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ORIGINAL ARTICLE

A phase I/randomized phase II, non-comparative, multicenter, open label trial of CP-547,632 in combination with paclitaxel and carboplatin or paclitaxel and carboplatin alone as first-line treatment for advanced non-small cell lung cancer (NSCLC)

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Abstract
Purpose To evaluate the toxicity profile and pharmacological properties of oral CP-547,632 alone and in combination with paclitaxel and carboplatin administered every 3 weeks, and to assess efficacy as measured by the objective response and progressive disease rates of oral CP-547,632 administered in combination with paclitaxel and carboplatin.
Patients and methods Patients with stage IIIB/IV or recurrent non-small cell lung cancer receiving first-line chemotherapy were treated with oral daily CP-547,632 in combination with paclitaxel 225 mg/m^2 and carboplatin AUC = 6 every 3 weeks. Pharmacokinetics parameters for CP-547,632 and paclitaxel were determined independently and during co-administration.
Results Seventy patients were enrolled and 68 patients were treated, 37 in phase 1 and 31 in phase 2 (14 with the combination and 17 with chemotherapy alone). Dose-limiting toxicity of CP-547,632 250 mg by mouth daily in combination with paclitaxel and carboplatin was grade 3 rash and grade 3 diarrhea despite medical intervention. CP-547,632 did not significantly affect the pharmacologic profiles of paclitaxel and carboplatin. No subject had CR. In phase I, seven subjects (22.6%) had a confirmed partial response. In phase II, four subjects (28.6%) receiving CP-547,632 plus chemotherapy had a confirmed partial response. In the phase II chemotherapy alone group, four subjects (25%) had a confirmed partial response.
Conclusion The combination of CP-547,632 and paclitaxel and carboplatin was well-tolerated at doses up to 200 mg by mouth daily. Dose-limiting toxicity of CP-547,632 at 250 mg consisted of diarrhea and rash. CP-547,632 did not increase the objective response rate to chemotherapy alone in patients with advanced non-small cell lung cancer.

Keywords Angiogenesis · Tyrosine kinase inhibitor · Paclitaxel · Carboplatin · VEGFR-2 · Phase I · Pharmacokinetics · NSCLC

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Introduction

High VEGF expression significantly affects prognosis in human cancer and is an important prognostic indicator in non-small cell lung cancer (NSCLC) [1]. High tumor VEGF mRNA expression is associated with

advanced tumor stage and lymph node metastasis in addition to shortened patient survival and early relapse [2–8] VEGFR-2 mediates the majority of VEGF effects, including microvascular permeability, endothelial cell proliferation, invasion, migration, and survival [9, 10]. Recent studies of the monoclonal antibody bevacizumab have validated the VEGF/VEGFR pathway as a therapeutic target in several tumor types including NSCLC [11–13].

Small molecule inhibitors of VEGFR-2 tyrosine kinase activity represent an alternative to blocking VEGF-mediated angiogenesis [14–19]. CP-547,632 is a potent and selective inhibitor of the VEGFR-2 tyrosine kinase with an IC_{50} of 6 ng/ml. Inhibition is selective (greater than 500-fold) relative to the concentrations required to inhibit other receptor tyrosine kinases [e.g., epidermal growth factor receptor (EGFR)]. Preclinical data demonstrate at least additive efficacy when CP-547,632 is co-administered with paclitaxel or carboplatin in human NSCLC xenograft-bearing animals compared to any of these agents alone (Pfizer, unpublished data).

NSCLC, once metastasized, is almost uniformly fatal with a 5-year survival rate of <2% [20]. Targeting the VEGF axis with bevacizumab in ECOG 4599 improved median and 1 and 2-year survival [11, 21]. The use of a VEGFR-2 inhibitor such as CP-547,632 in combination with chemotherapy may potentially result in improved clinical benefit. Early single agent clinical data with CP-547,632 indicate that the compound is safe and generally well-tolerated [22]. CP-547,632 is expected to have non-overlapping toxicities with paclitaxel and carboplatin. This phase I/II trial was designed to investigate the safety and potential clinical benefit of adding CP-547,632 to contemporary first-line chemotherapy for advanced NSCLC.

