Dynamic contrast-enhanced MRI (DCE-MRI) were obtained twice at baseline and approximately 4 hours after infusion on day 1, with additional studies obtained as feasible day 2, and day 15 of every other cycle. DCE-MRIs were analyzed centrally by a blinded reader at VirtualScopics. Adverse events reported were described using MedDRA coding and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Response was assessed per the response evaluation criteria in solid tumors for patients with solid tumors, and the International workshop to standardize response criteria for non-Hodgkin's lymphoma for patients with lymphoma (13, 14). Tumor measurements were obtained at baseline and every 8 to 12 weeks thereafter or as clinically indicated.

Pharmacokinetics

Blood sampling was performed predose, at the end of the infusion, at 15 and 30 minutes, and 1, 2, 4, 6, and 8 hours after infusion on days 1 and 15 (based on initial pharmacokinetic data, a 24-hour time point was added during the RP2D Cohort). Validated methods were used to analyze

plasma samples for the concentration of plinabulin by high-performance liquid chromatography (HPLC) with tandem mass spectrometry (MS). NPI-2358 and NPI-2386 (internal standard) were extracted from human plasma by liquid–liquid extraction using methyl-t-butyl ether: methylene chloride [75:25 (v/v)], the organic layer was evaporated to dryness and reconstituted in water: methanol [50:50 (v/v)]. The HPLC separation was conducted with 50 × 2.0 mm Luna, C8(2) columns, and HPLC/MS/MS detection was achieved using an /\PI 4000 mass spectrometer in negative electrospray ionization mode. Assays were performed at Tandem Labs and MPI Research).

Results

Demographics

Table 1 summarizes patient demographics and tumor histologies. Male/female ratio was well balanced. Performance status was good in the majority of patients. Patients with a broad range of malignancies were enrolled.

Treatment delivered

Table 2 provides dose levels tested and number of patients at each level. The median number of cycles received was 2 and median time on treatment was 1.5 months. Dose escalation was continued up to 30 mg/m^2 at which point toxicity was felt acceptable without DLT observed in this cohort, but significant, and indications of biologic effect such as DCE-MRI findings, hypertension, tumor pain, and fever were significant and

Table 1. Patient demographics

Characteristic	No. of patients
Median age (years)	56 .5 (28–76)
Male/female	24/14 (63%/37%)
Eastern Cooperative Oncology Group (ECOG) PS 0–1/2	32/6 (84%/16%)
Colorectal carcinoma	11
Sarcoma	4
Melanoma	4
Pancreatic carcinoma	3
Adenocystic	2
Breast carcinoma	2
Hemangiopericytoma	2
Renal cell carcinoma	2
Thyroid	2
Adrenocortical carcinoma	1
Anal squamous cell carcinoma	1
Esophageal carcinoma	1
Prostate cancer	1
Diffuse large cell non-Hodgkin's lymphoma	1
Squamous cell carcinoma head and neck	1

Table 2. Dose escalation schedule

Cohort	Dose (mg/m^2)	No. of patients
1	2	1
2	4	1
3	6	3
4	9	3
5	13.5	8
6	20	4
7	30	5
RP2D	30	13

comparable to findings reported at RP2Ds of other VDAs. Therefore, being less than an MTD, this dose was selected as the RP2D based on balancing tolerance and biologic effect. Thirteen patients were enrolled in the RP2D cohort, as 1 patient withdrew prior to becoming evaluable.

Safety

Table 3 lists adverse events reported in 10% or more of patients. Nausea, vomiting, tumor pain, and fever were considered the most common plinabulin induced side effects. It was unclear whether the remaining adverse events reported in Table 3 represented differences from what is expected as a baseline incidence in this patient population. Transient elevations in blood pressure were seen with

posttreatment vital sign assessments. Trends in changes of hematologic, chemistry, or coagulation parameters were not identified. One DLT of pulmonary embolus was reported in Cohort 5 (13.5 mg/m^2), leading to expansion of this cohort. No further DLTs were reported through Cohort 7 (30 mg/m^2). Although 9 grade 3-4 adverse events were reported in total in the 18 patients treated at 30 mg/m^2, only 5 of these events occurring in 3 patients were attributed as at least possibly related to study drug, as described in the following text, and largely controlled with additional supportive care or prophylaxis (vomiting, pain, and diarrhea).

