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ORIGINAL ARTICLE

A phase I dose escalation and pharmacokinetic study of vatalanib (PTK787/ZK 222584) in combination with paclitaxel in patients with advanced solid tumors

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Abstract
Purpose To define the maximum-tolerated dose (MTD) for weekly paclitaxel administered in combination with daily vatalanib (PTK787/ZK 222584, PTK/ZK) and assess for a drug–drug interaction.
Methods Patients were treated with escalating doses of weekly paclitaxel (75–85 mg/m^2), and daily PTK/ZK (250–1,000 mg). During the first cycle only, paclitaxel was given on days 1 and 15, and PTK/ZK on days 3–28. Pharmacokinetic studies were conducted on cycle 1 days 1 and 15 for paclitaxel, and on cycle 1 day 15 for PTK/ZK. Therapy was given until disease progression.
Results Twenty-seven patients were accrued to four dose levels. Two of five patients treated with paclitaxel 85 mg/m^2 and PTK/ZK 1,000 mg had Grade 3 transaminase elevation as dose-limiting toxicity. Paired PK analyses demonstrated a significant increase in paclitaxel clearance on day 15 ($p = 0.006$). Activity included one partial response and 11 patients with stable disease ≥4 months, including patients previously treated with paclitaxel.
Conclusions The MTD for weekly paclitaxel plus daily PTK/ZK is 75 mg/m^2 and 750 mg. PK analysis revealed a significant drug–drug interaction, with an increase in paclitaxel clearance. This combination was well tolerated with evidence of anti-cancer activity and provides guidance for phase 2 planning.

Keywords Paclitaxel · Phase I · PTK/ZK · VEGFR

Introduction

Angiogenesis is essential for tumor growth and metastasis, and inhibitors of this process have become integral for the therapy of many tumors. Tumor angiogenic and lymphangiogenic signals are transmitted via three tyrosine kinase cell surface receptors [VEGFR1 (Flt-1), VEGFR2 (KDR), and VEGFR3 (Flt-4)] located on host vascular endothelial cells, monocytes, and hematopoietic precursors. VEGF-R tyrosine kinases are up-regulated on endothelial cells of newly forming vessels in tumors, and have been proven to be a valid target for cancer therapy. PTK/ZK (vatalanib, Novartis Pharmaceuticals) is an orally active angiogenesis inhibitor blocking all known vascular endothelial growth factor receptors (VEGFR), the platelet-derived growth factor receptor (PDGFR) - tyrosine kinases, and c-kit [1, 2].

Paclitaxel exerts its cytotoxic effect by binding to tubulin and preventing microtubule disassembly. Animal tumor models and in vitro studies suggested that paclitaxel in lower weekly doses has anti-angiogenic activity by inhibiting the expansion of the endothelial compartment [3–5]. Preclinical data indicate that chemotherapy-induced

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cell kill is followed by an increase in VEGF levels associated with tumor regrowth [6], which suggests a benefit when combining chemotherapy and angiogenesis inhibitors. In addition, we have shown that taxanes inhibit angiogenesis in both in vitro and in vivo models and augment the anti-angiogenic properties of bevacizumab and 2-methoxyestrodiol [7]. Paclitaxel has clinical activity in many tumor types and in combination with bevacizumab improved the progression-free survival in metastatic breast cancer, and the overall survival with carboplatin and bevacizumab in lung cancer, compared with paclitaxel alone [8, 9]. These data support combining paclitaxel with anti-angiogenic agents because this approach both augments the anti-angiogenic activity of each agent, while the chemotherapeutic directly attacks the tumor compartment.

