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Sunitinib in combination with paclitaxel plus carboplatin in patients with advanced solid tumors: phase I study results

Elisabeth I. Heath,
Karmanos Cancer Institute, 4100 John R, Detroit, MI 48201, USA Tel: +1 313 576 8715; Fax: +1 313 576 8767

George R. Blumenschein Jr,
The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Roger B. Cohen,
Fox Chase Cancer Center, Philadelphia, PA, USA

Patricia M. LoRusso,
Karmanos Cancer Institute, 4100 John R, Detroit, MI 48201, USA Tel: +1 313 576 8715; Fax: +1 313 576 8767

Noelle K. LoConte,
University of Wisconsin Carbone Cancer Center, Madison, WI, USA

Sindy T. Kim,
Pfizer Oncology, Clinical Development, La Jolla, CA, USA

Ana Ruiz-Garcia,
Pfizer Oncology, Clinical Development, La Jolla, CA, USA

Richard C. Chao, and
Pfizer Oncology, Clinical Development, La Jolla, CA, USA

George Wilding
University of Wisconsin Carbone Cancer Center, Madison, WI, USA

Abstract

Purpose—To evaluate the maximum tolerated dose (MTD), safety, and antitumor activity of sunitinib combined with paclitaxel and carboplatin.

Methods—Successive cohorts of patients with advanced solid tumors received oral sunitinib (25, 37.5, or 50 mg) for 2 consecutive weeks of a 3-week cycle (Schedule 2/1) or as a continuous daily dose for 3-week cycles (CDD schedule) in combination with paclitaxel (175–200 mg/m^2) plus carboplatin (AUC 6 mg•min/mL) on day 1 of each of 4 cycles. Dose-limiting toxicities (DLTs) and adverse events (AEs) were evaluated to determine the MTD. Efficacy parameters were analyzed in patients with measurable disease.

Results—Forty-three patients were enrolled (n = 25 Schedule 2/1; n = 18 CDD schedule). Across all doses, 6 DLTs were observed (grade 4 papilledema, grade 5 GI hemorrhage, grade 3

Correspondence to: Elisabeth I. Heath.

heathe@karmanos.org.

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neutropenic infection, grade 4 thrombocytopenia [$n = 3$]). The MTD for Schedule 2/1 was sunitinib 25 mg plus paclitaxel 175 mg/m^2 and carboplatin AUC 6 mg•min/mL. The MTD was not determined for the CDD schedule. Treatment-related AEs included neutropenia (77%), thrombocytopenia (56%), and fatigue (47%). Of 38 evaluable patients, 4 (11%) had partial responses and 12 (32%) had stable disease. PK data indicated an increase in maximum and total plasma exposures to sunitinib and its active metabolite when given with paclitaxel and carboplatin compared with sunitinib monotherapy.

Conclusions—Myelosuppression resulting in prolonged dose delays and frequent interruptions was observed, suggesting that this treatment combination is not feasible in the general cancer population.

Keywords

Sunitinib; Phase I; Solid tumor; NSCLC; Antiangiogenesis; Chemotherapy

Introduction

Carboplatin and paclitaxel are frequently combined to treat a broad range of solid tumor types, including ovarian cancer and non-small cell lung cancer (NSCLC). Efficacy of chemotherapy is limited, however, especially in advanced cancer [1, 2]. Consequently, there is considerable interest in developing innovative treatment strategies, with one common approach being the combination of agents with different mechanisms of action such as chemotherapy with molecularly targeted drugs.

Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) signaling pathways play a critical role in angiogenesis and have been identified as therapeutic targets for multiple solid tumors [3, 4]. The targeted antiangiogenic agent bevacizumab, an anti-VEGF monoclonal antibody, has shown encouraging antitumor activity when combined with chemotherapy in patients with solid tumors [5–7]. In a randomized phase III study in NSCLC, overall survival was improved in patients treated with paclitaxel, carboplatin, and bevacizumab compared with patients treated with paclitaxel/carboplatin alone [8].

In addition to inhibition of VEGF, evidence suggests that inhibiting multiple signaling pathways in parallel, such as VEGF and PDGF pathways, may be more effective than inhibiting single pathways in isolation [9, 10]. Sunitinib malate (SUTENT®) is an oral multitargeted tyrosine kinase inhibitor (TKI) of VEGF and PDGF receptor (VEGFR and PDGFR) subtypes, stem cell factor receptor (KIT), FMS-like tyrosine kinase (FLT3), glial cell line-derived neurotrophic factor (REarranged during Transfection [RET]), and colony-stimulating factor 1 receptor (CSF-1R) [11, 12]. Sunitinib is currently approved for treatment of advanced renal cell carcinoma (RCC) and imatinib-resistant/-intolerant gastrointestinal stromal tumor (GIST) [13–15].

