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A Multicenter Phase I Study of Pazopanib in Combination with Paclitaxel in First-Line Treatment of Patients with Advanced Solid Tumors

Kari L. Kendra¹, Ruth Plummer², Ravi Salgia³, Mary E. R. O'Brien⁴, Elaine M. Paul⁵,
A. Benjamin Suttle⁷, Natalie Compton⁸, Chun-Fang Xu⁶, Lone H. Ottesen⁹, Miguel A. Villalona-Calero¹

¹Division of Medical Oncology and Comprehensive Cancer Center, Ohio State University, Columbus, Ohio, United States; ²Sir Bobby Robson Cancer Trials Research Centre, Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, United Kingdom; ³University of Chicago, Chicago, Illinois; ⁴Department of Medicine, Royal Marsden NHS Foundation Trust, Sutton, Surrey, United Kingdom; ^{5,6}Oncology Research and Development, GlaxoSmithKline, ⁵Research Triangle Park, North Carolina; and ⁶Uxbridge, United Kingdom; ⁷Salix US; ⁸PPD UK; ⁹Eisai Ltd, Oncology PCU, European Knowledge Centre, Hatfield, United Kingdom

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Corresponding Author: Kari L. Kendra, Ohio State University, B415 Starling Loving Hall, 320 West 10th Avenue, Columbus, Ohio 43210, United States.

Phone: 614-293-4320 Fax: 614-293-2584 e-mail: Kari.Kendra@osumc.edu

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Abstract

This study was designed to evaluate the safety, pharmacokinetics, and clinical activity of pazopanib combined with paclitaxel to determine the recommended phase II dose in the first-line setting in patients with advanced solid tumors. Patients were enrolled in a 3+3 dose-escalation design to determine the maximum tolerated regimen (MTR) of once daily pazopanib plus paclitaxel administered every 3 weeks at four dose levels (DL1-4). Safety, pharmacokinetics, pharmacogenetics, and disease assessments were performed. Twenty-eight patients received treatment. One patient at DL1 had dose-limiting toxicity (DLT) of elevated hepatic enzymes. After pazopanib discontinuation, liver enzyme concentrations remained high until a concurrent medication, simvastatin, was discontinued. This patient had the defective *CYP2C8**3*3 genotype. At DL2, 1 patient had DLT of elevated hepatic enzymes with rash and 1 patient had DLT of rash. The MTR was paclitaxel 150 mg/m² plus pazopanib 800 mg. The most common toxicities were alopecia, fatigue, hypertension, nausea, diarrhea, dysgeusia, neutropenia, myalgia, hair color changes, and peripheral neuropathy. Co-administration of pazopanib and paclitaxel resulted in a 38% increase in systemic exposure to paclitaxel, relative to administration of paclitaxel alone, at the MTR. Of the 28 patients treated with the combination, 10 achieved a partial response and 10 achieved stable disease of ≥ 12 weeks. Pazopanib 800 mg daily plus paclitaxel 150 mg/m² every 3 weeks was the recommended phase II dose, with a manageable safety profile, and with clinical activity in both melanoma and NSCLC that suggest further evaluation of this combination is warranted.

Introduction

Angiogenesis remains an important pathway in tumor initiation, growth, and response to therapy. Vascular endothelial growth factor (VEGF) is a potent endothelial-specific angiogenic factor that is an important regulator of the angiogenic process (1, 2), and elevated VEGF receptor (VEGFR) levels have been found to confer a poor prognosis in many solid tumors, including non-small cell lung cancer (NSCLC) and melanoma (3, 4).

Randomized controlled trials have demonstrated the clinical benefit of inhibition of the VEGF pathway by small molecule multi-targeted tyrosine kinase inhibitors (TKIs), and a number of these agents including sunitinib, sorafenib, pazopanib, axitinib, and vandetanib are approved as monotherapy for a variety of advanced solid tumors (5–11). However, despite demonstration of single-agent activity, combination with standard chemotherapy regimens for these agents in other tumor types has been challenging. In some cases, combinations have not been tolerable (12, 13), while in other cases the combination was tolerable, but failed to deliver efficacy. For example, sorafenib had been reported to have promising activity in early phase studies for NSCLC (14, 15). Yet when sorafenib was added to paclitaxel and carboplatin in the first-line setting for NSCLC the primary endpoint of improved overall survival (OS) or even progression free survival (PFS) was not met. Furthermore, in the subgroup of patients with squamous cell histology, the sorafenib combination was associated with increased mortality (16). In contrast, bevacizumab, a monoclonal antibody to VEGF-A, when combined with paclitaxel and carboplatin, demonstrated a statistically significant survival advantage (median OS, 12.3 months versus 10.3 months) over chemotherapy alone (17) in patients with non-squamous NSCLC, while patients with squamous cell NSCLC did not tolerate this combination (18).

Pazopanib (Votrient) is an orally bioavailable, small molecule, competitive TKI of VEGFR (-1, -2, and -3), platelet-derived growth factor receptor (PDGFR) α -, β -, and c-Kit (19), which is approved as monotherapy at a dose of 800 mg daily for the treatment of patients with advanced renal cell carcinoma (RCC) (8) and advanced soft-tissue sarcoma (STS) who have received prior chemotherapy (9). Short-term treatment with pazopanib 800 mg demonstrated single-agent activity in patients with early-stage NSCLC in the pre-operative setting in a proof of concept study that supported further exploration of pazopanib in NSCLC (20).

Since paclitaxel is a backbone of standard chemotherapeutic regimens used in a number of malignancies, including NSCLC, we had an interest in exploring the combination of pazopanib and paclitaxel in solid tumors. Additionally, preclinical evidence suggested the possibility of synergy from the combination of anti-angiogenic agents with taxanes (21), and recent data suggested synergism between paclitaxel and pazopanib via inhibition of aurora A in anaplastic thyroid cancer (22). Previous studies demonstrated that pazopanib could not be readily combined with paclitaxel 175 mg/m² and carboplatin area under the plasma drug concentration curve (AUC) 5 administered every 3 weeks at doses higher than pazopanib 200 mg (23, 24). However, it was feasible to administer pazopanib 800 mg with a weekly regimen of paclitaxel 80 mg/m², which resulted in a 26% higher geometric mean paclitaxel AUC that was similar to the systemic exposure of a paclitaxel dose of 100 mg/m² (25).