Regarding the serious adverse events reported, as expected, a number were attributed to the underlying malignancy, such as dyspnea, pneumonia, and bowel obstruction. One patient developed pulmonary emboli and another deep venous thrombosis (attributed to the underlying malignancy). Infusion reaction was reported in which case the patient's symptoms were principally bradycardia associated with syncope or near syncope. Plinabulin was emetogenic and occasionally significant enough to result in dehydration or electrolyte disturbances and resulted in hospitalization in 2 patients. One patient reported 2 days of grade 3 nausea, vomiting, and diarrhea beginning 5 days after the last dose of plinabulin in cycle 2, resolving with antiemetics. Another patient reported 2 episodes of grade 3 vomiting, which were attributed to disease related esophageal stricture and candidiasis. Nausea and vomiting

Table 3. Adverse events reported in ≥10% of patients (regardless of attribution)

Adverse events	2–4 mg/m^2 ($n = 2$)		6–9 mg/m^2 ($n = 6$)		13.5–20 mg/m^2 ($n = 12$)		30 mg/m^2 ($n = 18$)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Nausea			1		7		14	1
Pain	1		4		6		11	3
Fatigue	1		1		5		6	
Vomiting			1		4		11	2
Pyrexia/fever	1		1		3		5	
Infection			1		2		5	
Anemia	1				1		6	
Constipation			1		3	1	6	
Diarrhea					3		9	1
Anorexia					2		7	
Dysgeusia					1		5	
Hypertension			1		2		3	
Headache					1		9	
Hypokalemia						1	4	
Arthralgia					1		3	
Dry mouth			1		1		5	
Dyspnea	1		1				3	1
Weight decrease							4	
Oedema peripheral	1				3		1	
Dizziness							5	
Insomnia			2				3	
Confusion state	1		1				1	1

generally occurred the day of and/or day following plinabulin administration. This was generally responsive to serotonin receptor antagonist antiemetics, and premedication with antiemetics was subsequently recommended. Tumor pain is also a known effect of VDAs and 3 patients in this study were hospitalized for pain management after plinabulin administration. One case of chest pain was reported in conjunction with drug induced emesis, without evidence of myocardial ischemia, and the patient continued to receive treatment with antiemetic prophylaxis without recurrence. Back pain in the 2 other patients was attributed to underlying disease leading to withdrawal from study for disease progression in 1 patient and continued treatment with antiemetics and analgesics without recurrence in the other. Two cases of mental confusion were attributed to polypharmacy with opiates, benzodiazapines, steroids, and/or dehydration, with these conclusions supported by continued plinabulin treatment without recurrence. A myocardial infarction occurred in a 73-year-old female with 95% left anterior descending and 50% circumflex stenosis 14 days after the sixth plinabulin treatment. This patient was removed from study as a significant decrement in cardiac function resulted. No significant drug-related neurologic events were reported in this study. Intensive cardiac monitoring including ECGs, echocardiograms, troponins, and BNPs did not indicate plinabulin affects cardiac functions such as systolic function (LVEF determined by echocardiography) or QT interval (QTcF), in spite of plinabulin administration and monitoring being continued for up to 2 years. Of note, only the patient experiencing a myocardial infarction showed a significant decrease in LVEF. ECGs did not suggest plinabulin increases QTc interval, in fact, mean QTcF interval was minimally and nonsignificantly shorter after plinabulin administrations. Transient elevations in blood pressure were also seen in the majority of patients treated at or above the biologically effective dose (BED), although these were often not sufficient to elicit reporting as an adverse event. A mean 18% increase in diastolic blood pressure was seen immediately after infusion, with a return to baseline 2 to 4 hours later in most patients.

Pharmacokinetics

Figure 1 shows the concentration maximum (Cmax) and area under the curve (AUC) dose level relations for plinabulin. Pharmacokinetic analysis of plinabulin indicated Cmax and AUC were dose proportional over the range of 2 to 30 mg/m^2 without evidence of drug accumulation. Mean Cmax and $AUC_{0-\infty}$ increased from 34.4 to 527 ng/mL, and from 101 to 3319 ng/mL·h, respectively. Mean $T_{1/2}$ was 6.35 hours, mean clearance was 31 L/h, and mean distributive volume was 208 L.