The primary objective of this phase I study was to assess the maximum tolerated dose (MTD) and overall safety of sunitinib administered on two different schedules in combination with paclitaxel and carboplatin, for the treatment of patients with advanced solid tumors. Secondary objectives included evaluation of the pharmacokinetics (PK) of the combination and antitumor activity in patients with measurable disease.

Materials and methods

Patient eligibility

Patients ≥ 18 years with advanced solid tumors refractory to standard therapy or for which no curative therapy exists were eligible if they were considered suitable for treatment with standard doses of carboplatin and paclitaxel and had a life expectancy of ≥ 12 weeks. A maximum of two prior chemotherapy regimens was permitted. Additional inclusion criteria included an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and adequate organ function. Exclusion criteria included prior treatment with high-dose chemotherapy requiring stem cell rescue or prior irradiation to ≥ 25% of bone marrow; and surgery, systemic therapy or any investigational agent within 4 weeks prior to starting study treatment (except palliative radiotherapy). Other exclusion criteria included history of untreated brain metastases and severe acute or chronic cardiovascular abnormalities.

Study design and treatment

In this phase I, open-label, multicenter, dose-finding study (3 + 3 design) patients were scheduled to receive sunitinib in combination with paclitaxel and carboplatin for 4 cycles. A treatment cycle consisted of 3 weeks of once-daily dosing of oral sunitinib given on either Schedule 2/1 (2 weeks on treatment followed by 1 week off treatment) or on a continuous daily dosing (CDD) schedule, in combination with intravenous (iv) paclitaxel and carboplatin administered once every 21 days. The starting doses of each drug were sunitinib 25 mg/day, paclitaxel 175 mg/m^2, and carboplatin area under the curve (AUC) 6 mg•min/mL.

The MTD was defined as the highest dose at which 0/6 or 1/6 patients experienced a dose-limiting toxicity (DLT) during the first cycle, with at least 2/3 or 2/6 patients experiencing a DLT at the next higher dose level. In general, treatment-related grade 3 or 4 toxicities were considered DLTs including: grade 4 neutropenia lasting ≥ 7 days, febrile neutropenia lasting > 24 h, neutropenic infection, grade ≥ 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia lasting ≥ 7 days, lymphopenia accompanied by an infection, and grade 3 or 4 non-hematologic toxicities lasting ≥ 7 days. Persistent nausea, vomiting, or diarrhea (despite maximal medical therapy) were also considered DLTs.

Escalating doses of sunitinib and paclitaxel and carboplatin were first studied on sunitinib Schedule 2/1 starting at dose level 1 (Table 1). According to the protocol, once the DLT assessment period was completed on dose level 1 of Schedule 2/1, the sunitinib CDD schedule was evaluated, starting at dose A (Table 1). Dose escalation occurred as summarized in Table 1. Once the MTD was determined for both sunitinib treatment schedules, additional patients were to be enrolled at the MTD(s) to better characterize safety and antitumor activity. In addition, there was the option to enrol further subjects at specific dose levels to further explore the observed toxicity and PK profile. Further details relating to the dose-escalation decisions made during the trial are described in the Results section.

Patients could be treated with 4 cycles of combination therapy until disease progression, unacceptable toxicity, or withdrawal of consent. Dose reductions were permitted at the discretion of the investigators. Patients deriving clinical benefit upon completion of 4 cycles could continue to receive sunitinib alone under a separate continuation protocol.

All patients provided written informed consent. The study was performed with institutional ethics committee approval, and in accordance with International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki (1996 Version), and applicable local and Federal regulatory requirements and laws.

Study endpoints and assessments

The primary endpoints were the MTD and overall safety of the combination. Secondary endpoints included PK parameters and assessment of antitumor activity. Safety was assessed by recording adverse events (AEs), graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0. Hematology and blood chemistry parameters were also monitored at baseline and throughout the study. Other safety assessments included physical examinations and vital signs, and 12-lead electrocardiograms (ECG) performed at screening, during cycle 1, and at end of treatment.

Tumor assessments were performed at screening and at the end of cycles 2 and 4, and whenever disease progression was suspected according to Response Evaluation Criteria In Solid Tumors (RECIST) [16]. Objective tumor response was assessed in patients with measurable disease.

Full PK profiles were obtained on Schedule 2/1 from 5 patients receiving dose level 1, 4 patients receiving dose level 2, and 2 patients receiving dose level 3. On the CDD schedule, full PK profiles were obtained from 1 patient receiving dose level A and 5 patients receiving dose level B (dose levels described in Table 1). Plasma samples for PK analyses were analyzed using validated analytical methods. Sunitinib and SU12662 were assayed using LC-MS/MS (assay dynamic range was 0.100– 60.0 ng/mL for sunitinib and 0.100–20.0 ng/mL for SU 012662). Paclitaxel was assayed using LC-MS/MS with solid phase extraction; the assay had a dynamic range of 10.0–2000 ng/mL. Carboplatin was assayed using ICP/MS (assay dynamic range was 2.00–1000 ng/mL).

