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PHASE I STUDIES

Phase 1 study of the novel vascular disrupting agent plinabulin (NPI-2358) and docetaxel

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Summary *Background* Plinabulin (NPI-2358) is a vascular disrupting agent (VDA) that destabilizes tumor vascular endothelial cell architecture resulting in selective collapse of established tumor vasculature producing anti-tumor activity alone or in combination with cytotoxic agents. The objective of this study was to assess the recommended Phase 2 dose (RP2D) of plinabulin combined with docetaxel. *Patients and Methods* Patients received 75 mg/m^2 docetaxel on day 1 and plinabulin on days 1 and 8 intravenously in 21 day cycles. Plinabulin was escalated from the biologically effective dose (BED) of 13.5 mg/m^2 to the standard single agent dose of 30 mg/m^2 using a "3+3" design. *Results* Thirteen patients were enrolled. Adverse events were consistent with those of both agents alone. Fatigue, pain, nausea, diarrhea and vomiting were the most common events. One dose limiting toxicity of nausea, vomiting, dehydration and neutropenia occurred. The RP2D was 30 mg/m^2 of plinabulin with 75 mg/m^2 docetaxel. Pharmacokinetics did not indicate drug-drug interactions. Of the 8 patients with NSCLC evaluable for response, 2 achieved a partial response and 4 demonstrated lesser decreases in tumor measurements. *Conclusions* The combination of full doses of plinabulin and docetaxel is tolerable. With encouraging antitumor activity, this supported further development of this combination.

Keywords Angiogenesis · Docetaxel · Non-small cell lung cancer (NSCLC) · Vascular disrupting agent (VDA) · Vascular targeting

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Introduction

Tumor vasculature is a validated drug target in oncology, with the differences between tumor vasculature and normal vasculature now being exploited by several drugs that have been approved for use by the FDA and other regulatory agencies based on improvements in efficacy in a number of oncology indications. Tumor blood vessels differ from normal blood vessels in their immature characteristics, in particular structural disorganization. Indeed, tumor vessels are tortuous and composed largely of rapidly proliferating endothelial cells, and are characterized by poor structural support lacking connective tissue, pericytes and smooth muscle as well as by high permeability [1–3]. Vessel growth through endothelial cell proliferation and migration is induced by a number of growth factors in particular vascular endothelial growth factor (VEGF), a pathway that has been successfully targeted both through antibodies

against VEGF (e.g. bevacizumab) and small molecule inhibitors of the vascular endothelial growth factor receptor (VEGFR) (e.g. sunitinib and sorafanib), leading to regulatory approval of these agents for the treatment of colorectal, lung, breast, renal cell and hepatocellular carcinomas [4–9].

Vascular disrupting agents (VDAs) are a class of oncology drugs of which clinical evaluation has recently progressed into Phase 3 trials. Like agents targeting the VEGF pathway, VDAs selectively target tumor blood vessels. They do so, however, through different molecular targets, affecting the structure of existing tumor vascular endothelium instead of the growth of the neovasculature through the VEGF pathway. To this point, the efficacy and safety profiles of VDAs, cytotoxic agents and anti-angiogenesis agents appear to largely differ, and there is in fact data supporting combining members of all three classes to improve the efficacy of current regimens [10–13]. In particular, although transient as opposed to maintained hypertension is seen with VDAs, toxicities of concern for VDAs have generally been neurotoxicity or cardiac toxicity, but not myelosuppression, mucositis or bleeding events [14–16]. There have been indications of activity in patients with NSCLC with good safety, including those with squamous cell carcinoma where other classes of standard of care agents have been challenged [14, 17, 18].