Materials and methods

Patient selection

Chemotherapy-naïve patients with NSCLC (stage IIIB/IV or recurrent with previous treatment limited to surgery and/or radiation) were candidates for this study. Additional eligibility criteria included: age ≥26 years; ECOG performance status ≤1; bi-dimensionally measurable disease; adequate hematopoietic (ANC ≥1,500/μl, platelets ≥100,000/μl), hepatic (total bilirubin ≤1.5 normal, AST and ALT <5 times normal), and renal (serum creatinine ≤1.5 times normal or calculated creatinine clearance ≥60 ml/min) function; adequate unassisted oral intake; no active peptic ulcer disease, prior systemic treatment for NSCLC, uncontrolled brain metastasis, coexisting uncontrolled medical condition, history of cerebrovascular event in the past twelve months, chronic glucocorticoid therapy, significant active cardiac disease (including uncontrolled hypertension), or major surgical procedure or radiation therapy within 4 weeks of study drug administration; non-pregnant; and no known hypersensitivity to Cremophor®. Informed consent was obtained according to Federal and institutional guidelines.

Drug administration

CP-547,632 was supplied by Pfizer as 10, 25 or 100 mg tablets. The starting dose of CP-547,632 was 100 mg by mouth daily. The doses for paclitaxel and carboplatin were 225 mg/m^2 and AUC = 6, respectively. For the full characterization of pharmacokinetics of CP-547,632 as a single agent, subjects enrolled in the phase I portion of the study received a single lead-in dose of CP-547,632 followed by a 1-week washout period before the start of combined therapy.

In phase I, three patients were enrolled to each dose level (DL) in succession until dose-limiting toxicity (DLT) occurred during the first course of therapy. Adverse events and other symptoms were graded according to the CTC (Version 2.0). DLT was defined as: (a) grade 3 or greater gastrointestinal toxicity despite the use of maximal medical intervention and/or prophylaxis, (b) grade 3 or greater hemorrhage or coagulation toxicity, (c) any other non-hematologic grade 3 or greater toxicity, (d) grade 4 neutropenia for ≥7 days or complicated by fever and requiring hospitalization, (e) platelets <10,000/mm^3 or grade 3 thrombocytopenia associated with bleeding requiring transfusion, or (f) inability to resume CP-547,632 within fourteen days of stopping due to treatment-related toxicity. The maximal tolerated dose (MTD) was defined as the highest dose at which <2 of six patients experienced DLT in the first course. An additional six subjects were to be enrolled at the MTD to characterize further the safety of the combination prior to initiation of phase 2. In the expanded cohort at the MTD the effect of CP-547,632 on the pharmacokinetics of paclitaxel was characterized by employing a modified dosing plan, in which daily dose of CP-547,632 was initiated on day 2 of cycle 1. In phase 2, patients were randomly assigned to Arm A (chemotherapy with CP-547,632) or Arm B (chemotherapy alone).

Safety monitoring

Investigators were responsible for DLT attribution, which was defined for the combination therapy. Thus,

assignment of a DLT to either CP-547,632 or chemotherapy was not considered a DLT. Subjects who developed a DLT or toxicity that was subjectively intolerable had CP-547,632 interrupted. Appropriate follow-up assessments were done at least weekly until recovery to ≤ CTC grade 1 or baseline. Upon recovery, treatment was resumed at the same or lower dose. If CP-547,632 therapy was interrupted for toxicity, missed doses were skipped (treatment cycles were always 21 days). If paclitaxel/carboplatin therapy was delayed, CP-547,632 dosing continued. Subjects who experienced a CP-547,632-related DLT resumed dosing at the next lower dose level after adequate recovery. Any subject with recurring, subjectively intolerable toxicity (i.e., interruption of at least 1 week for the same toxicity on at least two separate occasions), resumed dosing at the next lower dose level following recovery. Up to two dose reductions of CP-547,632 were permitted. Dose reductions for carboplatin and paclitaxel were permitted for chemotherapy toxicities.

Pre-treatment and follow-up clinical assessments

Within 4 weeks before Cycle 1 day 1, relevant baseline radiology studies were obtained. Within 2 weeks before Cycle 1 day 1, a complete history and physical, electrocardiogram, CBC, serum chemistries, coagulation studies, urinalysis, and pregnancy testing were performed. Before each course of treatment, an interval history and physical exam, CBC, serum chemistries, blood coagulation studies, and urinalysis were performed. Tumor status was re-assessed every two cycles. Responses meeting WHO criteria for objective response were confirmed after no less than 28 days [23].