In this study we evaluated the safety and pharmacokinetics of escalating doses of weekly paclitaxel in combination with daily PTK/ZK in patients with advanced solid tumors. As PTK/ZK has been shown to increase its own clearance via CYP3A4 isoenzyme autoinduction [10, 11], and possibly other effects on CYP2C8 and CYP2D6 [12], we were particularly interested in exploring its effects on paclitaxel pharmacokinetics, and ruling out a possible decrease in exposure. By comparison, studies of other VEGFR- TKI such as sorafenib or AZD2171 (cediranib) showed no or little influence upon paclitaxel PK parameters [13–15]. The once daily administration of PTK/ZK in this study was chosen based on its possible interaction with paclitaxel, and the data regarding twice daily dosing at study inception was not available. Moreover, while twice daily dosing of PTK/ZK has been explored to maximize drug exposure, data show that for equivalent daily doses, AUC and C_{max} are similar, but trough concentrations (C_{min}) were higher with twice daily versus once daily dosing [11]. The target dosing for PTK/ZK is based on prior pharmacodynamic DCE-MRI studies which indicate that its biological effect might plateau at doses above 1,000 mg daily. PTK/ZK attains steady state after 10 days of continuous dosing; thus the pharmacokinetics of paclitaxel was performed on cycle 1 days 1 (without PTK/ZK) and 15 (with PTK/ZK at steady state), and trough level was determined for PTK/ZK on cycle 1 day 15.

Patients and methods

Eligibility criteria

Adult patients of at least 18 years of age were eligible if they had a histological diagnosis of advanced solid tumors refractory to standard therapy, an Eastern Cooperative Oncology Group Performance Status ≤ 2, adequate hematopoietic function, alanine aminotransferase (ALT) < 3 x ULN, creatinine ≤ 1.5 x ULN, and urine protein/creatinine ratio ≤ 1. Patients may have received but not progressed on taxane-based therapy, and were excluded if they had prior treatment with anti-VEGF agents. Other exclusion criteria were active cardiovascular disease within the prior 6 months, a history of brain metastases, concomitant use of warfarin or heparin, and grade ≥ 2 neuropathy. All patients signed an informed consent form approved by the Indiana University Institutional Review Board.

Study design

This was a single-center phase I, dose-escalation study of once-daily oral PTK/ZK combined with weekly intravenous paclitaxel. Patients were recruited in cohorts of three to six according to the $3 + 3$ design until dose-limiting toxicity (DLT) was observed. The maximum-tolerated dose was defined as the highest dose level at which no more than 1 of 6 patients experienced DLT in both cycles 1 and 2, as paclitaxel was only given on days 1 and 15 in cycle 1. A total of ten evaluable patients were treated at the maximum-tolerated dose (MTD). An alternating dose escalation plan of PTK/ZK and paclitaxel was employed and the planned dose levels were as follows: (1) 250 mg/75 mg/m^2; (2) 500 mg/75 mg/m^2; (3) 750 mg/75 mg/m^2; (4) 1,000 mg/85 mg/m^2; (5) 1,250 mg/85 mg/m^2, and (6) 1,250 mg/100 mg/m^2. PTK/ZK was administered orally at night starting with day 3 (i.e. after paclitaxel PK) and given continuously thereafter. Paclitaxel was infused intravenously over 1 hour on days 1 and 15 of the first 28-day cycle to ensure concomitant dosing of paclitaxel when PTK/ZK was at steady state [10, 16], and on days 1, 8 and 15 every 28 days thereafter. Premedication for paclitaxel consisted of dexamethasone 20 mg intravenous 1 hour prior to paclitaxel dosing, ranitidine 150 mg orally twice daily, and diphenhydramine 50 mg orally prior to infusion.

DLT was defined as any of the following events: grade 4 thrombocytopenia, grade 4 neutropenia lasting more than 7 days, grade 3 or 4 febrile neutropenia, any grade 3/4 non-hematologic toxicity related to the combination therapy except nausea/vomiting or alopecia, and toxicity resulting in inability to give day 8 of paclitaxel in cycle 2 or missing >7 days of PTK/ZK in cycles 1 or 2. Dose reductions were based on hematologic and non-hematologic toxicities. No more than two dose modifications were allowed for any one patient. Paclitaxel was dose reduced first by patient starting dose minus 20 mg/m^2 and the second dose reduction was patient starting dose minus 30 mg/m^2, and PTK/ZK dose reductions were by 250-mg decrements for both possible dose reductions. Paclitaxel was dose adjusted for toxicities according to toxicities well recognized to be associated with this agent, including myelosuppression.