Plinabulin is a novel VDA which elicits selective disruption of established tumor vascular by binding to the colchicine binding site of β-tubulin inhibiting polymerization. This leads to loss of cytoskeletal function, and thus morphology and cohesion in immature endothelial cells, resulting in tumor vascular endothelial architectural destabilization and selective tumor vascular collapse. Plinabulin also demonstrated direct cytotoxicity to rapidly proliferating cells, which may contribute to proliferating endothelial cell and/or tumor cell cytotoxicity. In having been discovered as a synthetic analogue of the chemical halimide isolated from a marine fungus, the chemical structure and properties of plinabulin differ significantly from other VDAs, and particularly from combretastatin analogs that also act on the colchicine binding site [19]. The binding site and effect on tubulin dynamics are also different from those of vinca alkaloids and taxanes, resulting in the differences in mechanism of action (predominance of anti-vascular vs. cytotoxic effects), safety and efficacy profiles. Clinical evaluation of plinabulin was begun based on the hypothesis that the structural differences would result in improved efficacy and toxicity profile from these other tubulin binding agents, as was indicated by preclinical animal studies. Plinabulin was evaluated as a single agent in a dose escalation Phase 1 study in patients with advanced malignancies [20]. Toxicities frequently attributed to plinabulin included nausea, vomiting, fatigue, fever, tumor pain and transient blood pressure elevations, with a noticeable paucity of effect on cardiac or neurologic function. The recommended phase 2 dose (RP2D) was found to be 30 mg/m^2, with a biological effect dose (BED) of 13.5 mg/m^2 at which pharmacodynamic and adverse event data indicated plinabulin to be affecting tumor blood flow. Plinabulin also induces tumor regression alone and synergistically with other standard chemotherapeutic agents in tumor models, as illustrated by synergistic efficacy and improved tolerance when plinabulin and docetaxel are combined in murine NSCLC models [21, 22]. Based on these findings, as well as on clinical trial data from plinabulin and other VDAs, this clinical trial was initiated with the objective of assessing the basis for a Phase 2 evaluation of plinabulin in combination with docetaxel, including the safety, pharmacokinetics and preliminary evidence of anti-tumor activity, leading to determination of a maximum tolerated dose and/or recommended Phase 2 dose of the combination.

Patients and methods

Eligibility

Patients were eligible if they had advanced non-small cell lung cancer that had progressed after treatment with at least one chemotherapy regimen or another metastatic malignancy for which docetaxel could be used, were ≥18 years of age, with Eastern Cooperative Oncology Group performance status ≤1 with adequate hematopoietic, electrolyte, hepatic, renal, coagulation and cardiac laboratory findings and had signed informed consent. Patients were excluded if they had specified oncology therapies within 3–12 weeks (depending on the therapy) prior to study entry, significant cardiac history, requirement for anti-coagulant or anti-convulsant use, history of VDA or docetaxel treatment, seizure disorder, brain metastases, specified gastrointestinal bleeding disorders and vascular disorders, a history of whole abdomen or perioperative pelvic radiotherapy, or were pregnant, breast feeding, or had a significant active infection or second malignancy. The presence of measureable disease was not required. The study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval and informed consent were obtained prior to participation.

Study design

A 3+3 dose escalation design was used. Patients were entered into cohorts of at least 3 patients starting with the initial dose group at 13.5 mg/m^2 plinabulin (the single agent Biologically Effective Dose (BED), the dose at which biologic effects of plinabulin on tumor blood flow appear

[20]) and 75 mg/m^2 docetaxel (the FDA approved dose for docetaxel in NSCLC). The dose of plinabulin was escalated in sequential patient cohorts after the safety data from cycle 1 was reviewed. Thereafter, the dose of plinabulin in each subsequent cohort was escalated by approximately 50% increments. If one patient of a cohort experienced dose limiting toxicity (DLT), then the cohort was expanded to at least six evaluable patients. If no more than one of the 6 patients experienced a DLT, then the next dose level could be evaluated. If two or more patients entered in any cohort experienced a DLT, then the maximum tolerated dose (MTD) had been exceeded, and the previous dose level would be considered the MTD. Any dose level at or below an MTD could be selected as the RP2D based on safety and/or pharmacokinetic data. Intrapatient dose escalations were allowed with escalation to the next highest dose tested for individual patients, provided patients in the higher dose level cohort had completed at least one treatment cycle and it was below the MTD. DLT was defined as the occurrence of any of the following drug related adverse events during Cycle 1 as defined by the Common Terminology Criteria for Adverse Events (CTCAE v3.0): Grade 4 hematologic adverse events of duration >7 days, Clinically significant ≥ Grade 3 non-hematologic adverse events, with the exception of alopecia, anorexia and fatigue (Grade ≥ 3 nausea, vomiting, or diarrhea would only be considered a DLT if not controlled with optimal supportive care and/or prophylaxis) or any treatment delay >14 days secondary to recovery from drug related adverse events.