Pharmacokinetics sampling

During phase 1, blood samples were collected for the characterization of CP-547,632 plasma pharmacokinetics following a single dose and following daily dosing in combination with paclitaxel and carboplatin. Following the lead-in single dose of CP-547,632, blood specimens were collected over 7 days after dosing. On day 18 in cycle 1, blood specimens were collected over the 24-h dosing interval. In the phase l expansion cohort, blood specimens were collected for characterization of paclitaxel pharmacokinetics over the 24 h following the start of paclitaxel infusion on day 1 of cycle 1 and day 1 of cycle 2. CP-547,632 was not dosed on day 1 of cycle 1 but was dosed on day 1 of cycle 2, allowing a comparison of paclitaxel pharmacokinetics with and without concomitant dosing with CP-547,632. In phase 2, all subjects receiving CP-547,632 had blood samples collected for determination of multiple dose CP-547,632 pharmacokinetics when given in combination with paclitaxel and carboplatin. Blood specimens were collected over a 24-h period after dosing on day 18 of cycle 1.

For analysis of CP-547,632 plasma concentrations, blood samples sufficient to provide 3 ml of plasma were collected in heparinized tubes, immediately placed on ice, and centrifuged at ~3,000 RPM for 30 min. Plasma was stored in screw-capped polypropylene tubes at −70°C. The interval between collection of the specimen and storage of plasma was less than 1 h.

For analysis of paclitaxel plasma concentrations, blood specimens were placed on ice immediately after collection and centrifuged at ~3,000 RPM for 10–15 min at 4°C. From each sample, 2 ml of plasma was placed into screw-capped polypropylene tubes and stored at −70°C. The interval between collection of the specimens and ultrafiltration was less than 1 h.

Assay methods and pharmacokinetics analysis

Plasma samples were assayed for CP-547,632 concentration using a validated LC/MS/MS method. Separation was performed using reverse phase HPLC with detection by turbospray tandem mass spectrometry (assay working range 0.5–250 ng/ml). Plasma concentration–time data of CP-547,632 were analyzed by standard non-compartmental methods (WinNonlin version 3.2, Pharsight®, Mountain View, CA, USA). Trough plasma concentration (C_{trough}) was only determined at steady state (day 18). Oral clearance (CL_{oral}), $t_{1/2}$ and area under plasma concentration time curve from time 0 to infinity (AUC_{0-inf}) were determined after single dose CP-547,632.

Plasma samples were assayed for paclitaxel using a validated LC/MS/MS method. Following the precipitation of plasma protein, an aliquot of the reconstituted extract was injected onto a SCIEX API 3000 LC-MS-MS equipped with a LC/MS column (assay working range 1.00–1,000 ng/ml). The area under paclitaxel plasma concentration–time profile from 0 to 24 h (AUC_{0-24}) was determined using standard non-compartmental methods (WinNonlin version 3.2, Pharsight®).

Statistical methods

The primary objective of the phase 1 portion of the trial was to define the MTD and assess the safety and tolerability of CP-547,632 when given in combination with paclitaxel and carboplatin. The primary objective of the

randomized phase 2 portion was to estimate the objective response rate of CP-547,632 in combination with paclitaxel and carboplatin. In phase 2 patients were randomized by an automated electronic system on a 1:1 basis. There were no randomization strata. A 2-stage design was employed [24]. In stage l, the combination treatment was not considered of further interest if the true objective response rate was ≤5% and the early progression rate was ≥60% [H_0: response rate ≤5% and proportion with progressive disease (PD) as best response ≥60%]. PD in the first 2 cycles of treatment was defined as early progression. In addition to these planned analyses we also performed conditional probability calculations based on response rate based on emerging data showing an improved response rate with the combination of bevacizumab and chemotherapy [21].