The current study was designed to evaluate the safety of pazopanib in combination with paclitaxel administered every 3 weeks and to determine the recommended phase II dose for this combination in the first-line setting in patients with advanced solid tumors. Due to the expected increase in exposure of paclitaxel when administered in combination with pazopanib, careful dose escalation and real-time pharmacokinetic analyses were performed.

Patients and Methods

Patients with previously untreated advanced solid tumors for whom paclitaxel-based therapy was considered appropriate; age ≥ 18 years; Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1; measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST version 1.0) (26); adequate bone marrow, hepatic, and renal function; and life expectancy ≥ 12 weeks were eligible. Exclusion criteria included clinically significant gastrointestinal abnormalities; poorly controlled hypertension; a history of cerebrovascular accident including transient ischemic attack, pulmonary embolism or untreated deep venous thrombosis, and cardiac dysfunction within the past 6 months; evidence of active bleeding or bleeding diathesis; recent hemoptysis; and known endobronchial lesions. Co-administration of pazopanib plus paclitaxel with strong CYP3A4 inhibitors was prohibited beginning 14 days before the first dose of study drug until the end of study treatment.

This study (Clinicaltrials.gov NCT00866528) was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines, and was approved by institutional review boards. All patients provided written informed consent before any study procedures were performed.

Study Design and Treatment

This was an open-label, multicenter, phase I study of pazopanib in combination with paclitaxel. Pazopanib (Votrient™, GlaxoSmithKline, North Carolina, USA) was administered orally once daily starting on day 2 of cycle 1 in combination with paclitaxel (TAXOL® [paclitaxel] INJECTION, Bristol-Myers Squibb Company, New Jersey, USA) administered as a 3-hour intravenous (IV) infusion on day 1 of each 3-week treatment cycle for up to 6 cycles.

After the 6 cycles, single-agent pazopanib treatment continued until disease progression, unacceptable toxicities or death. Initial doses tested were pazopanib 800 mg plus paclitaxel 135 mg/m² and a standard 3+3 dose escalation design was applied.

Dose-limiting toxicity (DLT) was defined as one of the following events occurring within cycle 1 (a grade 2 or higher toxicity occurring after cycle 1 that was considered dose-limiting by the investigator may also have been a DLT): febrile neutropenia, grade 4 granulocytopenia (>5 days), grade 4 thrombocytopenia, grade 3 or 4 clinically significant non-hematological toxicity (excluding transient grade 3 alanine aminotransferase [ALT] or aspartate aminotransferase [AST] elevations without elevated bilirubin, grade 3 hypertension adequately controlled with anti-hypertensive medications, asymptomatic grade 3 proteinuria that improved within 14 days in the absence of hypertension and/or renal impairment, grade 3 nausea, vomiting, or diarrhea for which adequate supportive therapy had not been instituted, and alopecia) and the inability to begin the next course of treatment within 2 weeks of scheduled dosing due to toxicity. The maximum tolerated regimen (MTR) was defined as the highest combined dose of pazopanib and paclitaxel where ≤ 1 of 6 patients experienced a DLT; once the MTR was reached, 6 additional patients were treated at the MTR.

Dose modification guidelines for adverse events were pre-specified. Dose interruptions or reductions of pazopanib (in 200 mg decrements) were required following potential drug-related toxicities including hypertension, proteinuria, hepatotoxicity, bleeding events, vascular thrombosis, thrombocytopenia, and neutropenia; 400 mg was the lowest dose of pazopanib permitted. Cycle delays for paclitaxel or interruption of pazopanib treatment for up to 14 days were permitted for recovery from adverse events. Patients with hepatotoxicity were evaluated for symptoms of hypersensitivity, and investigations including liver imaging, viral serology

(hepatitis A, B, and C; Epstein-Barr virus; cytomegalovirus), antinuclear antibody (ANA), pharmacokinetics, and pharmacogenetic testing were performed to rule out other contributing causes.

Endpoints and Safety and Response Assessments

The primary outcome measure was safety and tolerability of pazopanib in combination with paclitaxel based on the frequency and nature of DLTs, adverse events (graded according to NCI CTCAE version 3.0), vital signs, electrocardiograms, and clinical laboratory parameters. Safety assessments were performed every week until completion of cycle 2, on days 1 and 8 of subsequent cycles, and then every 4 weeks during pazopanib monotherapy treatment.

Disease assessments were performed approximately every 6 weeks for the first 18 weeks and every 8 weeks thereafter until disease progression. Tumor response was assessed according to RECIST, version 1.0 (26).

Pharmacokinetic Assessments

To determine the effect of pazopanib on the pharmacokinetics of paclitaxel, blood samples (2 mL) were collected for the analysis of plasma paclitaxel concentrations on day 1, cycle 1 (paclitaxel alone) and on day 1, cycle 2 (paclitaxel plus pazopanib) pre-dose, and at the following times after the start of the paclitaxel infusion: 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8 to 10, and 24 hours. To estimate the pharmacokinetics of pazopanib in the presence of paclitaxel, additional blood samples (2 mL) were collected on day 1, cycle 2 pre-dose, and 1, 2, 4, 8, and 24 hours after the start of the paclitaxel infusion. Plasma samples were analyzed for pazopanib using a validated analytical method based on protein precipitation followed by high-performance

liquid chromatography tandem mass spectrometry (HPLC/MS/MS) analysis. Plasma samples were analyzed for paclitaxel by Advion Bioanalytical Labs (Ithaca, New York, USA) using a validated analytical method based on solid-phase extraction followed by HPLC/MS/MS analysis.

To investigate observed hepatotoxicity in one patient, 3 plasma samples obtained during the course of the event were analyzed for pazopanib and were also analyzed for simvastatin and simvastatin acid using a validated analytical method based on solid-phase extraction followed by HPLC/MS/MS analysis.