PK parameters for sunitinib, its primary metabolite (SU12662), total drug (sunitinib plus SU12662), paclitaxel, and carboplatin are reported for paired observations. On Schedule 2/1, patients received a single dose of sunitinib 7 days prior to the start of cycle 1 (day –7). Following this dose, 24-h plasma samples were taken to assess sunitinib and SU12662 PK. During cycle 1, paclitaxel and carboplatin were given on day 1 and sunitinib was started on day 3 and given through cycle 1, day 16. This dosing schedule allowed PK data to be collected for sunitinib alone (day –7), paclitaxel and carboplatin alone (cycle 1, day 1), and sunitinib plus paclitaxel and carboplatin (cycle 2, day 1). From cycle 2 onwards, sunitinib plus paclitaxel and carboplatin were administered starting on day 1 of each cycle. On the CDD schedule, sunitinib was started on day 3 in cycle 1. This allowed PK analysis of paclitaxel and carboplatin alone (cycle 1, day 1), sunitinib alone at steady state (cycle 1, day 15), and paclitaxel and carboplatin plus steady-state sunitinib (cycle 2, day 1). From cycle 2 onwards, sunitinib plus paclitaxel and carboplatin were administered starting on day 1 of each cycle.

Statistical methods

The observed safety profile on each schedule determined the number of patients per dose level and number of dose escalations. Due to the exploratory nature of this study, no inferential analyses were planned.

Results

Patient characteristics

Forty-three patients were enrolled into the trial: 25 patients on Schedule 2/1 and 18 patients on the CDD schedule. The median age of patients was 58 years (range: 32–76). Baseline characteristics are summarized in Table 2.

Subject evaluation groups

The doses of study treatment evaluated are shown in Table 1. The sponsor and investigators agreed to further expand dose level 2 for Schedule 2/1 and dose level B for the CDD schedule to better characterize the safety profile of the combination regimens. Initially, 6 patients were enrolled in the first cohort at dose level 1 on Schedule 2/1 (including 2 patients who were not evaluable for DLT: $n = 1$ developed a hypersensitivity reaction to paclitaxel; $n = 1$ experienced disease progression prior to cycle 1 day 1). One DLT (grade 4 papilledema) was observed and this cohort was expanded to 9 patients, resulting in 7 patients evaluable for DLTs. Because no additional DLTs were observed, patients were next enrolled at dose level 2 and, among 3 patients initially enrolled who were evaluable for DLTs (1 further patient discontinued early due to disease progression prior to cycle 1, day 1), one DLT was observed; this cohort was then expanded to 13 patients. While the dose level 2 cohort was being expanded, the protocol was amended to allow concurrent enrollment into Schedule 2/1 and the CDD schedule. Three patients were enrolled onto dose level 3 and no DLTs were observed. Following enrollment into dose level 3, further DLTs were observed in the expanded dose level 2 cohort. On the CDD schedule starting at dose level A, 3 patients were enrolled and no DLTs were observed. Enrollment of the CDD schedule cohorts continued as described in Table 1.

A total of 13 patients (30%) completed the study (receiving the 4 planned cycles of study treatment) and 30 patients discontinued before completion. Of the 13 patients who completed, 12 ($n = 4$ from Schedule 2/1 cohorts, $n = 8$ from CDD cohorts) enrolled in a continuation protocol and received sunitinib as a single agent. One additional patient who was discontinued from the study due to AEs after cycle 1 was also enrolled in the continuation protocol. Twenty of the 25 patients (80%) on Schedule 2/1 discontinued treatment early: 11 patients due to insufficient clinical response and 9 due to AEs, including 6 who had AEs that were considered treatment-related (papilledema, gastrointestinal [GI] hemorrhage, syncope, pyrexia, pneumonia, leukopenia, and hemoptysis [all $n = 1$ each], anemia [$n = 3$], thrombocytopenia [$n = 3$], and neutropenia [$n = 2$]). Ten of the 18 patients (56%) on the CDD schedule discontinued treatment early: 6 patients due to insufficient clinical response; 2 due to AEs (1 patient had AEs considered to be treatment-related: neutropenia, anemia, and thrombocytopenia); 1 patient on the CDD schedule died due to disease progression; and 1 patient withdrew consent.

The number of sunitinib treatment cycles started ranged between 0–4 and 1–5 on Schedule 2/1 and the CDD schedule, respectively. One patient on the CDD schedule received 5 cycles of sunitinib on the study, receiving an additional cycle of treatment while awaiting enrollment in the continuation protocol. In total 11 patients received all three drugs through to the start of cycle 2 without dose reductions, dose delays or dose interruptions (Schedule 2/1 dose level 1, $n = 2$; dose level 2 $n = 2$; CDD schedule dose B, $n = 5$; dose B1, $n = 2$).