Fifteen subjects evaluable for response were to be enrolled in each treatment arm in stage 1. Enrollment stopped after accrual of the pre-specified number of stage 1 patients in order to analyze the data for efficacy. If no responses were observed, or one response with ≥7 cases of early progression were observed, or ≤3 responses with ≥9 cases of early progression occurred, then accrual in arm A was stopped and it was concluded that no further study of the combination/schedule would occur in this setting.

Results

General

Seventy subjects were assigned and 68 received treatment: 37 patients in phase 1 and 31 patients in phase 2. Baseline patient characteristics and demographics are presented in Table 1. The study population was approximately 50% male-to-female in all treatment groups. The majority of enrolled subjects were <65 years with ECOG scores of 0 or 1 at baseline. Most (86%) were Caucasian. All treated patients were evaluable for toxicity.

As shown in Table 2, CP-547,632 was started at 100 mg po daily and increased in 50 mg increments to 250 mg daily, with paclitaxel and carboplatin doses fixed at 225 mg/m^2 and AUC = 6, respectively. In phase 1, 37 patients received 221 cycles of therapy; 19 of 37 subjects received five or more cycles of therapy. The median number of cycles ranged from 3 to 9 across the four dose levels. In phase 2, 14 patients received 75 cycles of combined treatment (median 4 cycles) and 17 patients received 83 cycles of chemotherapy alone (median of 6); 6 of 14 and 9 of 17 patients received five or more cycles of CP-547,632 plus chemotherapy or chemotherapy alone, respectively. A total of 21 subjects discontinued due to adverse events (AEs), 7 of which were felt related to study drug. Most AEs leading to discontinuation were generally not considered related to CP-547,632 but to chemotherapy or underlying disease. AEs leading to discontinuation considered related to CP-547,632 included: rash and nausea (2 subjects each); asthenia, dyspepsia, xerophthalmia, GI hemorrhage, rectal hemorrhage, anemia and anorexia (1 subject each).

Dose-limiting toxicity

Dose-limiting toxicities judged due to CP-547,632 included grade 3 SVT (one patient at DL1), grade 3

Table 1 Demographics and disease characteristics

	Phase I	Phase 2 combination	Phase 2 chemotherapy only
No. of pts (M/F)	37 (19/18)	16 (9/7)	17 (9/8)
Mean age (range)	60.9 (47–75)	58.9 (38–77)	60.2 (41–79)
Prior XRT	8	1	2
ECOG			
0	12	3	7
1	25	11[a]	10
Histology			
Adenocarcinoma	24	11	5
NSCLC-NOS	4	0	6
Squamous cell	3	3	1
Large cell	3	2	4
Bronchoalveolar	2	0	1
Anaplastic	1	0	0
Stage			
IIIB	4	1	2
IV	33	15	15

[a] One patient was PS 2 and in 1 patient not recorded

Table 2 Phase 1 dose levels and dose limiting toxicities

Dose level	CP-547,632 (mg QD)	No. of patients/ No. evaluable for Phase I	Dose-limiting toxicity (no. of pts)
1	100	8/6	Gr 3 SVT (1)
2	150	8/6	Gr 3 stomatitis (1)
3	200	8/6	Gr 3 rash (1)
4	250	5/5	Gr 3 diarrhea despite intervention (1) Gr 3 rash (1)
5[a]	200	8/7	None

[a] Expansion cohort at MTD

stomatitis (one patient at DL2), grade 3 rash (one patient at DL3), and one instance each of grade 3 diarrhea despite medical intervention and grade 3 rash (both at DL4) (see Table 2). DL4 (250 mg) was therefore judged to exceed the MTD, prompting expansion of DL3 (200 mg) with additional patients without the occurrence of further CP-547,632-related grade 3/4 AEs.

Non-hematologic toxicity

The most common treatment-emergent side effects in phase 1 were fatigue, diarrhea, sensory neuropathy, nausea, alopecia, anorexia, rash, vomiting, neutropenia, arthralgia/myalgia, and anemia. The most frequently reported treatment-related AEs in phase 1 judged related to CP-547,632 were rash, asthenia, hypertension and nausea. There were three instances of grade 3 hypertension, unrelated to dose, readily managed and not considered dose-limiting. In the phase 2 CP-547,632 plus chemotherapy treatment group, the most frequently reported treatment-related AEs other than diarrhea were nausea, vomiting, rash and asthenia. Diarrhea was reported for more than four subjects in each CP-547,632 treatment group (phase 1 and phase 2). Treatment-related AEs of grade 3 or 4 in severity were infrequent. At the highest CP-547,632 doses (200 and 250 mg), no treatment-related AE of grade 3 or 4 severity was reported in more than one subject or treatment group. Grade 3/4 events in the 200 or 250 mg dose groups included syncope, diarrhea, gastrointestinal hemorrhage, dyspnea, hypophosphatemia, rash and pruritus.