Pharmacogenetic Assessments

The evaluation of the association of genetic variations in host DNA with safety, tolerability, and pharmacokinetics was an exploratory objective in this study. Each patient had a 10-mL blood sample taken for analysis. DNA extraction was performed by Covance (United Kingdom). The *UGT1A1* and *HFE* markers were genotyped by GSK Genetics (Research Triangle Park, North Carolina, USA) using the Third Wave Invader® assay and TaqMan® SNP Genotyping assays, respectively. Polymorphisms in *ABCB1*, *ABCG2*, *CYP2C8*, *CYP3A4*, and *SLCO1B1* were evaluated via the Affymetrix DMET Plus Array by Expression Analysis (Durham, North Carolina, USA).

Statistical Analysis

Analyses were based on all patients who received at least one dose of pazopanib and one dose of paclitaxel within at least one cycle of treatment. Pharmacokinetic parameters were calculated by standard noncompartmental methods using WinNonlin Professional Edition version 5.2 (Pharsight Corporation, California, USA). The objective response rate (ORR),

defined as the percentage of patients achieving either a complete or partial response (CR or PR) was summarized overall and for the subgroups of patients with NSCLC and melanoma. A patient was defined as a responder if he/she sustained a CR or PR which was confirmed after no less than 28 days. Approximate 95% confidence intervals (CIs) for response rates were calculated for each treatment but no p-values were calculated. Waterfall plots of the percent change at the maximum reduction from baseline in tumor measurement were produced separately for each tumor type.

Results

Patient characteristics

Thirty patients were enrolled from 4 study sites from July 2009 to May 2011. Two patients did not receive pazopanib and were not included in the analyses. All patients had a diagnosis of either NSCLC or melanoma. Table 1 summarizes patient characteristics.

Dose escalation and toxicity

Four dose levels were explored and are shown in Table 2 together with DLTs and neutrophil counts for baseline and cycle 1 nadir (day 15) values. The first DLT occurred at the lowest dose level tested (Cohort 1: PAC 135/PAZ 800) leading to expansion of this cohort. Two DLTs occurred at the next (and highest) dose level tested (Cohort 2: PAC 175/PAZ 800); subsequently two intermediate dose levels were explored (Cohort 3: PAC 150/PAZ 800 and Cohort 4: PAC 175/PAZ 400) with no further DLTs reported. Both cohorts 3 and 4 qualified for the MTR; however, cohort 3 was selected for expansion to a total of 12 patients and subsequently determined to be the recommended dose for the pazopanib and paclitaxel combination.

The first DLT, asymptomatic grade 4 elevated hepatic enzymes, with grade 2 bilirubin elevation, occurred in cohort 1 after the administration of one dose of paclitaxel (135 mg/m²) and 21 days of pazopanib, which the patient took as 400 mg twice daily (in error) instead of 800 mg once daily. Pazopanib treatment was permanently discontinued; however, hepatic enzymes remained high until a concurrent medication, simvastatin (80 mg daily), was also discontinued (see Supplementary Table S1). Three blood samples drawn during the course of this event revealed plasma pazopanib concentrations within the expected range. However, plasma

concentrations of simvastatin and simvastatin acid approximately 7 h after the last dose of pazopanib and 16.5 h after the last dose of simvastatin were 14.7 ng/mL (approximately 4-fold greater than expected) and 20.1 ng/mL (approximately 10-fold greater than expected), respectively (27), indicating that a drug-drug interaction between pazopanib and simvastatin was present in this patient (see Supplementary Table S2). This patient received one dose of paclitaxel in the absence of pazopanib, with pazopanib treatment starting no sooner than 24 hours after the administration of paclitaxel. Paclitaxel pharmacokinetic samples drawn over the 24 hours following the administration of paclitaxel (as a 3-hour infusion) demonstrated exposures in the expected range for paclitaxel 135 mg/m² (peak plasma concentration at 3 hours was 3205 ng/mL) (28). Viral serology and ANA tests were negative. Pharmacogenetic analysis of a blood sample revealed wild-type genotypes for *UGT1A1*, *HFE*, *CYP3A4*, *ABCG2* (BCRP), and *SLCO1B1* (OATP1B1), and a heterozygous *ABCB1* (Pgp) genotype that are expected to have normal to nearly normal activity for these enzymes and transporter proteins; however, the patient did have a homozygous defective *CYP2C8**3*3 genotype, predicted to have a poor metabolizer status for CYP2C8. After resolution of this event, the patient subsequently resumed treatment with paclitaxel and simvastatin outside of the study, with no further reported hepatic enzyme elevations.

In cohort 2 (PAC 175/PAZ 800) one DLT included grade 3 increases in ALT and AST with eosinophilia and subsequent development of grade 2 pruritic rash, which led to permanent discontinuation of pazopanib. No pharmacokinetic or pharmacogenetic blood samples were available for this patient. No abnormalities were detected by transabdominal ultrasound, and viral serology and ANA tests were negative. A second DLT in this cohort was grade 3 maculopapular rash. Pazopanib treatment was interrupted, but later successfully re-introduced at a

lower dose (600 mg daily). Of note, there were no DLTs of neutropenia in this study; however, the lowest median neutrophil count in cycle 1 was observed in cohort 2 (Table 2).

In cohort 3 (PAC 150/PAZ 800), two patients had grade 3 ALT elevations during the second cycle of treatment that did not meet DLT criteria. In both patients, plasma pazopanib concentrations were within the expected range of concentrations for an 800 mg dose of pazopanib; viral serology and ANA tests were negative. In one patient, treatment with pazopanib was interrupted and later re-started for cycle 3 of treatment at a reduced dose (400 mg); after re-challenge there was a mild and transient grade 2 ALT elevation. There was no elevation of bilirubin. No pharmacogenetic testing was performed. In the second patient, pazopanib treatment was discontinued. Pharmacogenetic analysis of a blood sample revealed wild-type genotypes for *UGT1A1*, *HFE*, *ABCB1*, *CYP3A4*, *CYP2C8*, and *SLCO1B1*; however, the patient was homozygous for the *ABCG2* *2/*2 genotype, associated with functional impairment of the transporter.