Treatment

Plinabulin {NPI-2358; 2,5-piperazinedione, 3-[[5-(1,1-dimethylethyl)-1 H-imidazol-4-yl]methylene]-6-(phenylmethylene)-, (3Z,6Z)} is a yellow to orange solid supplied as a solution in 40% Solutol® HS-15 and 60% propylene glycol in amber vials containing 80 mg of drug in 20 mL (4 mg/mL). Plinabulin was stored between 15–30°C (59–86°F) and protected from light at all times. The drug was diluted in dextrose 5% in water (D5W) at a dilution between 1:20 and 1:200 and administered intravenous (IV) with an in-line filter.

Commercially available vials of docetaxel injection concentrate were initially diluted with diluent (13% ethanol in water for injection) resulting in a 10 mg docetaxel/mL solution. The appropriate volume was then transferred into 250 mL of 5% dextrose solution (or 0.9% Sodium Chloride solution) for injection [23].

Study drugs were administered in 21-day cycles. On day 1 docetaxel was administered via IV infusion at 75 mg/m^2 over 1 h, followed 2 h later (from the time the docetaxel infusion began) by plinabulin, which was administered via IV infusion over 30 min. Oral dexamethasone (16 mg) was given the day prior to, the day of and the day following docetaxel infusion (day 1). On day 8, only plinabulin was administered via IV infusion over 30 min.

Depending on the assessment, in patients experiencing drug related Grade ≥2 treatment emergent adverse events according to the CTCAE (v3.0) treatment could be delayed until the adverse event has recovered to ≤ Grade 1. Safety laboratory tests needed to meet the following criteria prior to re-dosing: AST ≤ 2.5 × ULN, ALT ≤ 2.5 × ULN (≤1.5 × ULN if alkaline phosphatase is ≥2.5 × ULN); bilirubin ≤ ULN; creatinine ≤ ULN; hemoglobin ≥9 g/dL, absolute neutrophil count ≥1.5 × 10^9/L and platelets ≥100 × 10^9/L.

Intrapatient dose escalation to the next highest dose tested could occur for individual patients (to occur at the start of the next cycle), provided all patients in the higher dose level cohort had completed at least one cycle with ≤1/6 (0/3) patients experiencing a first cycle DLT, and the patient considered for intrapatient dose escalation had not experienced prior drug related Grade 3 or greater adverse events.

If a patient had a study-defined DLT assessed as related to plinabulin or the combination of plinabulin with docetaxel, as their worst adverse events during a cycle or if a patient required a 14 day (inclusive) delay in therapy during a cycle (in order to meet minimum requirement for re-treatment), then the plinabulin dose was to be reduced to that of the next lowest level tested for the subsequent cycle. If the patient subsequently experienced a DLT-Grade adverse events or dose delay ≥14 days within a cycle utilizing a reduced plinabulin dose, then the patient was to be removed from the study.

The following actions were to be taken in case of toxicities commonly associated with docetaxel administration (a similar dose reduction algorithm could be used in accordance with local institutional practices if approved by the Medical Monitor). In case of febrile neutropenia or ANC <500/mm^3 for >1 week or Grade 4 thrombocytopenia, docetaxel was to be withheld until ANC >1,500/mm^3 and platelets >100,000/mm^3, then resumed at 50 mg/m^2. For severe or cumulative cutaneous reactions or grade 3/4 non-hematologic docetaxel related toxicities docetaxel was to be withheld until resolution and then resumed at 50 mg/m^2. For AST/ALT >2.5 to ≤5 × ULN, or AST/ALT > 1.5 to ≤5 × ULN and AP > 2.5 to ≤5 × ULN the docetaxel dose was to be reduced by 20%. For grade 3/4 peripheral neuropathy or AST/ALT or AP > 5 × ULN, docetaxel was to be discontinued.