Therapy with PTK/ZK was discontinued for grade 4 toxicity and held for grade 3 toxicity; PTK/ZK could be restarted after resolution to grade 1 at one dose level lower. Patients requiring more than two dose reductions were removed from protocol therapy. If a patient required discontinuation of one study drug due to toxicity, the other study drug was allowed to be continued. Response to therapy was assessed every 8 weeks using the Response Evaluation Criteria in Solid Tumors (RECIST) [17].

Treatment was administered until disease progression, unacceptable toxicity, patient refusal to continue on study, or therapy delay for more than 3 weeks because of any toxicity. At study initiation patients were to be treated with paclitaxel for up to 6 cycles and until progression with PTK/ZK, but after a study amendment, the last 18 patients were allowed to continue paclitaxel, in the absence of toxicity, until disease progression.

Pharmacokinetic studies

Paclitaxel was infused over one hour on days 1 and 15 of cycle 1. To investigate the effects of PTK/ZK on the pharmacokinetics of paclitaxel, we collected blood samples at 0 h (prior to paclitaxel infusion), at the end of paclitaxel infusion (1 h), then at 1.25, 1.5, 2, 3, 5, 7, 9, and 25 h after starting the paclitaxel infusion. PTK/ZK was dosed nightly starting with day 3 of cycle 1, so that at least a 12-h period existed after paclitaxel infusion, to avoid dosing of paclitaxel around the time of PTK/ZK maximum concentration (C_{max} occurs 1–2.5 h after ingestion), thus decreasing the chances of adverse drug effects. Plasma samples for PTK/ZK steady-state levels were collected prior to paclitaxel on cycle 1 day 15 (approximately 12 h after PTK/ZK administration). Samples were cryopreserved at $\leq -20°C$ until analysis.

Plasma concentrations for paclitaxel and metabolites (3′-OH paclitaxel and 6α-OH paclitaxel) were determined by high-performance liquid chromatography-tandem mass spectrometry (HPLC–MS/MS) assay (Applied Biosystems, API 4000) using docetaxel as the internal standard. Paclitaxel, paclitaxel metabolites, and docetaxel were extracted from plasma using a liquid–liquid procedure. The lower limit of quantification of the assay was 0.1 ng/ml using 100 μL of plasma. Pharmacokinetic parameters for paclitaxel and the hydroxyl metabolites including area under the curve (AUC) and half life ($t_{1/2}$) were estimated using non-compartmental methods with Excel®. The maximum plasma concentration (C_{max}) was obtained from the data. Paclitaxel AUC was estimated from time zero (start of infusion) to infinity. The concentration at time zero was below the limit of quantification for all compounds so it was set at zero. The paclitaxel concentration at 1 hr (immediately at the end of the infusion) was estimated by extrapolating the slope of the exponential line (using the concentrations at 1.25 and 1.5 h, which is the same as 0.25 and 0.5 h from the end of the infusion) to 1 h. The AUC from the last concentration, C_{last}, to infinity for paclitaxel was estimated with the rate constant of elimination, e.g., C_{last}/k_{el}. The AUCs of each hydroxyl metabolite were estimated from time zero to the last quantifiable concentration. The systemic clearance (Cl) of paclitaxel was calculated from the dose and AUC.

PTK/ZK plasma concentration was determined using high-performance liquid chromatography (HPLC). PTK/ZK was extracted from plasma samples by liquid–liquid extraction and was detected using ultraviolet detection at 315 nm. The chemical name of the internal standard is CGP80805 (4 chlorophenyl)-(4 2, 6 dimethylpyridin-4 ylmethyl-phtalazin-1yl), $C_{22}H_{19}ClN_4$; M.W: 374.87. This extract was then subjected to reverse-phase high-performance liquid chromatography on a Prodigy ODS-2, 125 × 4.6 mm, and 5 μm column. PTK/ZK and CGP80805 (IS) in the effluent were detected using a Shimadzu SPD-10A absorbance detector. This method was previously validated over a range of 5 to 5,000 ng/mL [10–12].