Of the 25 patients on Schedule 2/1, 10 (40%) required sunitinib dose delays and 2 (8%) required dose reductions. Of the 18 patients on the CDD schedule, 8 (44%) required sunitinib dose delays and 3 (17%) required dose reductions. In all but 2 patients, sunitinib dose delays were attributed to neutropenia, thrombocytopenia or leukopenia (all grades). The duration of sunitinib dose delays was most commonly ≥ 3 weeks ($n = 18$ patients overall).

In the Schedule 2/1 cohorts, 10 patients experienced dose delays for paclitaxel and 10 patients experienced dose delays for carboplatin. Five patients experienced at least one dose reduction of paclitaxel and 1 patient experienced ≥ 2 dose reductions of carboplatin. In the CDD cohorts, 9 and 8 patients experienced dose delays for paclitaxel and carboplatin,

respectively, and 3 and 1 patients experienced at least one dose reduction of paclitaxel and carboplatin, respectively.

Determination of MTD

Across all schedules, DLTs occurring in the first treatment cycle were reported in 6 patients (14%; Table 1). All DLTs were reported as serious AEs (SAEs) and considered to be related to sunitinib and/or paclitaxel and carboplatin treatment. On Schedule 2/1, the MTD was determined as sunitinib 25 mg/day plus paclitaxel 175 mg/m^2 and carboplatin AUC 6 mg•min/mL. The MTD was not determined for the CDD schedule.

Other safety findings

Treatment-emergent (all-causality) non-hematologic AEs occurring in ≥ 10% of patients across all treatment combinations are shown in Table 3. Most nonhematologic AEs were grade 1 or 2 in severity. The most common were fatigue (58%), nausea (44%), alopecia (30%), and dyspnea (28%).

Overall, 35/43 patients (81%) experienced at least one AE (grade ≥ 3) considered related to study treatment. The most common treatment-related AEs were neutropenia (77%; grade 3 [23%] or 4 [42%]), thrombocytopenia (56%; grade 3 [19%] or 4 [14%]), and fatigue (47%; grade 3 [7%]). The frequency of treatment-related AEs was similar for Schedule 2/1 and the CDD schedule, although the incidence of treatment-related thrombocytopenia was higher for patients on the CDD schedule (11/18 subjects, 61%) compared with Schedule 2/1 (13/25 subjects, 52%).

All causality hematologic AEs reported in all cycles and cycle 1 are shown in Table 4. Neutropenia (79%) and thrombocytopenia (74%) were the most frequent events. Hematologic laboratory abnormality shifts from grade ≤ 2 to grade ≥ 3 (all patients, both schedules) included neutropenia (70%), leukopenia (49%), thrombocytopenia (40%), lymphopenia (35%), and anemia (23%). No patient experienced grade 4 lymphopenia. One patient experienced a shift to grade 4 anemia.

Cardiovascular disorders occurred infrequently. Grade 3 thrombosis, grade 1 sinus tachycardia, and grade 1 tachycardia were reported in 1 patient each. None of these AEs was considered related to study treatment. One patient receiving dose level 2 on Schedule 2/1 experienced grade 3 syncope deemed treatment-related by the investigator. There were no clinically significant changes at any timepoints for the mean heart rate, blood pressure, and ECG parameters.

Three patients died on study. Two deaths were attributed to disease progression (bladder cancer [$n = 1$] and esophageal adenocarcinoma [$n = 1$]). The third patient, a 59-year-old male patient with pancreatic carcinoma who was receiving treatment on Schedule 2/1 dose level 2, died due to GI hemorrhage and hypotension, which were considered possibly related to study treatment.

Antitumor activity

Of the 38 patients with measurable disease at baseline and evaluable for response, 4 patients achieved a partial response (PR) for an objective response rate of 10.5% (95% confidence interval [CI]: 2.9%, 24.8%) across all cohorts. Two PRs occurred on Schedule 2/1 (one at dose level 1 and the other at dose level 2). Two PRs occurred on the CDD schedule (one at dose level B and the other at dose level B1). Patients with PRs had the following primary diagnoses: SCLC ($n = 1$), NSCLC ($n = 2$), and peritoneal carcinomatosis ($n = 1$), and 2

patients had received prior chemotherapeutic regimens (carboplatin plus etoposide and topotecan; carboplatin plus paclitaxel; and carboplatin plus gemcitabine).

Across both dosing schedules, stable disease (SD) with duration ≥ 42 days after the first dose of study drug was observed in 12 patients (n = 6 on Schedule 2/1 and n = 6 on the CDD schedule). Twelve patients (32%) experienced progressive disease (PD) as their best response (6 on Schedule 2/1 and 6 on the CDD schedule). Response status could not be determined for 10/38 evaluable patients because post-baseline scans were not available (patients either discontinued early or lesions identified at baseline were not assessed).