Antiemetics such as serotonin antagonists or lorazepam could be used at the discretion of the investigator after documented nausea or vomiting has occurred during a previous infusion without antiemetics. High-dose steroids were not to be used as antiemetic therapy. Similarly, use of antidiarrheals such as loperamide and diphenoxylate/atropine

was permitted at the discretion of the investigator after documented diarrhea had occurred without medications having been used. Use of hematologic support, such as erythropoietin, darbopoetin, G-CSF, or platelet transfusions, within 4 weeks of the first dose of study drug, in order to meet entry criteria was not permitted. Initiation of erythropoietin or darbopoetin during the first 4-week cycle was discouraged in the absence of severe anemia

Clinical and laboratory evaluations

Physical exam, performance status, complete blood counts (CBC), and serum chemistry were assessed at baseline and weekly on study. Troponin I was tested at baseline and on cycle 1 day 8. Coagulation parameters and urinalysis were collected at baseline only. Vital signs were taken before and immediately after infusion and at 30, 60 and 120 min after infusion during cycle 1. Collection of electrocardiograms (ECG) was amended into the study during the 30 mg/m^2 cohort. ECGs were performed in triplicate at baseline, cycle 1 day 1 and cycle 2 day 1 one hour after infusion of plinabulin. Tumor measurements were assessed every 2nd cycle for patients with measureable disease at study entry, in accordance with the response evaluation criteria in solid tumors (RECIST). Adverse events reported were described using MedDRA coding and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAEv3.0).

Pharmacokinetic evaluations

Blood sampling was performed on day 1 and day 8. On day 1, both plinabulin and docetaxel plasma samples were drawn before, 0.5 and 1 h after docetaxel infusion, prior to end of plinabulin infusion and 15, 30 min, and 1, 2, 3, 4, 6 and 24 h after plinabulin infusion. On day 8, plinabulin plasma samples were collected before plinabulin infusion, prior to end of plinabulin infusion, and 15, 30, and 1, 2, 3, 4, 6 and 24 h after plinabulin infusion. Validated methods were used to analyze plasma samples for the concentration of plinabulin and docetaxel by high-performance liquid chromatography with tandem mass spectrometry.

Docetaxel was isolated and quantified in human plasma by High Performance Liquid Chromatography (HPLC) coupled to a tandem Mass Spectrometer Detector (LC/MS/MS). Docetaxel and internal standard (doecetaxel d9) were extracted from acidified human plasma with 20% methanol in dichloromethane. The organic phase was evaporated to dryness and the samples reconstituted with 0.2% acetic acid in 50:50 methanol:water. The HPLC separation is conducted with Waters Sunfire C18 2.1x30mm columns and LC/MS/MS detection is achieved using an API 5,000 in positive electrospray ionization mode. Blanks, double blanks and calibration curves were run with all assays (MPI Inc., State College, PA; MPI Research Method No. V0004287-2).

Plinabulin and NPI-2386 (internal standard) are extracted from human plasma by liquid-liqui 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 mm Luna C8 (2) columns and LC/MS/MS detection is achieved using an API 4,000 in negative electrospray ionization mode. Blanks, double blanks and calibration curves were run with all assays (Tandem Inc., Salt Lake City, UH; Tandem Laboratories Study No. TSLS05-184).

Results

Patient characteristics

Between March 2008 and February 2009, 13 patients received a total 55 cycles of the combination over three dose levels. Table 1 summarizes patient demographics and tumor histologies.

