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Phase I, pharmacogenomic, drug-interaction study of sorafenib and bevacizumab in combination with paclitaxel in patients with advanced refractory solid tumors

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Abstract

Vascular endothelial growth factor (VEGF) blockade does not uniformly result in clinical benefit. We evaluated safety, dose-limiting toxicities (DLTs), recommended phase II dose (RP2D), antitumor efficacy, and exploratory biomarkers including pharmacogenomics and pharmacokinetics with sorafenib, bevacizumab and paclitaxel in refractory cancer patients.

The study had a “3+3” design, using paclitaxel 80 mg/m^2 QW x 3 every 4 weeks, bevacizumab 5 mg/kg Q2W, and sorafenib 200 or 400 mg BID, 5 or 7 days/week (5/7, 7/7). The maximum tolerated dose (MTD) cohort was expanded. Twenty-seven patients enrolled in 3 cohorts: sorafenib 200 mg BID 5/7, 200 mg BID 7/7, 400 mg BID 5/7. DLTs were grade 3 neutropenia > 7 days (cohort 1, 1), grade 3 hypertension (cohort 2, 1), grade 3 hand-foot skin reaction (HFSR) (cohort 3, 2). MTD was sorafenib 200 mg BID 7/7. Six DLTs occurred in cohort 2 expansion: grade 3 HFSR (2), grade 2 HFSR with sorafenib delay > 7 days (2), grade 4 cerebrovascular accident (1), grade 3 neutropenia > 7 days (1). RP2D was sorafenib 200 mg BID 5/7. Most patients (62%) dose reduced sorafenib to 200 mg QD 5/7 after a median 3 (range 2–17) cycles. Response rates were 48% overall (27), and 64% for ovarian cancers (14). *VEGF-A*-1154AA and −7TT recessive homozygous genotypes conferred worse overall survival vs alternative genotypes (7 vs 22 months). Intermittent, low-dose sorafenib (200 mg BID 5/7) combined with bevacizumab and paclitaxel was tolerable and had high antitumor efficacy in refractory cancer patients (NCT00572078).

Keywords

bevacizumab; sorafenib; paclitaxel; phase I; pharmacogenomics

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INTRODUCTION

Angiogenesis inhibition by targeting vascular endothelial growth factor (VEGF) ligand with bevacizumab or the VEGF receptors (VEGF-R1, 2 or 3) with multi-kinase inhibitors (MKIs) such as sorafenib has been used successfully in multiple malignancies but has limited efficacy as monotherapy.[1] Pro-angiogenic cytokines such as basic fibroblast growth factor (bFGF), angiopoietins, hepatocyte growth factor (HGF), and the platelet derived growth factor (PDGF) surge when tumors progress on bevacizumab, thus combination strategies with vertical VEGF and VEGFR signaling blockade may prevent resistance and increase efficacy.[2,3] Sorafenib is a VEGF-R1, 2, 3, fms-like tyrosine kinase 3 (FLT3), KIT, RAF-1, and PDGFR-β MKI. Dual VEGF and VEGFR blockade yielded promising results in phase I trials, particularly in epithelial ovarian (ORR of 9% to 47%), and renal cell carcinomas, but tolerability was limited by sorafenib-related toxicity at full or reduced doses (400 mg or 200 mg twice daily, BID).[4–6] Several phase II studies evaluated dual angiogenic blockade with bevacizumab plus sorafenib in glioblastoma, renal, breast, and neuroendocrine tumors, but did not report superior benefit compared to bevacizumab monotherapy or historical controls.[7–10]

Chemotherapy (fluoropyrimidines, topoisomerase inhibitors, platinum, paclitaxel) is synergistic with bevacizumab in colorectal, lung, ovarian and cervical cancers, [11–16] and with sorafenib in ovarian cancer.[17] This synergy may be due to improved tumor perfusion and chemotherapy delivery by antiangiogenic agents, but mechanisms have not been fully elucidated. Sorafenib targets additional pathways involved in tumor neo-vascularization and microenvironment given its broader anti-VEGF-R1–3 and anti-PDGFR-β activity. Aside from its well-established cytotoxic effects, paclitaxel has direct anti-proliferative activity against endothelial cells and downregulates VEGF.[18] Schultheis et al reported a small study where paclitaxel (90 mg/m^2 weekly x 3 every 4 weeks, Q4W) and full dose sorafenib (400 mg BID) were not tolerable in combination with escalating doses of bevacizumab (0 to 10 mg/kg Q2W).[19]

Previous phase I studies identified the maximum tolerated dose (MTD) of bevacizumab plus sorafenib as 5 mg/kg Q2W and 200 mg twice daily (BID), respectively.[4,6] In this phase I trial we report the safety, tolerability, dose limiting toxicities (DLTs), maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), anti-tumor efficacy, pharmacokinetics (PK), pharmacogenomics (PG) of angiogenesis and paclitaxel metabolism gene single nucleotide polymorphisms (SNPs), and pharmacodynamic (PD) markers of paclitaxel with bevacizumab and escalating doses of sorafenib in patients with advanced refractory solid tumors.