All 28 patients who received at least one dose of both study drugs reported at least one adverse event regardless of causality during the study. Overall, the most frequently reported treatment-emergent adverse events (any grade occurring in $\geq 30\%$ of patients) were alopecia (86%), fatigue (82%), hypertension (71%), nausea (68%), diarrhea (61%), vomiting (54%), dysgeusia (50%), myalgia (50%), rash (50%), neutropenia (46%), arthralgia (43%), decreased appetite (43%), , hair color changes (43%), headache (43%), peripheral neuropathy (43%), pain in extremity (39%), constipation (32%), dizziness (32%), and hepatic enzyme increased (32%); most were grade 1 or 2 in severity (Table 3). At the MTR (PAC 150/PAZ 800), the incidences were fatigue (92%), alopecia (83%), nausea (75%), rash (75%), hypertension (67%), diarrhea (67%), dysgeusia (58%), myalgia (50%), vomiting (50%), neutropenia (42%), headache (42%),

peripheral neuropathy (33%), arthralgia (33%), decreased appetite (33%), and hair-color changes (33%). Overall, the most frequently reported treatment-emergent grade 3 and 4 adverse events were neutropenia (6 and 3 patients, respectively) and hepatic enzyme elevations (4 and 1 patient, respectively). There were no embolic or thrombotic events and no severe (grade 3 or above) hemorrhagic events reported in the study. Permanent discontinuation of study treatment due to adverse events occurred in 5 patients; three patients due to elevations in liver enzymes, one patient due to subcutaneous (paravertebral) abscess, and one patient due to tachycardia (for this patient paclitaxel was discontinued but not pazopanib).

Treatment exposure

The median number of cycles of paclitaxel administered was 5 to 6 cycles across all cohorts and the median dose of paclitaxel and pazopanib administered was the planned dose for each cohort, with the exception of cohort 2 where the median pazopanib dose was lower (737 mg) than the intended dose (800 mg) (see Supplementary Table S3). The median duration of pazopanib treatment was 3.8, 5.3, 6.9, and 5.0 months for cohorts 1, 2, 3, and 4, respectively. One patient with ocular melanoma continued to receive treatment with 800 mg pazopanib monotherapy for 24 months after completion of his 6 cycles of paclitaxel plus pazopanib; his overall treatment duration was 28 months (Figure 1).

Pharmacokinetics

Co-administration of pazopanib and paclitaxel resulted in an increase in systemic exposure to paclitaxel relative to administration of paclitaxel alone by approximately 38% at the

MTR (Figure 2). There was no dose- or concentration-dependent effect of pazopanib 400 mg or 800 mg once daily on the systemic disposition of paclitaxel (see Supplementary Table S4).

There were no consistent changes in systemic exposure to pazopanib as measured by maximum concentration (C_{\max}), AUC from time of dose to 24 hours ($AUC_{(0-24)}$), or concentration at 24 hours following administration (C_{24}) across the paclitaxel dose levels explored. These results indicate that there was no concentration-dependent affect of paclitaxel on the systemic exposure of pazopanib.

Clinical activity

Clinical activity was observed in all four cohorts, with 10 of 28 evaluable patients achieving a PR for an ORR of 36% for the total population (Figure 3 and Supplementary Table S5), and stable disease of ≥ 12 weeks in 10 additional patients. In the subset of patients with NSCLC, the ORR was 45%, (PR in 5 of 11 patients) and stable disease of ≥ 12 weeks was observed in 3 of 11 patients. In the subset of patients with melanoma, the ORR was 29%, (PR in 5 of 17) patients and stable disease of ≥ 12 weeks in 7 additional patients.

Discussion

This Phase I study was conducted to evaluate the safety of pazopanib in combination with paclitaxel administered every 3 weeks and to determine the recommended phase II dose in the first-line setting in patients with advanced solid tumors. Secondary objectives included an evaluation of the pharmacokinetics of each agent and of the clinical activity of this combination.

This study demonstrated that pazopanib could be safely combined with paclitaxel administered once every three weeks with either full dose pazopanib (800 mg) in combination with paclitaxel 150 mg/m² (cohort 3) or with a lower dose of pazopanib (400 mg) in combination with a higher dose of paclitaxel 175 mg/m² (cohort 4). Minor differences in the tolerability profile and treatment exposures led to a decision to expand the pazopanib 800 mg and paclitaxel 150 mg/m² dose level and declare this as the recommended phase II dose for patients with advanced solid tumors. The observed pharmacokinetic interaction between pazopanib and paclitaxel supported the selection of full dose pazopanib with a dose of paclitaxel that provides clinically relevant paclitaxel exposure.

Co-administration of paclitaxel 150 mg/m² and pazopanib 800 mg once daily resulted in a 34% and 37% increase in paclitaxel AUC extrapolated to infinity and C_{max}, respectively, relative to administration of paclitaxel alone. Consequently, although higher doses of paclitaxel (up to 225 mg/m²) may typically be administered every 3 weeks to patients with solid tumors (29, 30), the presence of pazopanib increased the exposure of a 150 mg/m² dose of paclitaxel to a level that would be expected from a dose of 200 mg/m² (31). A drug-drug interaction was expected, since paclitaxel is a substrate for CYP2C8 and CYP3A4 and pazopanib is a weak inhibitor of CYP3A4 and CYP2C8. The extent of the interaction observed in this study appears similar to that previously reported for pazopanib in combination with paclitaxel administered on

a weekly schedule (25) and in combination with paclitaxel and carboplatin (23) administered with various doses of pazopanib. Collectively, these studies suggest that co-administration of pazopanib results in a consistent increase in systemic exposure to paclitaxel regardless of the paclitaxel dose regimen and pazopanib doses investigated.