Treatment delivered

The dose of plinabulin was escalated from 13.5 mg/m^2 (Cohort 1, 3 patients) through 20 mg/m^2 (Cohort 2, 3 patients) to 30 mg/m^2 (Cohort 3, 7 patients). One patient enrolled in the 13.5 mg/m^2 cohort was inadvertently treated with 30 mg/m^2 plinabulin, and received 2 cycles at this dose prior to being withdrawn secondary to progressive

Table 1 Patient demographics

	Patients (13)
Median age (years)	57 (45–69)
Male/Female	8/5 (62%/38%)
ECOG PS 0/1	5/8 (38%/62%)
Number of Cycles Delivered	55
Median (range) number of cycles delievered	4 (1–8)
Median (range) number of prior chemotherapy regimens	1 (1–4)
Median (range) number of prior radiation therapy regimens	0 (1–2)
NSCLC—Adenocarcinoma	7
NSCLC—Large cell carcinoma	2
NSCLC—Squamous cell carcinoma	1
Gastrointestinal Stromal Tumor (GIST)	1
Liposarcoma	1
Melanoma	1

disease (pharmacokinetic and safety data for this patient were analyzed with the 30 mg/m^2 cohort). A total of 55 cycles were delivered. The median number of cycles patients received was 4 (range 1–8) and median time on treatment was 2.5 months. Only one patient was reported to have a dose delayed, during the process of being removed from study for progressive disease. There were no deaths due to study drug toxicity reported. One patient treated at 30 mg/m^2 experienced a DLT consisting of nausea, vomiting, dehydration and neutropenia, and the cohort was therefore expanded to contain at least 6 evaluable patients. This was also the only patient with dose modification on study, being dose reduced from 30 mg/m^2 plinabulin to 20 mg/m^2 plinabulin and from 75 mg/m^2 docetaxel to 50 mg/m^2 docetaxel. A total of 7 patients were enrolled in this cohort without additional DLTs. At this point the single agent RP2D of plinabulin [20] had been reached and evidence of antitumor activity reported, leading to the selection of 30 mg/m^2 plinabulin in combination with 75 mg/m^2 docetaxel as the RP2D.

Safety

Table 2 lists adverse events reported in 10% or more of patients and Table 3 lists serious adverse events reported. Fatigue, pain, nausea, diarrhea and vomiting were the most common events. Nausea/vomiting and tumor pain were felt most clearly consistent with the previously reported effects of both plinabulin and docetaxel, with it being unclear whether the remainder represents differences from what is expected as background incidence in this population. Tumor pain is also a known effect of VDAs. There were no patients in this study that were hospitalized for pain management after plinabulin administration. Transient hypertension or elevated blood pressure is also thought to be elicited by plinabulin based on post-treatment vital sign assessments, although the degree of elevation of blood pressure was generally not sufficient to elicit reporting as an adverse event of hypertension. With regards to hematologic toxicity, one patient each was reported to have a clinically significant adverse event of neutropenia and anemia on study. In weekly CBCs results, 3 patients each were seen to have grade 2 and 3 neutrophil counts, and one grade 4, at some point on study. Nine patients were seen to have hemoglobin levels one grade lower on study compared to baseline at some point on study, and one patient was seen to have a two grade level decrease. Only 2 patients were seen to have grade 1 decreases in platelet counts at any time on study. ECGs did not demonstrate any QTc interval increases ≥30 msec, ≥60 msec or to ≥500 msec.

Regarding the serious adverse events reported (principally being defined by adverse events that elicited hospitalization), as expected a number were attributed to the underlying malignancy or docetaxel. Plinabulin was emetogenic and occasionally resulted in dehydration or electrolyte disturbances with one patient requiring inpatient IV rehydration; thus, anti-emetic prophylaxis is now recommended.

Overall, the incidence, type and severity of adverse events was not noticeably different than what is expected with each agent, although neutropenia seemed to be generally mild with the exception of one grade 4 neutropenia event (Tables 2 and 3).