Statistical analysis

Acceptable toxicity of this regimen was considered if none of 3 or ≤1 in six patients had DLT. Based on the binomial distribution for toxicity occurrence, there was at most a 17% chance of escalating to the next dose level when the true toxicity rate exceeded 50%. With six patients in a cohort, there was at least a 74% chance of observing any toxicity with a true rate of >20%. All toxicity was summarized in a tabular manner for all encountered events. The PK measurements of paclitaxel between cycle 1 day 1 and day 15 in each cohort were compared using paired *t* test to assess for drug–drug interactions.

Results

Patient population

Characteristics of the 27 patients enrolled in this study are summarized in Table 1. The median time on study was 3 cycles (12 weeks). Six patients discontinued therapy before completing the first cycle: one due to DLT (grade 3 transaminase elevation), three patients due to rapid disease progression, one patient due to port-a-cath related deep vein thrombosis, and one patient due to refusing daily PTK/ZK dosing. One patient had a grade 3 infusion reaction to paclitaxel and received PTK/ZK alone.

Table 1 Patient characteristics ($n = 27$)

Characteristic	Number	%
Age, median (range)	59 (38–76)	
Sex, female/male	9/18	33/67
Race		
Caucasian	26	96
African–American	1	4
Hispanic	0	0
ECOG performance status		
0	16	59
1	10	37
2	1	4
Tumor type		
Transitional cell	7	26
Ovarian	5	18
Esophageal	5	18
Prostate	4	15
Non-small cell lung	1	4
Small cell lung	1	4
Adrenocortical	1	4
Neuroendocrine	1	4
Urethral clear cell	1	4
Unknown primary	1	4
Prior therapy		
Chemotherapy	20	74
Paclitaxel	9	33
Radiotherapy	8	30
Surgery	18	67
Hormonal/biological	7	26
None	2	7

ECOG Eastern Cooperative Oncology Group

Toxicity

Treatment summary of the 27 patients evaluable for toxicity, among whom 23 patients completed at least 1 cycle, is provided in Table 2 (three patients with rapid disease progression and one patient who refused daily dosing of PTK/ZK were discontinued from study during cycle 1 with no study drug-related DLT and were replaced to have enough patients evaluable per the 3 + 3 cohort design). None of the patients in the paclitaxel 75 mg/m^2 and PTK/ZK 250 or 500 mg cohorts required dose reductions during their treatment. Two of 14 patients in the paclitaxel 75 mg/m^2 and PTK/ZK 750 mg cohort had study-drugs related grade 3 transaminase elevation: one patient on cycle 2 day 1 (DLT), but after paclitaxel and PTK/ZK dose reduction to 55 mg/m^2 and 500 mg, respectively, remained on study for 12 cycles with no further toxicity; another patient had transaminase elevation on cycle 4 day 1, but discontinued study due to disease progression. Two of five patients in the 85 mg/m^2 paclitaxel and 1,000 mg PTK/ZK cohort experienced DLT with grade 3 transaminases elevation during cycle 1 (on days 15 and 28, respectively). Upon transaminase decline to grade 1 within 7 days, both patients were re-treated with 750 mg PTK/ZK alone to achieve steady state, but within 7 days had prompt recurrence of grade 3 transaminase elevation and were discontinued from study. The MTD for this combination was therefore paclitaxel 75 mg/m^2 with PTK/ZK at 750 mg daily.

To detail the tolerability beyond cycle 2, toxicities reported in at least 10% of patients and all grade 3 and 4 toxicities which occurred any time during treatment ($n = 27$) are summarized in Table 3. One patient had grade 3 hypertension in cycle 3, controlled with anti-hypertensive medications. No patients had proteinuria. Thrombotic events occurred in five patients: two deep venous thromboses (one thought to be catheter related), two pulmonary embolisms (asymptomatic and both incidental findings on CT scans), and one patient with adrenocortical carcinoma with inferior vena cava tumor thrombus thought to be disease related. There was minimal hematological toxicity, with two patients experiencing grade 2 neutropenia.