Adverse events leading to temporary discontinuation or reduction in study drug dose included: diarrhea (seven subjects), rash (six subjects), vomiting (seven subjects), hematuria (seven subjects), asthenia (three subjects), and headache, mouth ulceration, abnormal vision, dehydration, allergic reaction, hypotension, hypertension, mucous membrane disorder, febrile neutropenia, urinary tract infection, and pruritus (one subject each). There were no deaths from study medication; three subjects died on study or within 30 days after the last dose of study drug, all from disease progression (one in each treatment group).

Gastrointestinal toxicity regardless of cause for all dose levels is summarized in Table 3. As indicated, toxicities were mostly low grade and readily managed with conventional medical measures. Dermatologic toxicity other than alopecia (Table 4) consisted of rash and pruritus and was mostly low grade ($\leq$ grade 3). Given concerns about bleeding and thrombosis in studies of agents targeting VEGF/VEGFR, Table 5 presents all bleeding and thrombosis events across all dose levels regardless of cause. The most common bleeding events were epistaxis and hematuria. There was a single instance of grade 3 bleeding (melena) not felt by the investigator to be related CP-547,632 and a single instance of pulmonary embolism (grade 4) attributed to NSCLC.

Abnormal grade 3 or 4 liver function tests occurred in $\leq$1 subject in any treatment group; mild changes (grades 1 or 2) were sporadic without dose-related trends. Renal function abnormalities were rare (one occurrence of grade 3 proteinuria).

Hematologic toxicity

Changes in clinical laboratory parameters were those typically observed in patients with advanced NSCLC undergoing chemotherapy. Hematologic abnormalities (decreased WBC, ANC and platelets) were common and in some cases grade 3/4 in severity but were felt to be due to chemotherapy rather than to the addition of CP-547,632. Other grade 3 or 4 abnormalities were limited to hemoglobin, PT, and PTT and were not related to CP-547,632. There was no difference in the type or grades of hematologic toxicities comparing the chemotherapy alone to the chemotherapy plus CP-547.632 group.

Dose intensity/dose modifications

All evaluable subjects in each treatment group received at least one cycle of treatment. In phase 1, at least five cycles of treatment were administered to 50% of subjects treated with CP-547,632 100 and 150 mg, 44% of subjects treated with CP-547,632 200 mg, and 80% of subjects treated with CP-547,632 250 mg. The median number of cycles ranged from 3 to 9 (range 1–18). In phase 2, at least five cycles of treatment were administered to 43% of subjects treated with CP-547,632 plus chemotherapy and 53% of subjects treated with

Table 3 Gastrointestinal toxicity, treatment-emergent AEs, all causality, all dose levels

CTC term	Grade 1–2		Grade 3		Grade 4		All	
	n	(%)	*n*	(%)	*n*	*n*	(%)	*n*
CP-547,632 patients (phase 1 and 2), *n* = 51								
Diarrhea	30	58.8	6	11.8	0	0	36	70.1
Nausea	28	54.9	6	11.8	0	0	34	66.6
Anorexia	21	41.2	2	3.9	0	0	23	45.1
Vomiting	25	49.0	4	7.8	0	0	29	56.9
Stomatitis	8	15.7	0	0	0	0	8	15.7
Constipation	16	31.4	0	0	0	0	16	31.4
Dehydration	7	13.7	5	9.8	0	0	12	23.5
Patients receiving chemotherapy without CP-547,632 (Phase 2), *n* = 17								
Diarrhea	5	29.4	0	0	0	0	5	29.4
Nausea	10	58.8	0	0	0	0	10	58.8
Anorexia	5	29.4	0	0	0	0	5	29.4
Vomiting	7	41.2	0	0	0	0	7	41.2
Stomatitis	0	0	0	0	0	0	0	0
Constipation	7	41.2	0	0	0	0	7	41.2
Dehydration	0	0	2	11.8	0	0	2	11.8