Table 2 Adverse events reported in ≥10% of patients

Adverse events reported in >10% of patients	13.5 mg/m^2 (n=2)		20 mg/m^2 (n=3)		30 mg/m^2 (n=8)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Fatigue	1	0	2	0	4	0
Pain	1	0	2	0	4	0
Nausea	1	0	1	0	2	1
Diarrhea	1	0	1	0	2	0
Vomiting	0	0	1	0	1	1
Lower extremity edema	0	0	1	0	2	0
Alopecia	0	0	0	0	2	0
Anorexia	1	0	0	0	1	0
Constipation	0	0	0	0	2	0
Dyspnea	0	0	1	0	1	0
Flu like syndrome	1	0	0	0	1	0
Hypomagnesemia	0	0	0	0	2	0
Infection	1	0	0	0	1	0
Nail changes	1	0	1	0	0	0

Table 3 Serious adverse events reported

Patient	Dose (mg/m^2)	Serious Adverse Event (SAE)	Grade	Relationship to plinabulin	Relationship to docetaxel
002–002	20	Pneumothorax	2	Not related	Not related
002–004	30	Cellulitis	3	Not related	Probable
		COPD	3	Not related	Not related
001–005		Neutropenia	4	Not related	Definite
		Nausea	3	Probable	Probable
		Vomiting	3	Probable	Probable
		Dehydration	2	Probable	Probable

Pharmacokinetics

Pharmacokinetics of plinabulin and docetaxel were analyzed for twelve of the patients treated. Fig. 1 demonstrates the blood concentrations over time at different dose levels of plinabulin when administered alone or in combination with docetaxel. Pharmacokinetic analysis of plinabulin indicated Cmax and $AUC_{0-\infty}$ were dose proportional over the range of 13.5–30 mg/m^2 without evidence of drug accumulation. For plinabulin mean Cmax and $AUC_{0-\infty}$ increased from 223.7 to 542.1 ng/mL, and from 1159.8 to 3565.8 ng/mL*hr, respectively. Mean $T_{1/2}$ was 7.9 h, mean clearance was 31.93 L/h and mean distributive volume was 207.86 L. Fig. 2 demonstrates the blood concentrations over time of docetaxel when administered in combination with plinabulin in this study, compared to historical data reported for docetaxel administered alone. For docetaxel mean Cmax and $AUC_{0-\infty}$ were 260.3 ng/mL, and 1218.8 ng/mL*hr, respectively. Mean clearance was 135.98 L/h and mean distributive volume was 1859.94 L. These results of the drugs given in combination were not markedly different from those given alone. Plasma docetaxel levels at the early time points appear lower, however, these time points are prior to the first administration of plinabulin thus cannot represent an interaction.

Efficacy

Tumor response (greatest decrease in tumor measurements on study) to treatment is summarized in Fig. 3. For note, of the 8 patients with NSCLC with evaluable lesions there was one confirmed partial response, one unconfirmed partial response (interval development of atelectasis prevented measurement of target lesions on subsequent CT scans), and 4 other patients with lesser regressions of target lesions. Overall, of the 13 patients treated, 8 (62%) had at least stable disease at the cycle 2 assessment, and of these patients 6 maintained stable disease until at least cycle 6, with one patient remaining on study through 8 cycles. The 2 patients with responses remained on study for 6 and 8 cycles, respectively.