Pharmacokinetics

AEs prevented many patients from taking sunitinib daily on both schedules. On the CDD schedule, plasma concentration profiles at steady state were collected for only 5 patients (paired observations) at sunitinib 37.5 mg/day plus paclitaxel 175 mg/m^2 and carboplatin AUC 6 mg•min/mL (dose level B), and 1 patient at sunitinib 25 mg/day plus paclitaxel 175 mg/m^2 and carboplatin AUC 6 mg•min/mL (dose level A). Therefore, PK parameters are presented only for the dose levels on both treatment schedules with a sufficient number of evaluable patients: sunitinib 37.5 mg/day plus paclitaxel 175 mg/m^2 and carboplatin AUC 6 mg•min/mL (dose levels 2 and B; Table 1). The data indicated an increase in maximum and total plasma exposures to sunitinib and its active metabolite SU12662 when sunitinib was given with paclitaxel and carboplatin compared with sunitinib monotherapy (Table 5). No notable difference in PK was observed between Schedule 2/1 and the CDD schedule.

Discussion

The objective of this phase I, dose-finding, PK study was to determine the MTD and overall safety of sunitinib plus paclitaxel and carboplatin in patients with solid tumors for whom curative therapy was not available. Sunitinib was investigated on intermittent (Schedule 2/1, 2 weeks on treatment, 1 week off treatment) and CDD schedules. The MTD on Schedule 2/1 (investigated in 25 patients) was determined to be sunitinib 25 mg/day plus paclitaxel 175 mg/m^2 and carboplatin AUC 6 mg•min/mL. The MTD for the CDD schedule was not determined (investigated in 18 patients) because the study was stopped before formal determination of the MTD, based upon the toxicity patterns observed in the sunitinib Schedule 2/1 cohort. Frequent and sometimes prolonged dose delays and dose interruptions also made assessment of the MTD challenging. In total 11 patients (Schedule 2:1 n = 4; CDD schedule n = 7) received all three drugs through to the start of cycle 2 without dose reductions, dose delays or dose interruptions.

Most non-hematologic AEs reported with sunitinib plus paclitaxel and carboplatin were grade 1 or 2 in severity. No unexpected AEs were reported and no significant cardiac abnormalities were noted during this study. Even though AEs greater than grade 1 or 2 in severity were infrequent, the cumulative effect of multiple grade 1/2 side effects in individual patients and the prolonged duration of these toxicities resulted in the need for dose interruptions and treatment delays in a significant proportion of patients, and suggested that the regimens studied were ultimately unfeasible. Similar observations have been reported in clinical trials of other targeted therapies when combined with each other or cytotoxic chemotherapy [17].

The most common non-hematologic AEs were fatigue, nausea, alopecia, and dyspnea. The AE profile in this study was generally similar to that of other studies of a taxane plus carboplatin [18–20], single-agent sunitinib [21–23], or sunitinib in combination with chemotherapy [24–26] . However, grade 3/4 neutropenia and thrombocytopenia (laboratory abnormalities) occurred in 70% and 40% of patients, respectively, which is a higher

incidence than has been reported in trials of other targeted agents in combination with carboplatin and paclitaxel in patients with solid tumors [8, 27–29]. Temporary sunitinib dose interruptions/delays were needed by almost half of the patients enrolled in this study and were attributed to neutropenia, thrombocytopenia or leukopenia (all grades) at one or more times in all but 2 of these patients. Based on the investigators' observations, chemotherapy-naïve patients appeared to tolerate the treatment better than chemotherapy-refractory patients. Delays or interruptions in the dosing of paclitaxel and carboplatin were also frequent during this trial, further limiting the feasibility of this treatment regimen. Additionally, the majority of patients (70%) discontinued study treatment before receiving the 4 planned cycles: 80% of patients on Schedule 2/1 and 56% on the CDD schedule. Inline with the investigators' observations on tolerability, the imbalance in discontinuation rates between the two schedules might have been related to the fact that the majority of patients on Schedule 2/1 (80%) had received prior chemotherapy whereas over half of patients on the CDD schedule were chemotherapy-naïve (56%).

Complete PK data based on small sample sizes (4 and 5 patients in Schedule 2/1 and CDD cohorts, respectively) suggest that administration of sunitinib with paclitaxel and carboplatin led to an increase in maximum and total plasma exposures to sunitinib and its active metabolite SU12662 compared with sunitinib administered alone. This may have been the result of inhibition of the CYP3A4 metabolic pathway and/or P-glycoprotein (P-gp) efflux system (during absorption or elimination) by paclitaxel. Both sunitinib and SU12662 are substrates for CYP3A4 [30]; SU12662 is also a substrate for P-gp. Paclitaxel at higher concentrations has the potential to inhibit both CYP3A4 and the P-gp transport system [31–35]. Carboplatin, on the other hand, is very unlikely to inhibit either of these pathways. The administration of sunitinib with paclitaxel and carboplatin did not appear to affect the PK of either paclitaxel or carboplatin. The observed drug–drug interaction between sunitinib and paclitaxel may have contributed to some of the toxicities observed in this study, including neutropenia and thrombocytopenia resulting in dose interruptions/delays. However, other variables such as patient selection or overlapping mechanisms of action may have contributed

Of the 38 evaluable patients with measurable disease at baseline, 4 patients (with tumor types typically treated with paclitaxel and carboplatin) had confirmed PRs, 2 of whom where chemotherapy-naïve. Given the short duration of treatment (4 cycles) and limited patient numbers in this phase I trial, no time-to-event analysis was performed and no definitive conclusions can be drawn regarding the antitumor activity of the triple combination regimen.