The most common treatment-related toxicities observed for the combination of pazopanib and paclitaxel in the current study were expected based on the known safety profile of each individual agent and included alopecia, fatigue, hypertension, nausea, diarrhea, dysgeusia, vomiting, and neutropenia. Although events were mostly grade 1 or 2 in severity, the incidence of some events including fatigue, nausea, hypertension, dysgeusia, and rash was somewhat higher than expected. In the current study, a large proportion of patients (67%) entered with baseline hypertension; it is unclear whether this influenced the incidence of hypertension reported. Previous studies of the combination of pazopanib with weekly paclitaxel have also reported high incidences of fatigue and nausea (25, 32); therefore it is possible that these events could represent potential synergistic toxicities for the combination of pazopanib and paclitaxel. Of note, hematologic toxicity was not dose-limiting in the current study; this contrasts with the experience with the combination of pazopanib with paclitaxel 175 mg/m² and carboplatin AUC 5, where myelosuppression was the DLT for the combination (23, 24). DLTs reported in the current study included rash and hepatotoxicity.

Hepatotoxicity is an expected event for pazopanib, manifested by increases in serum transaminases (ALT, AST) and bilirubin, with the majority (92.5%) of transaminase elevations occurring within the first 18 weeks of treatment (33). In clinical trials in RCC and STS, approximately 18% of patients experienced elevations of ALT greater than 3x the upper limit of normal (ULN), 5% experienced elevations of ALT greater than 8xULN, and 2% had concurrent

elevations in ALT >3xULN and bilirubin >2xULN in the absence of significant alkaline phosphatase >3xULN (33). Although an expected event for pazopanib, efforts were made to explore potential underlying causes of the hepatotoxicity events observed in the 4 patients who experienced grade 3 or 4 transaminase elevations. Pharmacogenetic analyses included an evaluation of genetic markers in the *HFE* and *UGT1A1* genes, which have been associated with ALT and bilirubin elevation, respectively, in patients with RCC treated with pazopanib (34, 35); functional polymorphisms for enzymes involved in the metabolism of pazopanib and paclitaxel (CYP3A4 and CYP2C8); and transport proteins for which pazopanib and/or paclitaxel are substrates or inhibitors (ABCB1, ABCG2, and OATP1B1). In all 3 patients who provided a sample for pharmacokinetic and pharmacogenetic analysis, plasma concentrations of pazopanib were in the expected range, and in 2 patients, functional polymorphisms were detected that may have contributed to the observed liver event; one patient did not have pharmacogenetic testing performed. One patient had a functional impairment of the ABCG2 transporter protein (*ABCG2* *2/*2 genotype). It is possible that the presence of this genotype potentially contributed to the observed liver event; however no clear mechanism was identified. The second patient was homozygous for the defective CYP2C8*3*3 genotype, which is predicted to have a poor metabolizer status for CYP2C8. Of note, this patient was taking simvastatin concurrently with pazopanib. ALT levels remained elevated in this patient until simvastatin was discontinued, suggesting a key role of simvastatin administration in the occurrence of elevated ALT. Simvastatin is mainly metabolized by CYP3A to the active metabolite simvastatin acid which is metabolized further by CYP3A4 and CYP2C8 for elimination and transported into hepatocytes by OATP1B1 (36). The poor metabolizer status for CYP2C8 coupled with potential inhibition of this enzyme and of OATP1B1 by pazopanib may explain the observed drug-drug interaction

resulting in increased exposure to both simvastatin (4-fold) and simvastatin acid (10-fold) in this patient. Both pazopanib and simvastatin have been associated with transaminase elevations and may each have contributed to the observed hepatocellular injury; however, the individual contribution of each agent could not be determined.

This anecdotal observation of hepatotoxicity in conjunction with concurrent simvastatin treatment resulted in the conduct of a meta-analysis to evaluate the effects of concomitant pazopanib and statin use on the incidence of elevated ALT using data from 11 pazopanib clinical studies (37). The meta-analysis showed the incidence of ALT elevation ($\geq 3 \times \text{ULN}$) was 27% in patients receiving both pazopanib and simvastatin, which was significantly higher than the incidence of 14% in patients who did not receive statins ($p = 0.04$). Furthermore, the analysis demonstrated that the *ABCG2* (BCRP) 421C>A polymorphism may be associated with ALT elevation in patients taking pazopanib and simvastatin; patients with the variant 421C>A allele had a higher incidence of ALT > 3 x ULN (5/7, 71%) compared with those with the wild-type genotype (2/21, 10%; odds ratio = 19.6, 95% confidence interval 1.9-231.6; $p = 0.004$). This polymorphism was not associated with ALT elevations in patients treated with pazopanib without concurrent use of statins. This analysis resulted in a label change for pazopanib describing an increased risk of ALT elevations with concomitant use of pazopanib and simvastatin. Both the case history from the current study and the subsequent meta-analysis highlight the importance of signal detection and pharmacokinetic and pharmacogenetic characterization of serious adverse events in early phase trials in order to better understand potential mechanisms of injury and inform management of patients.

With the potential for synergism between anti-angiogenic agents and taxanes (21, 22), the combination of pazopanib and paclitaxel offered the possibility of developing a platinum-sparing

combination for first-line treatment of patients with metastatic NSCLC and other solid tumors. Although the study was open to all solid tumors, participating sites enrolled patients with only two tumor types in this study: melanoma and NSCLC. Patients with NSCLC and melanoma appeared to derive benefit from the therapy. Clinical activity was noted in all four cohorts with a best ORR of 36%. Partial responses occurred in 10 of 28 patients and stable disease > 12 weeks in 10 of 28 patients.

Paclitaxel has been used in the first-line treatment of metastatic melanoma both as a single agent and in combination with carboplatin, with reported response rates of approximately 12 to 16% (38–40) and 16 to 20%, respectively (30, 41, 42). Since VEGF expression has been shown to play a role in metastatic melanoma (43), studies to explore the combination of carboplatin, paclitaxel, and anti-angiogenic agents such as sorafenib and bevacizumab have been performed; however, these studies have not shown improved efficacy compared with the carboplatin and paclitaxel doublet (30, 42). In the current study, the response rate for melanoma was 29% (5 of 17 patients with PR) with an additional 41% (7 of 17 patients) demonstrating SD of >12 weeks and one patient diagnosed with ocular melanoma maintained antitumor response for more than 100 weeks. Additionally, an ongoing phase II study of pazopanib in combination with a weekly regimen of paclitaxel for the first-line treatment of unresectable melanoma has reported data from a planned interim analysis in 20 patients and demonstrated a response rate of 42% (32); this study will continue to accrue 60 patients with a primary endpoint of 6-month PFS. These studies suggest that the combination of pazopanib and paclitaxel is active in melanoma and warrants further investigation.