MATERIALS AND METHODS

Patient eligibility

Eligible patients were ≥18 years, with histologically proven advanced solid malignancies, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, life expectancy ≥ 12 weeks, and adequate organ function. Patients may have received prior taxanes including paclitaxel, or anti-angiogenic therapies, and had prior disease progression on either taxanes

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or anti-angiogenic therapy, but not both. Exclusion criteria included brain metastases, squamous cell lung cancer, peripheral neuropathy grade ≥ 2, unstable angina, myocardial infarction or thrombotic or embolic events within 6 months, congestive heart failure NYHA grade ≥1, uncontrolled hypertension (HTN), symptomatic peripheral vascular disease, impairment of gastrointestinal function which could affect sorafenib absorption, need for therapeutic warfarin, and known hypersensitivity to paclitaxel. All patients provided written informed consent approved by the Indiana University School of Medicine Institutional Review Board, and the study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines.

Study Design and Treatments

This phase I, dose-escalation study (NCT00572078) enrolled patients in a "3+3" design. Paclitaxel was administered intravenously (IV) at 80 mg/m^2 on days (D) 1, 8, 15 every 28 day - cycles (C), bevacizumab dose was 5 mg/kg IV Q2W, and sorafenib was to be dosed orally in escalating cohorts, 5 or 7 days per week: 200 mg BID D1–5 (200 BID 5/7, cohort 1), 200 mg BID (200 BID 7/7, cohort 2), 400 mg BID D1–5 (400 BID 5/7, cohort 3), and 400 mg po BID (400 BID 7/7 cohort 4). Cohort −1, sorafenib 200 mg daily (200 QD) was planned if ≥ 2 DLTs were seen in cohort 1. Dose escalation was allowed if DLT occurred in 0/3 or ≤ 1/6 patients in each cohort during cycle 1. The MTD cohort was to be expanded by 10–15 additional subjects to ensure 16 DLT evaluable patients were treated at MTD. With 16 DLT evaluable patients at MTD there was at least a 97% chance of observing a DLT which had a true rate of ≥ 0.20. Sorafenib dosing started on C1D2 to allow paclitaxel PK assessment as single agent on C1D1.

DLTs were defined during cycle 1 as any possible treatment related grade ≥ 3 toxicities (except grade 3 hyperglycemia, grade 3 deep venous thrombosis (DVT), and alopecia), any episode of malignant hypertension (HTN), HTN that was symptomatic and not managed by maximal use of three different classes of anti-hypertensives, any treatment-related toxicity that resulted in >7 days of missed sorafenib dosing, or any missed paclitaxel or bevacizumab doses in C1. Study treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Antitumor activity: overall response rate (ORR = CR+PR), stable disease (SD), duration of response (DoR), progression-free (PFS) and overall survival (OS) were assessed in all enrolled patients (intent to treat population, ITT) as well as in response evaluable patients. Responses were tabulated. DoR, PFS, and OS were estimated using the Kaplan-Meier method.

Study Assessments

Safety assessments were conducted weekly throughout the study. Adverse events (AEs) were graded using Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Tumor response was assessed every 8 weeks, according to RECIST version 1.0.

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Pharmacokinetic Analyses

Blood samples were collected for paclitaxel on C1D1 and on C1D15 pre-dose, at 15 min, 30 min, 1 hour (end of infusion), 2, 4, 6, 8, and 24 hours after the start of paclitaxel infusion. Paclitaxel was quantified in plasma using internal standardization, liquid-liquid extraction, and HPLC-MS/MS in the Clinical Pharmacology Analytical Core laboratory at Indiana University School of Medicine as previously described.[20] Blood samples for sorafenib PK were collected on C1D7 pre-dose, 30 min, 1, 2, 4, 6, 8, and 24 hours after dosing, and on C1D15 (sorafenib was dosed at the start of paclitaxel infusion), pre-dose, 15 min, 30 min, 1, 2, 4, 6, 8, and 24 hours after the start of paclitaxel infusion. PK parameters for paclitaxel and sorafenib including maximum concentration (C_{max}), half-life ($t_{½}$), and area under the curve (AUC), were estimated using noncompartmental methods with Excel® (Microsoft, Redmond, WA). Descriptive statistics were reported by dose level in the ITT population. At the MTD, changes in PK parameters across cycles/days were compared with paired t-tests. Mean sorafenib parameters at the MTD by objective response (yes/no) were compared with two-sample t-tests. All analyses were performed using SAS Version 9.2 (Cary, NC), except for the pharmacogenetic analyses described in the next section, which were conducted using the genetics package in R.