Table 4 Dermatologic toxicity, treatment-emergent AEs, all causality, all dose levels

CTC term	Grade 1–2		Grade 3		Grade 4		All	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
CP-547,632 patients (phase 1 and 2), *n* = 51								
Alopecia	30	58.8	N/A		N/A		30	58.8
Rash	18	35.3	5	9.8	0	0	23	45.1
Pruritus	7	13.7	2	3.9	0	0	9	17.6
Patients receiving chemotherapy without CP-547,632 (phase 2), *n* = 17								
Alopecia	13	76.4	N/A		N/A		13	76.4
Rash	1	5.9	0	0	0	0	3	5.9
Pruritus	2	11.8	0	0	0	0	2	11.8

Table 5 All bleeding events and thrombosis, treatment-emergent AEs, all causality, all dose levels

CTC term	Grade 1–2		Grade 3		Grade 4		All	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
CP-547,632 patients (phase 1 and 2), *n* = 51								
Epistaxis	12	23.5	2	4.0	0	0	14	27.5
Hematuria	8	15.7	1	1.9	0	0	9	17.6
Melena/bleed[a]	1	1.9	1	1.9	0	0	2	4.0
Hemoptysis	3	5.9	0	0	0	0	3	5.9
Rectal bleed/hematochezia	6	11.8	0	0	0	0	6	11.8
Thrombosis/embolism[b]	0	0.0	0	0	1	1.9	1	1.9
Hemorrhage-other	1	1.9	0	0	0	0	1	1.9
Chemotherapy without CP-547,632 (phase 2), *n* = 17								
Epistaxis	2	11.8	0	0	1	5.9	3	17.6
Hematuria	0	0	0	0	0	0	0	0
Melena/bleed	0	0	0	0	0	0	0	0
Hemoptysis	2	11.8	0	0	0	0	2	11.8
Rectal bleed/hematochezia	1	5.9	0	0	0	0	1	5.9
Thrombosis/embolism	0	0	0	0	0	0	0	0
Hemorrhage-other	0	0	0	0	0	0	0	0

[a] Grade 3 GI bleed attributed to carboplatin/paclitaxel therapy

[b] Grade 4 pulmonary embolism attributed to disease under study

chemotherapy alone. In the phase 2 CP-547,632 plus chemotherapy treatment group, the median number of cycles was 4 (range 1–16). For the phase 2 chemotherapy alone group, the median number of treatment cycles was 6 (range 1–6).

Anti-tumor activity

As shown in Table 6, 31 of 37 subjects in phase 1 were evaluable for efficacy. In phase 2 Arm A (CP-547,632 plus chemotherapy), 14 of 16 subjects were evaluable

for efficacy. In phase 2 Arm B (chemotherapy), 16 of 17 subjects were evaluable for efficacy. No subject had CR. In phase 1, 7 (22.6%) subjects had PR, 14 (45.2%) subjects had stable disease, and 10 (32.3%) subjects had progressive disease. In phase 2 Arm A, four subjects (28.6%) had a PR, six subjects (42.9%) had stable disease, and four subjects (28.6%) had progressive disease. In phase 2 Arm B, four subjects (25%) had PR, nine subjects (56.3%) had stable disease, and three subjects (18.7%) had progressive disease. Based on data with bevacizumab showing an improvement in response rate when added to chemotherapy [21], we also performed a conditional probability analysis of response rate, including subjects from phase I that met the II inclusion/exclusion criteria for phase 2. An interim analysis of all phase 1 and phase 2 stage 1 data, in which conditional power was applied to the data available at that time, demonstrated a low likelihood of achieving a true response rate superior to carboplatin/paclitaxel alone (true response rate ≥25%). Ten responses out of 30 patients would indicate a true response rate of at least 25% (80% CI). From the Phase 2 data (Arm A) the observed response rate was 23%. Combining the Phase 1 and Arm A phase 2 data, the observed response rate was 20%. The probability of achieving at least 7 more responses out of 17 more patients in Arm A if the current trend (3/13 = 23%) continued would be 7%. An improvement in disease stabilization from standard chemotherapy was a secondary endpoint for the study. As an indicator, time to progression (TTP) was also examined. The median TTP in Phase 2 CP-547,632 plus chemotherapy was 4.7 months. In the CP-547,632 plus chemotherapy Phase 1 and Phase 2 data combined the median TTP was 5.2 months. In the chemotherapy alone group the median TTP was 7.7 months. Given the low likelihood that continuation of the study would reveal clinical benefit (objective response or prolonged disease stabilization), the trial was stopped.