In the current study, the response rate for NSCLC was 45% (5 of 11 patients with PR) with an additional 27% (3 of 11 patients) demonstrating SD of >12 weeks. The clinical activity

observed in patients with NSCLC in the current study suggests further investigation of the combination of pazopanib and paclitaxel is warranted. Recent data reported with docetaxel and nintedanib in the second-line setting for advanced NSCLC demonstrated a significant improvement of both PFS and OS for the combination treatment compared with single-agent docetaxel (44). In this setting, combination treatment with docetaxel and nintedanib continued until disease progression; this approach may be worth considering in future studies of the combination of pazopanib and paclitaxel. In our phase 1 trial, 50% of patients completed the 6 cycles of combination therapy and were continued on single-agent pazopanib for a range of 2 to 24 months.

Since the current study was initiated, treatment paradigms in both melanoma and NSCLC have undergone a rapid transformation. In melanoma, the emergence of newer targeted agents including vemurafenib, dabrafenib, and trametinib have resulted in higher response rates and improved clinical outcomes, especially for patients with V600 mutation positive tumors (45). The current study did not prospectively test for the status of V600 mutations in the melanoma subset of patients. With the availability of an approved test for this marker, future studies should incorporate evaluation of this marker. Additionally, emerging data from studies in both melanoma and NSCLC with immune therapies including ipilimumab, the PD-1 checkpoint inhibitors, and combinations of these agents, suggest that the landscape of treatment in the first-line metastatic setting for each of these tumor types will continue to change (45, 46). In the face of these changes, future studies of the combination of pazopanib and paclitaxel will need to carefully evaluate the appropriate setting for use of this combination.

In summary, the current study identified pazopanib 800 mg daily and paclitaxel 150 mg/m² administered every 3 weeks as the recommended phase II dose for patients with

advanced solid tumors. The toxicity profile was consistent with the safety profile of each individual agent and was manageable; although the incidence of some toxicities may be higher than expected from single-agent treatment. In the presence of pazopanib, exposure to paclitaxel increased by 38%; however, there was no dose- or concentration- dependent effect of pazopanib 400 mg or 800 mg once daily on the systemic disposition of paclitaxel. Clinical activity of this combination in both melanoma and NSCLC suggests further evaluation of this combination is warranted.

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Table 1. Patient baseline and disease characteristics

Characteristics	
Treated patients, N	28
Male, n (%)	15 (54)
Female, n (%)	13 (46)
Median age, y (range)	57.5 (31-80)
ECOG PS, n (%)	
0	19 (68)
1	9 (32)
Baseline LDH (Melanoma, n=17), n (%)	
Normal	9 (53)
Elevated (> ULN)	8 (43)
Primary tumor type and histology, n (%)	
Melanoma stage	17 (61)
Stage IIIc	2 (7)
Stage IV	15 (54)
Melanoma histology	17 (61)
Malignant melanoma NOS	12 (43)
Spindle cell melanoma	2 (7)
Other/missing	3 (11)
NSCLC Stage IV	11 (39)
Adenocarcinoma	6 (21)
Poorly differentiated adenocarcinoma	2 (7)
Squamous cell carcinoma	2 (7)
Papillary adenocarcinoma	1 (4)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactic dehydrogenase;

ULN, upper limit of normal; NSCLC, non-small-cell lung cancer; NOS, not otherwise specified.

Table 2. Dose-limiting toxicities and absolute neutrophil counts by dose level

Cohort	Dose level	Patients treated (n)	Patients with DLT	ANC median (range), GI/L	
				Baseline	Cycle 1 Day 15 - nadir
1	Paclitaxel 135 mg/m ² + Pazopanib 800 mg	6	1 ^a	4.71 (3.00 – 8.70)	1.45 (0.51 – 3.50)
2	Paclitaxel 175 mg/m ² + Pazopanib 800 mg	4	2 ^b	4.73 (3.80 – 6.10) ^c	0.78 (0.71 – 4.30) ^c
3	Paclitaxel 150 mg/m ² + Pazopanib 800 mg	12	0	7.04 (2.60 – 11.92)	2.74 (0.90 – 9.60)
4	Paclitaxel 175 mg/m ² + Pazopanib 400 mg	6	0	4.91 (3.17 – 5.60)	1.58 (0.35 – 4.60)

^a DLT: grade 4 elevated hepatic enzyme (ALT and AST).

^b DLTs: 1) grade 3 elevated ALT and AST with grade 2 rash; 2): grade 3 rash.

^c n=3 patients.

Abbreviations: DLT, dose-limiting toxicity; ANC, absolute neutrophil count; PAC, paclitaxel; PAZ, pazopanib; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3. Treatment-emergent adverse events reported in at least 30% of patients that have at least one occurrence of grade 3 or 4 severity