In summary, a potential drug–drug interaction may have led to an increase in levels of sunitinib and SU12662, resulting in increased myelosuppression and consequent dose interruptions/delays, which limit the dose intensity and potential utility of this combination.

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Table 1

Planned dose levels and observed dose-limiting toxicities

Dose level[a]	Paclitaxel (mg/m^2)	Carboplatin (mg•min/mL)	Sunitinib (mg)	*N* (*n* evaluable for DLT)	DLTs
Schedule 2/1[b]					
1	175	6	25	9 (7)	Grade 4 papilledema (*n* = 1)
2	175	6	37.5	13 (10)	Grade 5 gastrointestinal hemorrhage (*n* = 1) Grade 4 thrombocytopenia (*n* = 2) Grade 3 neutropenic infection (*n* = 1)
3	200	6	37.5	3 (3)	None
CDD schedule[c]					
A	175	6	25	3 (3)	None
B	175	6	37.5	9 (9)	None
C[d]	175	6	50	2 (2)	Grade 4 thrombocytopenia (*n* = 1)
B1[d]	200	6	25	4 (4)	None

CDD continuous daily dosing; *DLT* dose-limiting toxicity

If 0/3 patients experienced a DLT during cycle 1, subjects were enrolled onto the next dose level

If 1/3 subjects experienced a DLT during cycle 1, the cohort was expanded to a total of *n* = 6 patients. If 1/6 subjects experienced a DLT, then dose escalation continued and subjects were enrolled in the next dose level

If ≥ 2 subjects in any cohort experienced a DLT during cycle 1, then the MTD had been exceeded and cohorts in preceding dose levels could be expanded to a total of *n* = 6 patients until the MTD was identified

If there was interest in further exploring the toxicity profile observed at a specific dose level and 2 DLTs were observed in the initial 6 patients enrolled, an additional 3 patients could be enrolled. If no additional DLTs were observed, dose escalation could continue after discussion between the sponsors and investigators

[a] Patients started sunitinib on day 3 and chemotherapy on day 1 of cycle 1. During subsequent cycles, patients started both chemotherapy and sunitinib on day 1

[b] On Schedule 2/1, the MTD was determined as sunitinib 25 mg/day plus paclitaxel 175 mg/m^2 and carboplatin AUC 6 mg•min/mL

[c] MTD was not determined on the CDD schedule

[d] Patients were enrolled concurrently onto doses C and B1

Table 2

Patient demographics

	Schedule 2/1 *n* = 25	CDD schedule *n* = 18	Total *N* = 43
Sex, *n* (%)			
Male / Female	17 (68) / 8 (32)	12 (67) / 6 (33)	29 (67) / 14 (33)
ECOG performance status, *n* (%)			
0/1	6 (24) / 19 (76)	5 (28) / 13 (72)	11 (26) / 32 (74)
Primary disease sites			
NSCLC	4 (16)	6 (33)	10 (23)
Esophageal adenocarcinoma	1 (4)	3 (17)	4 (9)
Pancreatic carcinoma	4 (16)	0 (0)	4 (9)
SCLC	3 (12)	1 (6)	4 (9)
Malignant melanoma	3 (12)	0 (0)	3 (7)
Mesothelioma	2 (8)	1 (6)	3 (7)
Other[a]	8 (32)	7 (39)	22 (51)
Prior treatments			
Chemotherapy[b]	20 (80)	8 (44)	28 (65)
Cancer-related surgery	23 (92)	16 (89)	39 (91)
Radiotherapy	12 (48)	5 (28)	17 (40)
Immunotherapy	3 (12)	0 (0)	3 (7)
Hormonal therapy	1 (4)	0 (0)	1 (2)
Unspecified	1 (4)	0 (0)	1 (2)

CDD continuous daily dosing; *ECOG* Eastern Cooperative Oncology Group; *NSCLC* non-small cell lung cancer; *SCLC* small-cell lung cancer

[a] Carcinoid, pleural mesothelioma, neuroendocrine carcinoma, metastatic neoplasm unknown primary, thyroid cancer (all *n* = 2 [4.7%]), adrenocortical carcinoma, transitional cell carcinoma bladder, breast cancer, mesothelioma, ovarian cancer, malignant hepatic neoplasm, seminoma, and metastases to peritoneum (all *n* = 1 [2.3%])

[b] Includes prior targeted therapies: erlotinib (*n* = 2), bevacizumab, BSI-201, figitumumab, sorafenib, and vorinostat (each *n* = 1)