Pharmacogenomic Analyses

Whole blood was collected at the time of study enrollment and stored at −80°C until analysis. DNA was extracted using the Versagene DNA Blood Purification Kit (Gentra Systems, Inc., Minneapolis, MN, USA) according to the manufacturer's instructions. Because of reports linking polymorphisms in *VEGF-A* or *FLT-1* receptor genes and response to anti-angiogenic agents,[21,22] and in CYP and MDR1 genes with taxane exposure and outcomes,[23,24] we evaluated the association between SNPs with PK parameters and OS: *VEGFA* [−3818G/T (rs833060); −2578C/A (rs699947); 2305G/T (rs36208049); −1498C/T (rs833061); 1210C/A (rs59260042); −1154 G/A (rs1570360); −634G/C (rs2010963); −7C/T (rs25648)]; *FLT-1* (rs9582036); CYP3A5*3 (rs776746), *6 (rs10264272), *7 (rs41303343); *CYP3A4*1B* (rs2740574); *CYP2C8*2* (rs11572103); and *MDR1*/*ABCB1* (rs1128503, rs2032582, rs1045642). Candidate SNPs were genotyped with Taqman-based real-time polymerase chain reaction (RT-PCR). Details for genotyping of each SNP have been previously described.[21,25] Hardy-Weinberg Exact Tests were performed to test for equilibrium and there were no violations to equilibrium. Associations between PK parameters and genotypes were tested with pairwise Wilcoxon rank-sum tests ($p < 0.01$ significance) with false discovery rate correction for multiple comparisons.

Pharmacodynamic Studies

PD studies included dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI), and plasma VEGF-A and soluble VEGFR-2 levels. DCE-MRI was performed at baseline and prior to dosing on C1D15. Kinetic modeling employing the compartmental Tofts model was used to assess the volume transfer between blood and extravascular extracellular space (K^{trans}), between the interstitial space to blood (k_{ep}), and the distribution volume in the extravascular extracellular space (V_e).[26] Changes in tumor vascular parameters were

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compared between baseline and C1D15 by using paired t-tests or Wilcoxon Signed-Rank tests, and between responders and non-responders via two-sample t-tests.

Plasma VEGF-A, and soluble VEGFR2 (sVEGFR-2) levels were measured by enzyme linked immunosorbent assay (ELISA) according to the manufacturer's protocol (R&D Systems, Minneapolis, MN) from samples collected before treatment, and on C1D15 and C2D1. Percent changes in plasma biomarker levels between baseline and C1D15, and between baseline to C2D1 were compared using paired t-tests or Wilcoxon Signed-Rank tests and were correlated with PK parameters via Pearson correlations and with response (yes/no) via two-sample t-tests.

RESULTS

Patients

Twenty-seven patients were enrolled between May 2005 and April 2010. Patients' baseline characteristics are summarized in Table 1; 70% had prior paclitaxel, 22% had prior anti-VEGF therapies. Patients completed a median of 6 cycles of treatment (range 1–30) as follows: cohort 1, 16 cycles (range 5–30); cohort 2, 4 cycles (range 1–11); cohort 3, 6 cycles (6, 6); cohort 2 expansion, 5 cycles (range 1–10). Median follow-up was 41.2 months (95% CI 30.1, 43 months).

Dose Escalation and Toxicity

Three patients were not evaluable for DLT in cycle 1 due to paclitaxel-related infusion reaction, viral gastroenteritis precluding treatment, and percutaneous endoscopic gastrostomy (PEG)-tube infection precluding sorafenib dosing (1 each, cohort 2). Four DLTs occurred during dose escalation: grade 3 neutropenia >7 days (n=1, cohort 1), grade 3 HTN (n=1, cohort 2), and grade 3 hand-foot skin reaction (HFSR) (n=2, cohort 3). Six DLTs occurred in cohort 2 expansion: grade 3 HFSR (n=2), grade 2 HFSR resulting in sorafenib delay > 7 days (n=2), grade 4 CNS cerebrovascular ischemia (CVA, cerebrovascular accident) (n=1), and grade 3 neutropenia resulting in treatment delay > 7 days (n=1).