Adverse event ^a	All grades	Paclitaxel 135 mg/m ² + Pazopanib 800 mg (n=6)		Paclitaxel 175 mg/m ² + Pazopanib 800 mg (n=4)		Paclitaxel 150 mg/m ² + Pazopanib 800 mg (n=12)		Paclitaxel 175 mg/m ² + Pazopanib 400 mg (n=6)	
		Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any event	28 (100)	4 (67)	1 (17)	2 (50)	2 (50)	9 (75)	0	4 (67)	1 (17)
Fatigue	23 (82)	0	0	0	0	1 (8)	0	0	0
Hypertension	20 (71)	0	0	0	0	1 (8)	0	1 (17)	0
Diarrhea	17 (61)	0	0	0	0	0	0	1 (17)	0
Rash ^b	14 (50)	0	0	1 (25)	0	0	0	0	0
Neutropenia	13 (46)	2 (33)	0	1 (25)	2 (50)	2 (17)	0	1 (17)	1 (17)
Headache	12 (43)	0	0	0	0	1 (8)	0	1 (17)	0
Peripheral neuropathy	12 (43)	0	0	0	0	1 (8)	0	0	0
Pain in extremity	11 (39)	0	0	0	0	0	0	1 (17)	0
Hepatic enzyme increased ^b	9 (32)	1 (17)	1 (17)	1 (25)	0	2 (17)	0	0	0

a. The following treatment-emergent adverse events reported in at least 30% of patients did not have events with grade 3 or 4 severity: alopecia, nausea, vomiting, dysgeusia, myalgia, arthralgia, decreased appetite, hair color changes, constipation, and dizziness.

b. Rash also includes: rash erythematous, rash macular, rash pruritic, and exfoliative rash; hepatic enzyme increased also includes elevated ALT

Figure Legends

Figure 1. Duration of pazopanib treatment by cohort and patient.

Cohort 1 = paclitaxel 135 mg/m² + pazopanib 800 mg; Cohort 2 = paclitaxel 175 mg/m² + pazopanib 800 mg; Cohort 3 = paclitaxel 150 mg/m² + pazopanib 800 mg; Cohort 4 = paclitaxel 175 mg/m² + pazopanib 400 mg. M = melanoma; L = NSCLC.

Figure 2. Median plasma paclitaxel concentration-time profiles after administration of paclitaxel 150 mg/m² alone (cycle 1 day 1) and in combination with pazopanib 800 mg (cycle 2 day 1).

Figure 3. Investigator-assessed maximum percent reduction from baseline in tumor measurement. A, NSCLC; B, melanoma.

C1 = paclitaxel 135 mg/m² + pazopanib 800 mg; C2 = paclitaxel 175 mg/m² + pazopanib 800 mg; C3 = paclitaxel 150 mg/m² + pazopanib 800 mg; C4 = paclitaxel 175 mg/m² + pazopanib 400 mg.

Abbreviations: C, cohort.