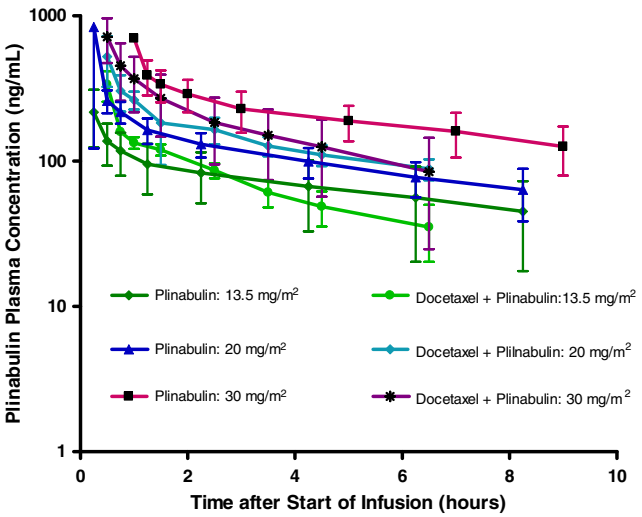


Fig. 1 Plinabulin plasma concentration over time

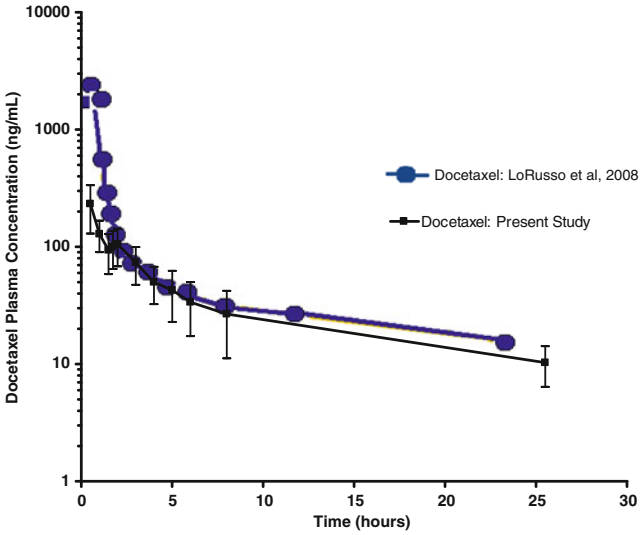
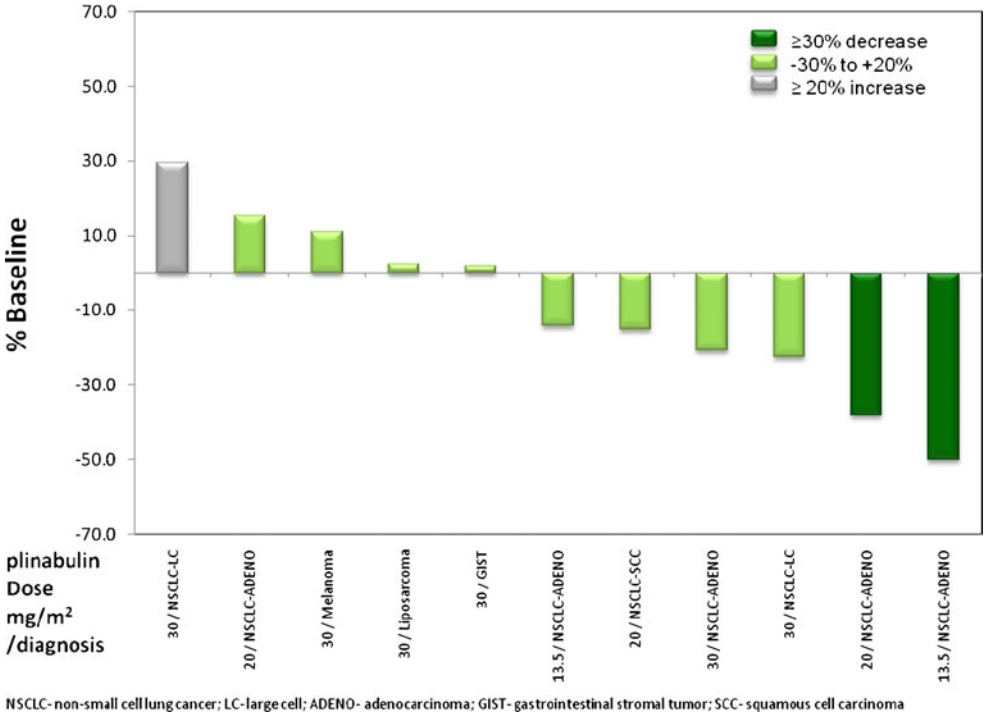


Fig. 2 Docetaxel plasma concentration over time *from LoRusso PM, Clin Oncol:26 (18): 3051–3056; June 20 2008 [24]