The most common treatment-related adverse events (TRAEs) were: HFSR (74%), HTN (70%), alopecia (63%), and mucositis (59%). The most common grade ≥ 3 TRAEs were HTN (33%), HFSR (30%), neutropenia (15%), pain and mucositis (11% each). One patient each with ovarian cancer (cohort 2 expansion) had grade 4 TRAEs: colon/bladder perforation and CVA. Table 2 summarizes TRAEs which occurred in >10% of the patients, and Table 3 shows all grade 3/4 TRAEs.

Dose modifications (dose reductions or delays/interruptions) were common: sorafenib (n=25, 93%), paclitaxel and bevacizumab (n=23 each, 85%). Reasons for study-treatment discontinuation were disease progression by RECIST (n=10), AEs (n=10), physician decision for patient symptomatic deterioration (n=5), or patient decision (n=2). AEs leading to study treatment discontinuation were: jaw osteonecrosis (prostate cancer – cycle 26, PR), catheter-associated DVT (cervical cancer - cycle 5, SD), mucositis (paraganglioma – cycle 24, SD), worsening hematuria (ovarian cancer – cycle 8, PR), PEG-tube site infection (gastroesophageal junction (GEJ) cancer – cycle 1, SD), colon/bladder perforation (cervical

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cancer – cycle 4, SD), paclitaxel infusion reaction (GEJ cancer – cycle 1, not evaluable, NE), CVA (ovarian cancer – cycle 1, NE), enterocutaneous fistula (ovarian cancer – cycle 2, NE), HTN (adrenocortical cancer – cycle 2, SD).

The MTD was sorafenib 200 mg BID 7/7 with bevacizumab 5 mg/kg Q2W, and paclitaxel 80 mg/m^2 QW x 3 every 4 weeks. Due to 6 additional DLTs in the expansion cohort, the RP2D was sorafenib 200 mg BID 5/7. Fifteen of 24 DLT evaluable patients (62%) required further sorafenib dose reduction to 200 mg QD 5/7 after a median of 3 cycles (range 2–17) due to grade 2/3 HFSR (9), grade 3 HTN (2) and grade 2/3 mucositis (2), grade 2 nausea (1) and grade 2 fatigue (1). Five patients (21%) needed further sorafenib dose reduction to 200 mg QOD for grade 2/3 HFSR (3), worsening grade 1 neuropathy (1) and grade 3 mucositis (1).

Antitumor Activity

Among 27 patients enrolled, 24 patients were evaluable for response, and 3 were not, due to study treatment discontinuation for paclitaxel infusion reaction, CVA, and entero-cutaneous fistula, respectively, before imaging evaluation. Best responses were: 2 CR, (confirmed: ovarian, endometrial), 11 PR (9 confirmed: ovarian (6), endometrial, prostate, bladder), 11 SD (8 SD ≥ 4 months), with ORR of 48% (13/27), confirmed in 41% (11/27), and the clinical benefit rate (CBR = ORR + SD ≥ 4 months) was 78% (21/27) in the ITT population (Figure 1). Median duration of confirmed response was 8.3 months (n=11, 95% CI 4.3–16 months). Median OS and PFS were 14.7 months (95% CI 8.8–32.8), and 7.9 months (95% CI 6.0–9.4 months), respectively in the ITT population. Among 14 ovarian cancer patients, 2 patients were not evaluable for response due to CVA (C1) and enterocutaneous fistula (C2), 9 had CR/PR (64%), 7 confirmed (50%), and 3 patients (21%) had SD ≥ 4 months, with a CBR rate of 86% (12/14). Median OS and PFS were 21.3 months (95% CI 8.8–32.8 months) and 8.5 months (95% CI 6.0–9.4 months), respectively. Ovarian cancer patients had a median 5 prior lines of systemic therapy (range 1–11), all had prior treatment with paclitaxel, and 4 patients had prior anti-VEGF therapy with bevacizumab (2) or sorafenib (2). Ovarian cancer patients received a median of 7 treatment cycles (range 1–11); 9 patients had sorafenib dose reductions to 200 mg QD 5/7 (after median 3 cycles), and 5 were dose reduced to 200 mg QOD (after median 7 cycles).