Pharmacokinetics

Twenty patients had completed paclitaxel pharmacokinetic studies (PK) on days 1 and 15 of cycle 1. Seven patients did not undergo full PK analysis because of rapid disease progression (3), non-compliance with PTK/ZK dosing (1), allergic reaction to paclitaxel after first dose (1), DLT before cycle 1 day 15 (1), and study discontinuation due to port-related DVT (1). Estimated paclitaxel $AUC_{0-\infty}$ demonstrated dose proportional increase. Seventeen patients had numerical increase in the paclitaxel clearance on cycle 1 day 15 compared to day 1 (Fig. 1). In the MTD cohort, a statistically significant increase in the mean paclitaxel clearance was noted from baseline to day 15 [49.6 L/h (28.6 L/h per m^2) vs. 68.6 L/h (39.6 L/h per m^2), $p = 0.006$]. Corresponding $AUC_{0-\infty}$ declined from 3.8 μg h/mL at baseline to 2.5 μg h/mL on day 15. The mean PK parameters of paclitaxel are shown in Table 4 and Fig. 1. These results are consistent with a drug–drug interaction of PTK/ZK with paclitaxel, causing a significant decrease in paclitaxel exposure.

Paclitaxel is metabolized by both CYP3A4 and CYP2C8 enzymes to 3′OH-paclitaxel and 6α-OH-paclitaxel, respectively. In an attempt to determine which enzyme was affected by PTK/ZK exposure we measured both metabolites, but no significant changes could be detected in the presence of PTK/ZK (data not shown). PTK/ZK trough concentrations (C_{trough}) 12 hours after dosing are shown in Table 5 vis-à-vis to historical controls of PTK/ZK administered as single-agent once daily [10].

Table 2 Treatment summary, DLTs ($N = 27$)

Paclitaxel (mg/m^2) D1, 8, 15 Q28 D	PTK787 (mg) daily	No. DLTs (in first 2 cycles)	No. cycles median (range)	Treatment-related Grade 3 toxicities beyond 2 cycles
75	250	0/5 (2 patients replaced because not evaluable for DLT)	2 (1–4)	Hypertension ($n = 1$)
75	500	0/3	2 (2–6)	PE incidental on CT scan ($n = 1$, cycle 6)
75	750	1/14 Grade 3 transaminase elevation ($n = 1$)	4.5 (1–13)	PE incidental on CT scan ($n = 1$, cycle 4)
				DVT ($n = 1$, cycle 3)
				Infusion reaction ($n = 1$, cycle 1)
				Transaminase elevation ($n = 1$, cycle 4.)
85	1,000	2/5 Grade 3 transaminase elevation ($n = 2$)	2 (1–5)	None

DLT dose-limiting toxicity, *PE* pulmonary embolism, *DVT* deep vein thrombosis, *CT scan* computed tomography scan

Table 3 Summary of all-cause toxicities by severity (NCI-CTCAE v 3.0) ($n = 27$)

Adverse event	All grades		Grades 3–4	
	No. of patients	%	No. of patients	%
Fatigue	9	33	–	–
Dyspepsia/Heartburn	9	33	–	–
Neuropathy	9	33	–	–
Nausea	8	29	–	–
Alopecia	7	25	–	–
AST/ALT	7	25	6	22
Vomiting	6	22	–	–
Diarrhea	6	22	–	–
Anorexia	6	22	–	–
Dizziness	5	18	–	
Thromboembolism	5	18	5	18
Hypertension	4	14	1	4
Headache	3	11	–	–
Mucositis	3	11	–	–
Taste alteration	3	11	–	–
Nose bleeding	3	11	–	–
Infusion reaction to Paclitaxel	3	11	1	3

Grade 4 toxicities were 2 incidental pulmonary embolism events on CT scan

Two patients had grade 3 transaminase elevation due to disease progression

Antitumor activity

Twenty patients who completed at least 2 cycles of therapy, and another patient with disease progression after 1 cycle, were evaluable for tumor response. One patient with esophageal adenocarcinoma had confirmed PR. Eleven patients (52%) (3 prostate, 3 ovarian, 2 transitional cell bladder, 1 non-small cell lung, 1 adrenocortical, 1 clear cell urethral cancers) had stable disease lasting ≥4 months (range 4–13 months).