Fig. 3 Best response



Discussion

This study demonstrated that the combination of plinabulin with docetaxel is feasible and tolerable at the recommended single-agent doses for each drug (30 mg/m^2 and 75 mg/m^2, respectively). Effects commonly ascribed to plinabulin at this dose include nausea/vomiting, fatigue, tumor pain and transient blood pressure elevations, and there was no evidence of prolonged or cumulative toxicities. Effects frequently associated with docetaxel such as neutropenia, infections, vomiting, diarrhea, alopecia, nail changes, peripheral edema and fatigue were also seen, albeit a higher rate of neutropenia would have been expected even in this small population (interim analysis of a randomized Phase 2 comparison of this combination suggested a markedly reduced incidence of neutropenia with the addition of plinabulin to docetaxel [25]). Many of the adverse events reported were also attributable to the patients' underlying malignancies. One event consistent with dose-limiting toxicity was reported with nausea, vomiting together with neutropenia leading to dehydration and hospital admission. Vomiting is a known effect of both docetaxel and plinabulin, and with plinabulin alone is occasionally significant enough to result in dehydration or electrolyte disturbances requiring hospitalization; however, this is manageable with antiemetic prophylaxis. Tumor pain is also a known effect of plinabulin and other VDAs, as this is hypothesized to result from structural and cytokine effects on surrounding tissues during the tumor necrosis elicited by these agents. As expected, the occurrence and severity is seen to vary considerably between patients depending on tumor sites and volume. Tumor pain in this study seemed to be lower than previously reported with plinabulin, possibly secondary to the greater proportion of lesions being located in unenervated lung parenchyma in contrast to solid tumor malignancies of other origins, and was manageable with analgesics appropriate to the severity [20]. Overall, this adverse event profile is consistent with what would be expected and accepted from experience with plinabulin and docetaxel administered alone, and continues to support a lack of noticeable effects of plinabulin on cardiac or neurologic function even when used in combination with a neurotoxic drug. Bleeding events were also lacking.

Likewise the pharmacokinetic data do not suggest an interaction between the drugs. The pharmacokinetic data collected principally allow assessment of docetaxel's effect on plinabulin. The data for docetaxel obtained from this study in comparison to historical data cannot definitively rule out drug-drug interaction and the Cmax and AUC are somewhat lower. This, however, likely reflects intra-study variability in sample acquisition or laboratory methodology rather than evidence of an interaction, as the difference is found principally in early time points that were collected prior to the first administration of plinabulin.

Of the patients with NSCLC, 8 had measureable disease of which 2 demonstrated a partial response (PR), with 4 others having lesser regressions (one with squamous cell carcinoma histology), thus a 25% response rate compared to the 5–10% response rate generally reported with docetaxel alone in this population [26, 27]. Thus, efficacy

in this study appears comparable to better than that reported with docetaxel alone in this docetaxel-naïve patient population, however, it is not possible to draw any conclusions from this small, non-randomized data set.

Overall, this study indicated that combining plinabulin at 30 mg/m^2 with docetaxel at 75 mg/m^2 is tolerable, and these doses were selected as the RP2D for subsequent studies. Although the main toxicities of neutropenia, nausea and vomiting expected with the standard doses of these drugs when administered alone were observed, combining the drugs did not appear to increase toxicity. These findings suggest a favorable combination profile in this patient population relative to other VDAs and approved oncology agents. Recent studies have suggested VDAs may have significant potential in the treatment of a number of malignancies, particularly non-small cell lung cancer. Moreover, secondary to the differences in the biologic target and subsequently safety and efficacy profiles, VDAs could potentially benefit to subsets of patients differentially from current standard therapies, such as NSCLC with squamous cell carcinoma histology or lesions at risk of hemorrhage. Based on the encouraging results of the present study, the combination of plinabulin with docetaxel is now being assessed in a randomized Phase 2 clinical trial in previously treated patients with all histologies of advanced or metastatic NSCLC [28].

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