Figure 1

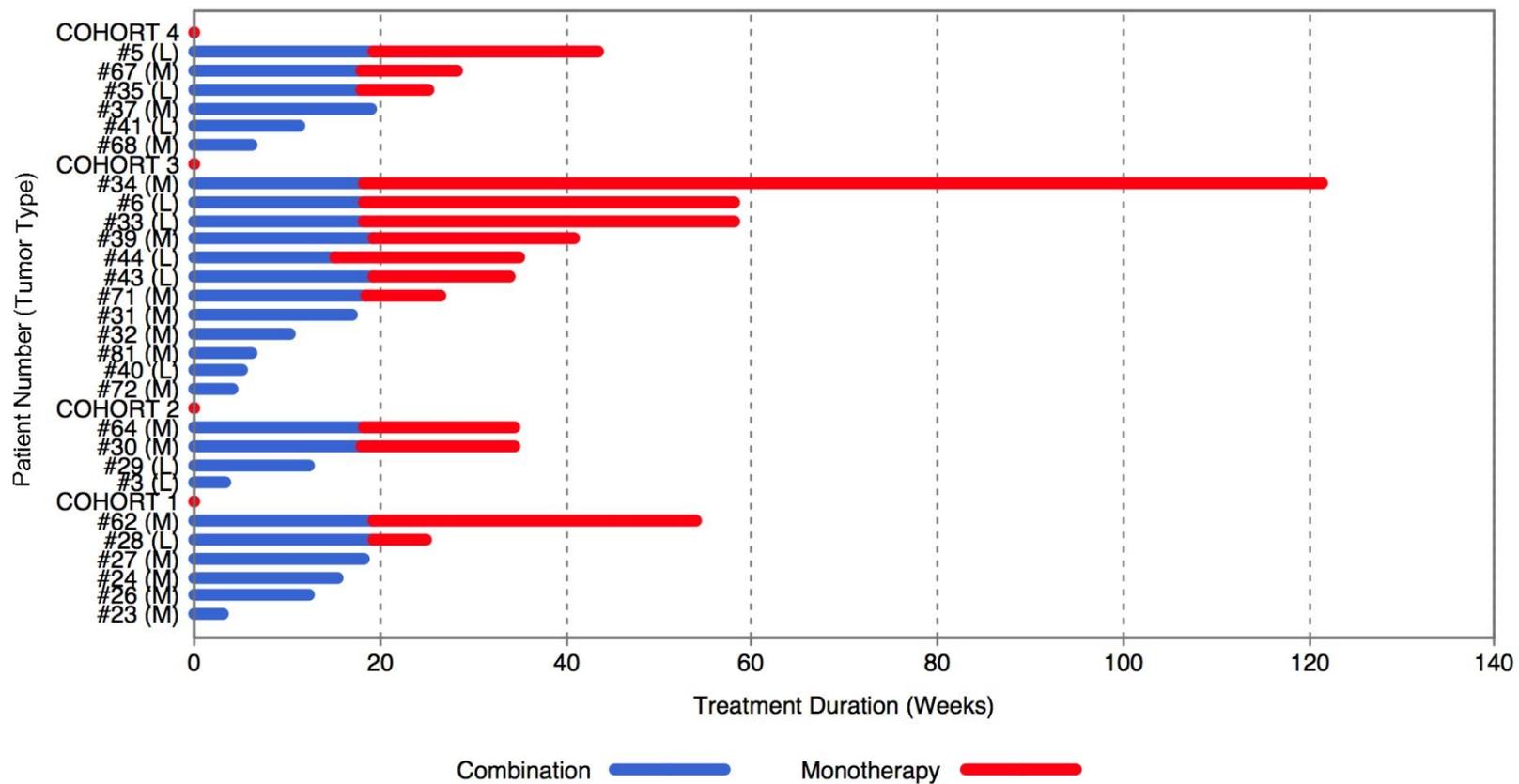


Figure 2

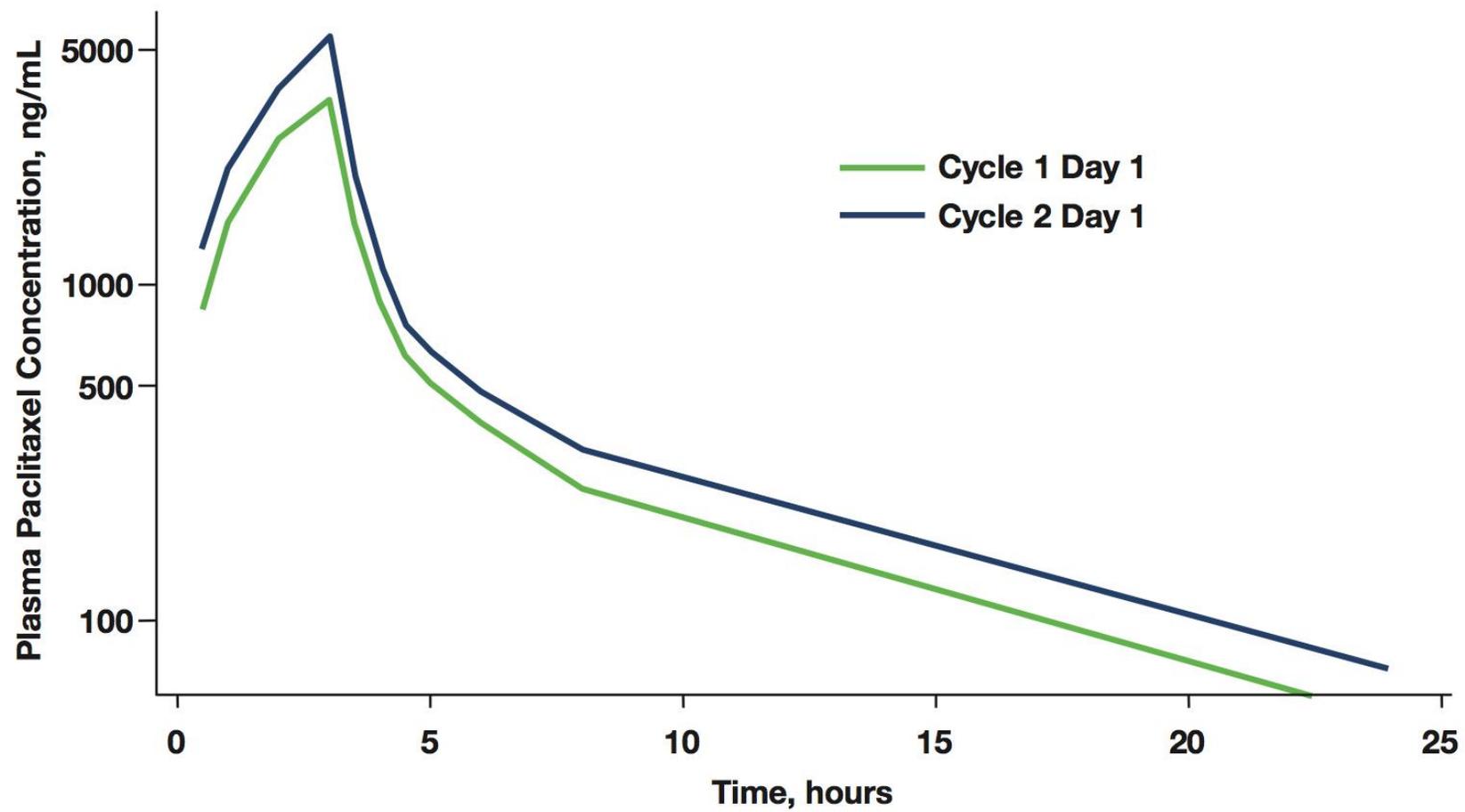
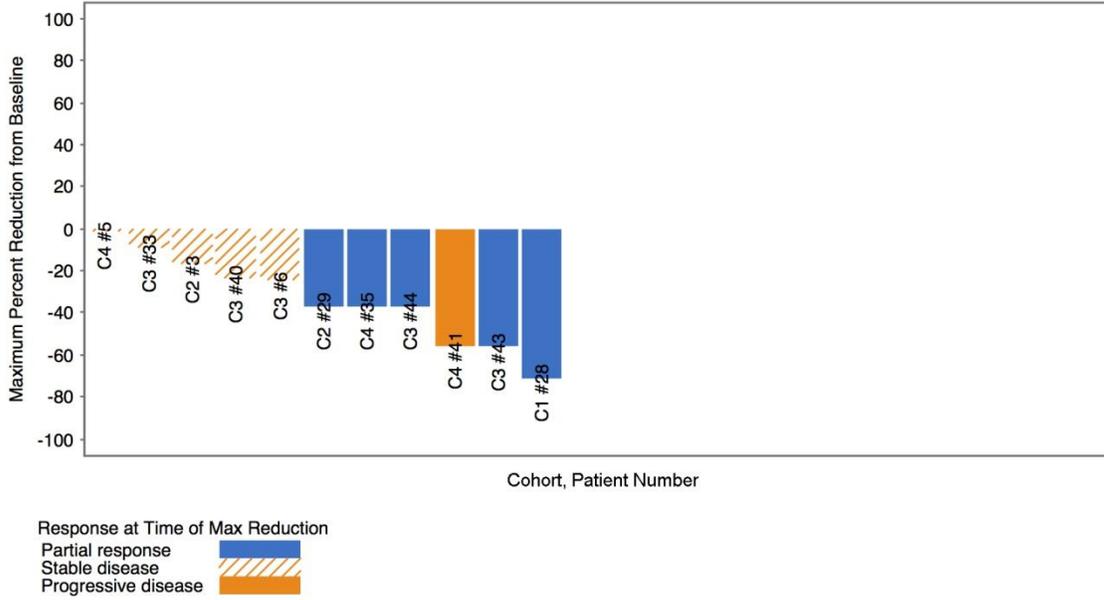


Figure 3

A



B