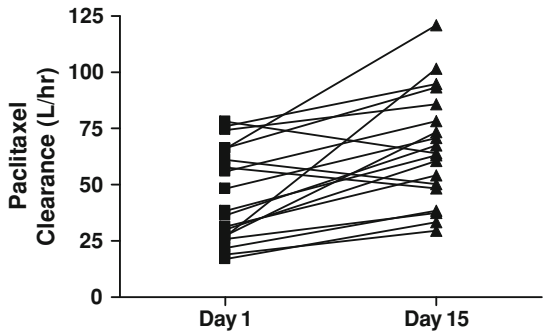

Fig. 1 Paclitaxel clearance for all patients cycle 1 day 1 and day 15 ($n = 20$)

Discussion

This phase I study shows the MTD of this combination is PTK/ZK 750 mg given orally at night and paclitaxel 75 mg/m^2 on days 1, 8, and 15 every 28 days. At this dose and schedule the combination had an acceptable toxicity profile. The majority of patients in the MTD cohort did not require any dose adjustments during the course of their treatment. Hypertension occurred infrequently (14%), but was easily controlled with standard medications. No significant hematological toxicity and only mild neuropathy was seen with this combination. The grade 3 transaminase elevation was dose limiting with 1,000 mg of PTK/ZK and 85 mg/m^2 of paclitaxel, but it was reversible and not associated with hyperbilirubinemia. The nature of this toxicity is consistent with what is seen with single agent PTK/ZK at doses of 250–750 mg twice daily (14% incidence) [11]. The transaminase elevation seen in our study, as well as the observation that PTK/ZK increased paclitaxel clearance points to a drug–drug interaction which is

Table 4 Paclitaxel pharmacokinetics

Paclitaxel (mg/m^2)	PTK787/ZK (mg)	*n*	Cl (L/h) mean ± SD		*p* value	$t_{1/2}$ (h) mean ± SD		*p* value
			Day 1	Day 15		Day 1	Day 15	
75	250	3	45.5 ± 22.4	67.5 ± 27.5	0.018	13.0 ± 6.0	10.9 ± 2.8	0.521
75	500	3	43.0 ± 15.9	57.3 ± 9.0	0.379	8.5 ± 2.2	10.3 ± 1.5	0.486
75	750	10	49.6 ± 20.7	68.6 ± 27.0	0.006	14.5 ± 3.8	14.4 ± 13.9	0.963
85	1,000	4	37.8 ± 27.1	67.1 ± 29.7	0.230	13.8 ± 4.1	8.7 ± 1.4	0.108

Cl clearance determined by dividing the dose by area under the curve (AUC), *SD* standard deviation, $t_{1/2}$, half-life

Table 5 PTK/ZK pharmacokinetics on cycle 1 day 15 versus single agent historical control at end of cycle 1

Paclitaxel (mg/m^2)	PTK/ZK (mg)	*n*	C_{trough} C1D15 (μM) 12 h post dosing			PTK/ZK control* mg	*n*	C_{min} EC1 (μM)		
			Mean	SD	90% 1-sided CI lower bound			Mean	SD	90% 1-sided CI upper bound
75	250	3	0.34	0.33	0.09	300	3	0.05	0.01	0.06^{π}
75	500	3	0.88	0.72	0.34	500	3	0.13	0.04	0.16^{π}
75	750	10	0.40	0.27	0.29	750	3	0.14	0.12	0.23^{π}
85	1,000	4	0.96	0.43	0.69	1,000	5	0.41	0.49	0.69

C_{trough} lowest plasma concentration measured 12 h after dosing, C_{min} minimum plasma concentration; C1D15, cycle 1 day 15, *EC1* end cycle 1 or cycle 1 day 28 in Ref. [10]

*Morgan et al. [10]

$^{\pi}$ Significant difference

clinically significant both in terms of organ toxicity (i.e. hepatic) and influencing the clearance of other drugs (affecting hepatocyte function). While paclitaxel has hepatic toxicity which is rarely dose-limiting [18, 19], PTK/ZK has a low incidence of hepatotoxicity, and dosing of 750 mg daily has been recommended for patients with underlying hepatic dysfunction [12].