Pharmacokinetics

Pharmacokinetic profiles of CP-547,632 were obtained after a single oral dose of CP-547,632 from 29 patients. Mean PK parameters of CP-547,632 at the four dose levels tested are listed in Table 7. The terminal half-life of CP-547,632 is similar across dose levels, ranging from 28.8 to 32.2 h. Systemic exposure of CP-547,632 measured as C_{max} and AUC increases approximately in proportion to dose over the dose range studied, and oral clearance (CL_{oral}) of CP-547,632 following single dose is similar across doses studied. Based on the apparent elimination half-life of ~30 h, steady-state levels of CP-547,632 will be reached after approximately 7 days of daily dosing. Thus, pharmacokinetic data from day 18 can be considered as steady-state data. AUC_{0-24} at steady-state when CP-547,632 given by daily oral dosing is similar to AUC_{0-inf} following a single oral dose of CP-547,632, indicating that there are no time-dependent changes in CL_{oral} for once daily dosing. Plasma paclitaxel concentrations were determined in cycle 1 (without CP-547,632) and cycle 2 (with concomitant daily CP-547,632 dosing). The mean ratio of paclitaxel AUC_{0-24} in cycle 2 to that in cycle 1 is approximately 1.4 for patients who received the same doses of paclitaxel in both cycles, but no conclusions can be drawn because of the very limited sample size ($n = 4$).

Discussion

This study was designed to explore the safety and efficacy of CP-547,623 administered with paclitaxel and carboplatin in patients receiving 1st-line treatment for advanced NSCLC. The principle toxicities of protocol therapy were fatigue, diarrhea, sensory neuropathy, nausea, alopecia, anorexia, rash/desquamation, vomiting, neutropenia, arthralgia, myalgia and anemia. Non-hematologic toxicities were generally mild to moderate. Dose limiting toxicities in this study were grade 3 rash and diarrhea. The combination of CP-547,632 and chemotherapy did not cause unexpected or unusually severe toxicities when compared to those seen with each drug alone. Hypertension and bleeding are two common adverse events in studies of angiogenesis inhibitors [25]; in this study hypertension was not dose-limiting and severe bleeding was rare. The

Table 6 Best response for evaluable subjects

Best response	Phase 1 (no. of pts)	Phase 2/Stage 1 arm A (no. of pts)	Phase 2/Stage 1 arm B (chemotherapy alone) (no. of pts)
CR	0	0	0
PR confirmed/unconfirmed	7/4	4/3	4/1
SD	14	6	9
PD	10	4	3
Total Evaluable Pts	31	14	16

Phase 1 subjects with early toxicity were not evaluable. Phase 2 subjects with early toxicity were considered PD

Table 7 Mean (SD) pharmacokinetic parameters of CP-547,632 in NSCLC patients

Dose (mg)	Single dose						Steady state				
	N	C_{max} (ng/ml)	AUC_{0-24} (h ng/ml)	AUC_{0-inf} (h ng/ml)	CL_{oral} (l/h)	$t_{1/2}$ (h)	*N*	C_{max} (ng/ml)	c_{trough} (ng/ml)	AUC_{0-24} (h ng/ml)	C_{avg} (ng/ml)
100	8	60.9 (34.1)	881 (471)	2090 (1070)	66.2 (43.3)	32.2	7	142 (81.6)	99.9 (86.8)	2940 (2120)	123 (88.3)
150	8	131 (33)	1890 (551)	4660 (1630)	36.8 (16.8)	28.8	4	311 (151)	190 (101)	5330 (2210)	222 (91.9)
200	8	142 (61.9)	2280 (791)	5180 (1300)	40.9 (10.5)	31.5	16	312 (114)	189 (93.6)	5650 (2480)	236 (104)
250	5	216 (98.8)	3720 (1540)	10900 (6140)	30.1 (16.5)	32.1	3	394 (199)	283 (221)	7680 (5000)	320 (209)