Tumor response

No confirmed responses were reported, however, a notable rate of stable disease (30% after 2 cycles) was observed, along with interesting outcomes in several patients. Four patients maintained stable disease for 4 months or more, including a patient with pancreatic adenocarcinoma
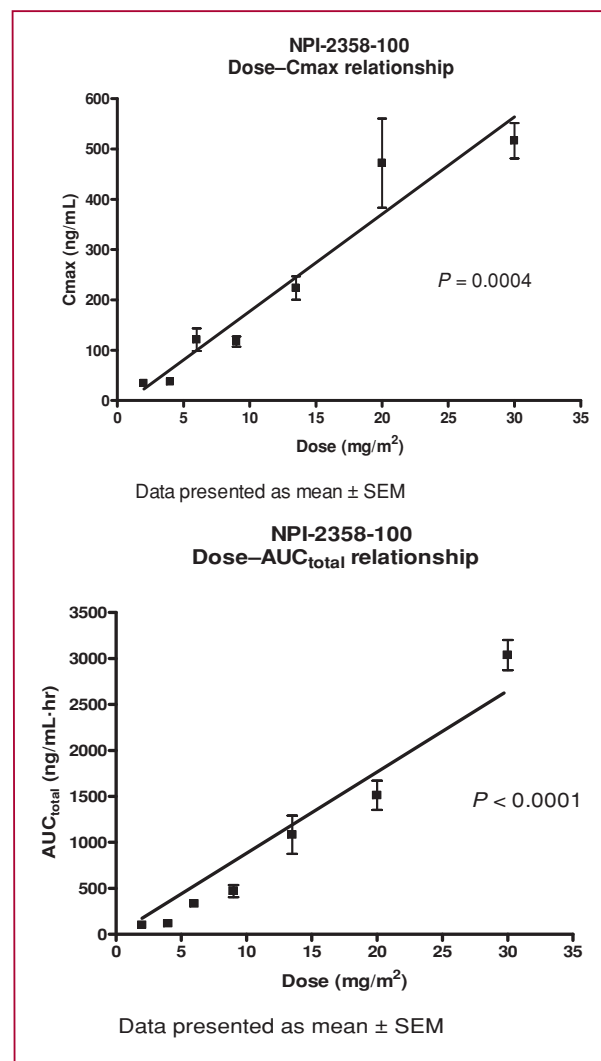

Fig. 1. Cmax and AUC by plinabulin dose level.

(4 months), and 1 with hemangiopericytoma (2 years; imaging assessments corresponded with this outcome, in that Ktrans decreased by 82% on DCE-MRI and contrast enhancement disappeared from his lesions on CT scan).

Pharmacodynamics

Changes in tumor blood flow were assessed using DCE-MRI in 17 patients. As seen in Figure 2, there was a trend in dose relationship with decreasing Ktrans as a surrogate for tumor blood flow. Objective tumor vascular response (reduction greater than 20%, based on previously measured uncertainty of ±10%) was not seen in any patients dosed at 6 mg/m^2 or 9 mg/m^2, but was observed in 2/5 (40%) patients dosed at 13.5 mg/m^2 and 20 mg/m^2, and in 7/9 (77%) patients dosed at 30 mg/m^2. At the highest dose level, a statistically significant reduction was seen in both Ktrans ($\mu = -18.4\%$, 95% CI = −27 to −9.6, $P = 0.006$) and AUC blood normalized (AUCBN; ref. 90) ($\mu = -17.7\%$, 95% CI = −24 to −11, $P = 0.001$). No
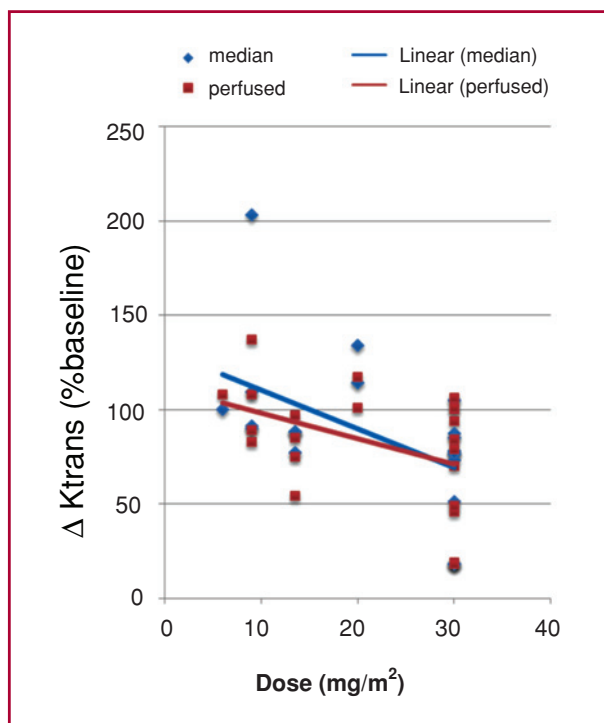
Fig. 2. Change in Ktrans from baseline by plinabulin dose level.