It has previously been reported that PTK/ZK achieves C_{max} (12–27 μM) within 1–2.5 h after dosing indicating rapid onset of absorption, and its terminal elimination half-life is 3–6 h [10, 20]. It has also been established that the systemic exposure to PTK/ZK is greater in the first few days and then stabilizes to steady-state around day 15 of treatment, thought to be secondary to CYP3A4 isoenzyme autoinduction, increasing its own clearance [10, 11]; other pathways involved include CYP2C8, CYP2D6, and CYP1A2. Therefore, PTK/ZK is liable to alter the clearance of the drugs metabolically cleared via these enzymatic pathways, and with reference to paclitaxel, it would be expected to alter the rate of 3'and 6α-hydroxylation [12]. In an attempt to determine which enzyme was affected by PTK/ZK exposure, we measured paclitaxel major metabolites, 3′OH and 6α-OH paclitaxel, which are derived from enzymatic metabolism through CYP3A4 and CYP2C8, respectively. While in vitro data have shown that altering the function of CYP enzymes would affect paclitaxel clearance [21, 22], non-significant declines in metabolite concentrations were noted; thus other paclitaxel clearance pathways may be affected, such as transporters, and possibly auto-induction [23]. Prior studies with weekly administered single-agent paclitaxel infused over 1 h at same dose range showed that pharmacologic exposure as determined by AUC (3.3–5.1 μg h/mL) [24] or clearance (5.2–30.2 L/h/m^2) [25] overlap the results observed in our study.

The higher PTK/ZK trough concentrations seen in our study, when compared to similar PTK/ZK doses administered as single-agent [10] may represent a drug interaction with paclitaxel or may simply reflect higher concentrations seen 12 h post drug administration, instead of the lower levels expected 24 h post dosing (C_{min}) (Table 5). Nevertheless, elevated PTK/ZK levels at time of paclitaxel dosing do not appear to be the reason for transaminase elevation/DLT, as day 15 trough levels for PTK/ZK were only 0.6–0.7 μM.

While efficacy was not the primary objective of this study, we observed encouraging clinical activity, with one esophageal cancer patient with sustained PR and 52% of patients with disease stabilization for more than 4 months. Six of the 11 patients with stable disease had prior treatment with paclitaxel. The relevance of the clinical benefit with paclitaxel and PTK/ZK in our study is underscored by prior knowledge that paclitaxel pharmacokinetics and dosing schedule are important. Paclitaxel plasma concentrations above a threshold of 0.05 μmol/L (43 ng/mL) for a duration longer than 60 h were shown to correlate with

response to treatment and improved survival when paclitaxel was dosed at 175 mg/m^2 every 3 weeks [26, 27]. While optimization of doses and administration schedules for anticancer agents is important [28], in our study only three patients (1 PR, and 2 SD) had paclitaxel plasma concentrations above 0.05 μmol/L for at least 24 h (data not shown), but this can be explained by the lower weekly doses administered.

To date, the phase 3 trials with benefit from paclitaxel plus anti-angiogenic agents have been with VEGF-A ligand inhibition (bevacizumab). Our study supports the notion of combining taxanes with VEGFR tyrosine kinase inhibitors. In conclusion, this study shows good tolerability of continuous daily PTK/ZK combined with weekly paclitaxel, with an MTD of 750 mg and 75 mg/m^2, respectively. While PTK/ZK induces the clearance of paclitaxel, this regimen has shown antitumor activity in a variety of heavily pretreated cancers, particularly ovarian, prostate, transitional cell and esophageal tumors, and provides guidance for further testing in phase II trials.

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