C_{max} maximum plasma concentration observed, AUC_{0-24} area under the plasma concentration–time curve from time 0 to 24 h, AUC_{0-inf} area under the plasma concentration-time curve from time 0 to infinity, CL_{oral} oral clearance, $t_{1/2}$ apparent elimination half life, C_{trough} trough plasma concentration, C_{avg} average plasma concentration

recommended phase 2 dose of CP-547,632 is 200 mg/day when combined with paclitaxel 225 mg/m^2 and carboplatin AUC = 6.

CP-547,632 conferred no apparent improvement in objective response rate when added to carboplatin and paclitaxel in chemotherapy-naive patients with advanced NSCLC. Although CP-547,632 was fairly well-tolerated, the clinical benefit in this study population was not considered promising and the study was halted. Based upon these data, further development of CP-547,632 in this setting is not warranted. These results are disappointing in light of additive or synergistic activities of CP-547,632 in combination with chemotherapy in preclinical models, but the results are similar to negative results seen in other studies adding small molecule EGFR inhibitors to chemotherapy in NSCLC [26–29] or more recent studies adding PTK787 (vatalanib) to first-line chemotherapy in metastatic colorectal cancer [30].

By contrast, VEGF ligand targeting in NSCLC with bevacizumab has been successful [21]. Why vascular targeting failed with CP-547,632 is not clear. Detailed pharmacokinetic analyses indicate that mean plasma concentrations of CP-547,632 at steady-state fell into the range of efficacious plasma concentrations for all dose levels studied (83–590 ng/ml for C_{avg} and 148–1,500 ng/ml for C_{max}), as defined using a preclinical anti-angiogenesis model (Fig. 1). [31] Due to the small sample size, no conclusions can be made regarding pharmacodynamic relationships between paclitaxel and CP-547,632 or carboplatin and CP-547,632, although the limited data for paclitaxel do not indicate any obvious negative interaction. Therefore, the apparent lack of therapeutic effect does not appear to be a problem of drug exposure. Indeed, there was dose-limiting skin and GI toxicity similar to that observed in studies of other small molecule TKIs [17, 18, 32–34], as well as grade 1/2 hypertension in a third of subjects suggesting in vivo biologic effects. Steady state plasma CP-547,632 concentrations are reached about 7 days after treatment begins and are greater than $C_{eff, low}$ throughout the treatment period with minimal fluctuation of (C_{max}/C_{trough} less than 2). Therefore, under the current dosing regimen for CP-547,632 (daily dosing), we believe the dosing sequence of CP-547,632 and chemotherapy does not explain the observed lack of benefit. It is conceivable that failure of the combination to yield improved anti-tumor effects reflects antagonism between cytostatic and cytotoxic agents.

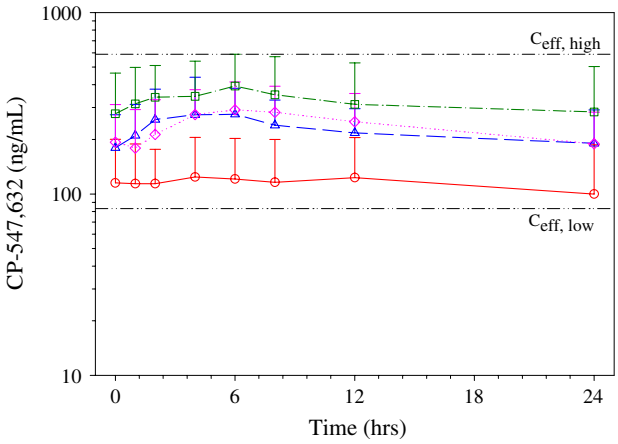

Fig. 1 Mean (SD) plasma concentration time profiles of CP-547,632 in NSCLC patients at steady-state (day 18) following daily oral doses of 100 mg (*circle*), 150 mg (*triangle*), 200 mg (*diamond*), and 250 mg (*square*) CP-547,632. The efficacious plasma concentrations (C_{eff}) predicted based on a pre-clinical anti-angiogenesis model are showed as *dashed lines*

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