significant reduction was seen in the lower dose cohorts in either Ktrans ($\mu = 11.2\%$, 95% CI = −12 to 34, $P = 0.472$) or AUCBN(90) ($\mu = 0.38\%$, 95% CI = −12 to 13, $P = 0.964$). These data, in combination with the appearance of class-associated adverse events, indicate the BED is between the dose levels of 9 to 13.5 mg/m².

Discussion

Plinabulin (NPI-2358) is a VDA that elicits tumor vascular endothelial architectural destabilization leading to selective collapse of established tumor vascular with additional direct cytotoxic effects (11, 12). In this study, a dose of 30 mg/m² was determined to be the RP2D on this schedule. Plinabulin was generally well tolerated without apparent irreversible or cumulative toxicities. Adverse events commonly ascribed to plinabulin at this dose included transient hypertension, tumor pain, fatigue, fever, and nausea/vomiting. Relevant adverse events and changes in DCE-MRI parameters became apparent at doses at and above 9.0 to 13.5 mg/m², thus this was determined to be the BED range. Consistent with what was predicted by preclinical toxicological assessment, plinabulin did not appear to induce QTc prolongation or impair LVEF, and the incidence of cardiac and neurologic events was not notably different than what would be expected in a phase 1 oncology population. Plinabulin also did not appear to affect hematologic, chemistry, or coagulation parameters, which is of particular interest given indications that doc-

etaxel induced neutropenia is markedly reduced when plinabulin is given with docetaxel (15).

Serious adverse events included infusion reaction, myocardial infarction, vomiting, confusion, and pain. Regarding infusion reaction, the symptoms consisted principally of bradycardia associated with syncope. As reported with CA-4P administration (16), these may represent a reactive decrease in heart rate from the transient increases in blood pressure or emesis induced by plinabulin as opposed to an allergic reaction. Emesis is a clear effect of plinabulin, which was occasionally significant enough to result in hospitalization in the absence of adequate antiemetic prophylaxis. However, this was generally limited to the day following plinabulin administration and manageable with antiemetics, thus routine antiemetic use before and after administration was subsequently recommended in this and other protocols. Tumor pain is a known effect of VDAs, and is proposed to result from structural and pain mediator effects on surrounding tissues from the tumor necrosis elicited by these drugs. As expected, the occurrence and severity was seen to have significant interpatient variability, and was generally managed well with analgesics and/or improved with continued treatment. Of particular interest, only 1 significant cardiac adverse event was reported, myocardial infarction remote from plinabulin administration, which differs from multiple occurrences of acute postinfusion ischemia reported in studies with a number of other VDAs. Furthermore, intensive cardiac monitoring did not show that plinabulin affects cardiac function, other than the transient changes in blood pressure and heart rate described.

Compared with toxicokinetic data in monkeys, the Cmax and AUC values reported in this study are consistent with what is expected in the range of a dose of 20 to 40 mg/m², which approximates the range from the no observed adverse effect level to the level where adverse effects begin to become evident. These also approximate levels that are effective in preclinical models, where plinabulin produces tumor cytotoxicity and loss of proliferative vascular endothelial cell morphological integrity in the 10 to 20 nmol/L range.

As is common with vascular targeted agents such as angiogenesis inhibitors and VDAs, pharmacodynamics were assessed with DCE-MRI. Plinabulin appears to have a measurable effect on tumor blood flow beginning at a dose level of 13.5 mg/m². This effect is dose dependent. These results are similar to published results with other VDAs (6–9). Although anecdotal, the corresponding outcomes in other imaging modalities (stable disease with CT scanning) are interesting in that VDAs are thought to produce optimal responses when used in combination with other agents, given that peripheral tumor cells are perfused by the surrounding normal tissue vasculature protecting them from vascular targeted therapies, but are conversely the most susceptible to cytotoxic agents and radiation (17).