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Table 3

Most common all-causality non-hematologic adverse events (≥ 10% incidence cut-off) in all cohorts

	All patients (*n* = 43)				
Adverse event	**Grade 1 *n* (%)**	**Grade 2 *n* (%)**	**Grade 3 *n* (%)**	**Grade 4 *n* (%)**	**Total *n* (%)**
Fatigue	12 (30)	9 (21)	4 (9)	0 (0)	25 (58)
Nausea	13 (30)	6 (14)	0 (0)	0 (0)	19 (44)
Alopecia	7 (16)	6 (14)	0 (0)	0 (0)	13 (30)
Dyspnea	4 (9)	6 (14)	2 (5)	0 (0)	12 (28)
Diarrhea	6 (14)	5 (12)	0 (0)	0 (0)	11 (26)
Constipation	8 (19)	2 (5)	0 (0)	0 (0)	10 (23)
Vomiting	8 (19)	2 (5)	0 (0)	0 (0)	10 (23)
Anorexia	5 (12)	3 (7)	1 (2)	0 (0)	9 (21)
Arthralgia	9 (21)	0 (0)	0 (0)	0 (0)	9 (21)
Pyrexia	7 (16)	2 (5)	0 (0)	0 (0)	9 (21)
Cough	6 (14)	2 (5)	0 (0)	0 (0)	8 (19)
Epistaxis	8 (19)	0 (0)	0 (0)	0 (0)	8 (19)
Headache	8 (19)	0 (0)	0 (0)	0 (0)	8 (19)
Neuropathy peripheral	7 (16)	1 (2)	0 (0)	0 (0)	8 (19)
Dehydration	2 (5)	3 (7)	2 (5)	0 (0)	7 (16)
Dysgeusia	6 (14)	1 (2)	0 (0)	0 (0)	7 (16)
Dizziness	6 (14)	0 (0)	0 (0)	0 (0)	6 (14)
Dyspepsia	6 (14)	0 (0)	0 (0)	0 (0)	6 (14)
Hypomagnesemia	3 (7)	2 (5)	0 (0)	1 (2)	6 (14)
Myalgia	6 (14)	0 (0)	0 (0)	0 (0)	6 (14)
Rash	6 (14)	0 (0)	0 (0)	0 (0)	6 (14)
Weight decreased	5 (12)	1 (2)	0 (0)	0 (0)	6 (14)
Aspartate aminotransferase increased	1 (2)	3 (7)	1 (2)	0 (0)	5 (12)
Chills	5 (12)	0 (0)	0 (0)	0 (0)	5 (12)
Hemoptysis	4 (9)	0 (0)	1 (2)	0 (0)	5 (12)

There was one grade 5 event (gastrointestinal hemorrhage)

Table 4

All-causality hematologic adverse events in all cohorts (occurring in cycle 1 and in all cycles)

	All patients (n = 43)				
Adverse event	**Grade 1 *n* (%)**	**Grade 2 *n* (%)**	**Grade 3 *n* (%)**	**Grade 4 *n* (%)**	**Total *n* (%)**
Cycle 1					
Anemia	2 (5)	4 (9)	5 (12)	3 (7)	14 (33)
Leukopenia	0 (0)	8 (19)	7 (16)	4 (9)	19 (44)
Neutropenia	0 (0)	5 (12)	8 (19)	14 (33)	27 (63)
Thrombocytopenia	3 (7)	5 (12)	5 (12)	8 (19)	21 (49)
All cycles					
Anemia	1 (2)	10 (23)	9 (21)	3 (7)	23 (54)
Leukopenia	0 (0)	6 (14)	10 (23)	5 (12)	21 (49)
Neutropenia	1 (2)	4 (9)	11 (26)	18 (42)	34 (79)
Thrombocytopenia	5 (12)	7 (16)	10 (23)	10 (23)	32 (74)

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Table 5

Pharmacokinetic parameters (subjects with paired observations only) at sunitinib 37.5 mg/day plus paclitaxel 175 mg/m^2 and carboplatin 6 AUC mg•min/mL

	Alone Mean (%CV) [median]	Combination Mean (%CV) [median]	Geometric mean ratio (combination/ alone)
Schedule 2/1 (n = 4)			
Sunitinib			
T_{max} (h)[a]	6.0 (4.0–8.0)	16.0 (6.0–24.0)	N/A
C_{max} (ng/mL)	19.1 (23) [20.0]	28.4 (51) [26.1]	1.37
AUC_{0-24} (ng·h/mL)	332 (27) [342]	501 (42) [503]	1.44
SU12662			
T_{max} (h)[a]	4.0 (2.0–6.0)	24.0 (4.0–24.0)	N/A
C_{max} (ng/mL)	3.11 (45) [2.99]	6.61 (68) [5.51]	1.93
AUC_{0-24} (ng·h/mL)	54.1 (48) [52.9]	96.5 (61) [86.0]	1.68
Total drug			
T_{max} (h)	6.0 (4.0–8.0)	15.0 (4.0–24.0)	N/A
C_{max} (ng/mL)	22.1 (23) [23.9]	33.2 (52) [30.6]	1.38
AUC_{0-24} (ng·h/mL)	386 (29) [408]	597 (44) [607]	1.48
Paclitaxel			
T_{max} (h)[a]	3.0 (3.0–3.0)	3.0 (3.0–3.0)	N/A
C_{max} (μg/mL)	4.45 (23) [4.58]	5.00 (27) [5.49]	1.11
AUC_{∞} (μg·h/mL)	15.5 (17) [16.3]	16.8 (22) [18.02]	1.08
Clearance (L/h)	21.1 (33) [18.4]	19.8 (41) [16.2]	0.92
$t_{1/2}$ (h)	8.80 (15) [8.36]	8.23 (17) [8.54]	N/A
Total platinum			
T_{max} (h)[a]	3.5 (3.5–4.0)	3.5 (3.5–3.5)	N/A
C_{max} (μg/mL)	20.6 (29) [19.2]	22.6 (20) [21.2]	1.11
AUC_{0-24} (μg·h/mL)	65.1 (23) [60.4]	60.3 (10) [60.3]	0.94
Free platinum			
T_{max} (h)[a]	3.5 (3.5–4.0)	3.5 (3.5–3.5)	N/A
C_{max} (μg/mL)	25.2 (37) [24.9]	21.3 (9) [20.7]	0.89
AUC_{∞} (μg·h/mL)	50.7 (25) [49.5]	43.0 (6) [42.8]	0.87
Clearance (L/h)	13.3 (39) [11.2]	13.2 (22) [12.4]	1.02
$t_{1/2}$ (h)	4.72 (24) [4.89]	5.27 (4) [5.27]	N/A
CDD schedule (n = 5)			
Sunitinib			

	Alone Mean (%CV) [median]	Combination Mean (%CV) [median]	Geometric mean ratio (combination/alone)
T_{max} (h)[a]	8.0 (6.0–10.0)	6.0 (4.0–10.0)	N/A
C_{max} (ng/mL)	42.1 (12) [43.7]	47.0 (15) [44.4]	1.11
$AUC_{0–24}$ (ng·h/mL)	874 (13) [918]	983 (18) [897]	1.12
SU12662			
T_{max} (h)[a]	8.0 (4.0–10.0)	6.0 (4.0–10.0)	N/A
C_{max} (ng/mL)	13.4 (39) [15.7]	19.2 (39) [19.8]	1.44
$AUC_{0–24}$ (ng·h/mL)	279 (39) [326]	395 (37) [430]	1.43
Total drug			
T_{max} (h)[a]	8.0 (6.0–10.0)	6.0 (4.0–10.0)	N/A
C_{max} (ng/mL)	55.3 (14) [50.9]	65.2 (17) [68.3]	1.17
$AUC_{0–24}$ (ng·h/mL)	1,153 (14) [1,115]	1,379 (15) [1,351]	1.19
Paclitaxel			
T_{max} (h)[a]	3.0 (2.0–3.0)	3.0 (3.0–3.0)	N/A
C_{max} (μg/mL)	3.96 (40) [3.62]	5.24 (50) [4.92]	1.28
AUC_{∞} (μg·h/mL)	14.3 (31) [13.2]	15.9 (33) [13.6]	1.11
Clearance (L/h)	26.5 (34) [29.8]	23.6 (32) [27.4]	0.89
$t_{1/2}$ (h)	8.89 (14) [8.69]	7.84 (29) [6.90]	N/A
Total platinum			
T_{max} (h)[a]	3.5 (3.5–4.0)	3.5 (3.5–4.0)	N/A
C_{max} (μg/mL)	23.1 (20) [24.5]	22.8 (13) [24.7]	1.00
$AUC_{0–24}$ (μg·h/mL)	67.6 (7) [65.5]	60.6 (11) [64.0]	0.89
Free platinum			
T_{max} (h)[a]	4.0 (3.5–4.0)	3.5 (3.5–4.0)	N/A
C_{max} (μg/mL)	20.7 (15) [19.3]	22.0 (16) [22.5]	1.06
AUC_{∞} (μg·h/mL)	48.3 (9) [49.2]	43.1 (9) [42.4]	0.89
Clearance (L/h)	17.1 (26) [16.5]	18.9 (22) [21.1]	1.11
$t_{1/2}$ (h)	5.18 (6) [5.09]	4.16 (26) [4.80]	N/A

Total drug sunitinib + SU12662; C_{max} maximum plasma concentration; $t_{1/2}$ terminal phase half-life; *AUC* area under the plasma concentration–time profile for time zero to infinity (AUC_{∞}) or 24 h ($AUC_{0–24}$); *CV* coefficient of variation; *N/A* not applicable; *CDD* continuous daily dosing

[a] T_{max} = time for C_{max}; median (min, max)