A number of VDAs have recently entered phase 2/3 clinical trials: DMXAA (vadimezan) in NSCLC [phase 3

with carboplatin–paclitaxel in first line and phase 3 with docetaxel in second line; a study of ASA404 or placebo in combination with docetaxel in second-line treatment for (Stage IIIb/IV) non–small cell lung cancer (ATTRACT-2), http://www.clinicaltrials.gov/ct2/show/NCT00738387]; CA4-P (fosbretabulin) in NSCLC (phase 2 with carboplatin–paclitaxel–bevacizumab), anaplastic thyroid carcinoma (phase 2/3 with carboplatin–paclitaxel), and ovarian carcinoma (phase 2 with carboplatin–paclitaxel; a study to assess the effectiveness of the combination of carboplatin, paclitaxel, bevacizumab, and combretastatin (CA4P) in patients with chemotherapy naive lung cancer, http://clinicaltrials.gov/ct2/show/NCT00653939; a study of combretastatin and paclitaxel/carboplatin in the treatment of anaplastic thyroid cancer, http://clinicaltrials.gov/ct2/show/NCT00507429; ref. 18); AVE8062 in sarcoma (phase 2/3 with cisplatin; a study of AVE8062 in advanced-stage soft tissue sarcoma after failure of anthracycline and ifosfamide chemotherapies; ref. 19); and MPC-6827 in glioblastoma (phase 2 with carboplatin; phase 2 study MPC-6827 for recurrent glioblastoma multiforme, http://www.clinicaltrials.gov/ct2/show/NCT00892931; ref. (20). At this mid stage of development some interesting trends are becoming apparent with these agents. Indications of improvements in efficacy outcomes have thus far been reported in NSCLC and ovarian cancer. Of note, loss of efficacy and hemoptysis in patients with NSCLC having squamous cell histology do not seem to be issues. VDAs do not seem to produce some of the toxicities associated with cytotoxic agents or angiogenesis inhibitors such as myelosuppression or bleeding events, but complementary efficacy has been suggested with both angiogenesis inhibitors and cytotoxics. Many questions still remain to be answered and are being addressed to some extent in these trials, include optimal scheduling, differentiation of toxicities related to the class as opposed to the structure of specific drugs, and determination of biomarkers and toxicities that correlate with or predict efficacy. With regards to the pattern of toxicities elicited by these agents as a class, it appears most VDAs produce transient hypertension and tumor pain in varying percentages of patients. On the other hand, ischemic events, QTc prolongation and neurologic toxicities have been associated with some VDAs but not others, thus may be related to the structure of the individual drug (i.e., "off target" effects, differential interactions with the same target, or differences in pharmacokinetics, metabolism or distribution). With the size of the current published data sets, variability, and incidence of the events relevant to what is expected in oncology patient populations with significant concomitant morbidities and medications, however, it is difficult to make firm conclusions at this time.

Overall, this study indicates that weekly plinabulin is generally well tolerated at 30 mg/m^2. The occasional occurrence of significant, albeit manageable, toxicity at 30 mg/m^2, along with evidence of significant biological effects and pharmacokinetic correlative data, indicate that this dose is at or close to maximizing antitumor effects within the limits of tolerability, leading to its selection as the RP2D for subsequent study. These results combined with preclinical studies showing plinabulin synergizes with docetaxel in NSCLC models, led to the initiation of a phase 1/2 study with plinabulin combined with docetaxel in patients with NSCLC (the ADVANCE study; refs. 15, 21). Interim data suggested that the addition of plinabulin was increasing tumor response rate whereas decreasing docetaxel induced neutropenia. Of interest, the indication of a BED of approximately 13.5 mg/m^2 in the current study led to the comparison of 20 mg/m^2 to the RP2D of 30 mg/m^2 plinabulin in the ADVANCE study to assess whether the dose could be lowered to an "optimal biologic dose" without overtly decreasing antitumor efficacy. As clinical and preclinical data suggest significant potential for VDAs in a number of malignancies, including differential use from other vascular targeted agents in selected patient subsets, additional studies of plinabulin in combination with standard therapies are planned in other solid tumors. In particular, combinations with plinabulin and irinotecan in colorectal carcinoma models and paclitaxel in breast carcinoma models suggest pursuing these combinations in clinical trials (11).

Disclosure of Potential Conflicts of Interest

Acknowledgment

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