Pharmacokinetics

Paclitaxel PK measurements were available for 27 (C1D1) and 21 patients (C1D15), respectively. Sorafenib PK measurements were available for 24 (C1D7) and 19 patients (C1D15), respectively (Table 4). At MTD, there were no significant differences in paclitaxel exposure with concurrent sorafenib (p= 0.44 for C_{max}, p= 0.30 for AUC), and sorafenib had lower C_{max} (p=0.05) with concurrent paclitaxel. In all patients tested, sorafenib exposure at C1D15 was higher among responders (n=8, $AUC_{0–8}$ 38,089.6 ng*hr/mL) vs non-responders (n=9, $AUC_{0–8}$ 17,265.9 ng*hr/mL), though not significant (p = 0.27). No correlations between PK and OS were observed.

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Pharmacogenetics

Genomic DNA was available for analysis for 25 patients. There were no associations between paclitaxel PK and CYP or MDR1 SNPs, nor between sorafenib PK and variants tested. Significantly worse OS was observed for *VEGFA*-1154AA vs -AG/GG (7.4 vs 22 months, p=0.014), and for *VEGFA*-7TT vs -CT/CC recessive homozygous genotypes (5.7 vs 21.3 months, p=0.001).

Pharmacodynamic studies

Eight patients underwent paired DCE-MRI analysis at baseline and on C1D15. Pre-treatment K^{trans} was lower for responding patients (n=4, K^{trans} 0.1522 mL blood/mL tissue-min) compared to those with stable disease (n=4, K^{trans} 0.3555 mL blood/mL tissue-min, p=0.07). K^{trans} decreased by an average of 23% during treatment in all patients.

Pre- and post-treatment plasma samples were collected from 26 patients and measurements for VEGF-A and sVEGFR-2 are summarized in Table 5. Both plasma VEGF-A and sVEGFR-2 increased from C1D1 to C1D15 ($p<0.0001$ and p=0.0141, respectively), and from C1D1 to C2D1 (p=0.0063 and p=0.0004, respectively), however sVEGRF-2 levels increased <15%, whereas VEGF-A increased 10-fold. There were no significant associations between on-study VEGF and sVEGFR2 changes with sorafenib PK or toxicities such as HTN and HFSR, but VEGF-A increased less in responders vs non-responders (932% vs 1569%, p = 0.09).

DISCUSSION

VEGF blockade with bevacizumab provides incremental benefits to chemotherapy for many solid tumors, including ovarian and cervical cancers.[1,13,14] VEGF-targeted MKIs such as sorafenib have not generally provided increased efficacy when added to chemotherapy, partly due to poor tolerability and higher toxicity.[27,28] Only recently, in ovarian cancer patients, sorafenib dosed sequentially to topotecan (topotecan days 1–5 and sorafenib days 6–15 every 21 days) was tolerable and increased efficacy compared to topotecan alone.[17] Previous reports of combined vertical VEGF inhibition with bevacizumab and sorafenib required lower sorafenib doses but noted encouraging efficacy (ORR 9–47% in refractory ovarian cancers) with higher toxicity (24–79% HFSR and 21–67% HTN), and as a result this approach has not been tested further in randomized trials.[4–6]

In this phase 1 study we assessed the safety and antitumor efficacy of dual VEGF inhibition in combination with paclitaxel in refractory cancer patients. The MTD was sorafenib 200 mg BID, however, most patients required dosing 5 days/week (5/7) after cycle 1, and 200 mg QD 5/7 after a median of 3 cycles, for long-term treatment. We observed a higher incidence of sorafenib and bevacizumab-related, including overlapping, toxicities compared to those expected with anti-VEGF monotherapy: 74% HFSR (30% grade 3) vs 25–50% (10% grade 3), and 70% HTN (33% grade 3) vs 15–30% (2–4% grade 3) with sorafenib or bevacizumab monotherapy, respectively.[1,29] Early occurrence (<60 days) and grade ≥ 2 HFSR correlated with improved OS and PFS from sorafenib in HCC patients.[30] In our study, HTN and HFSR occurred at all dose levels and did not correlate with outcomes. Mechanisms explaining the

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higher than anticipated HFSR rates with dual anti-VEGF therapy have not been elucidated, but it is likely that the combination hinders vascular repair.[31]

We evaluated the potential for PK interactions between paclitaxel and sorafenib, given that both drugs share a common metabolic pathway via cytochrome P450 3A (CYP3A).[32,33] We found no significant impact of sorafenib on paclitaxel PK, consistent with prior data.[34] Sorafenib exposure at steady state (C1D7) with 200 mg BID was higher than historical values with sorafenib alone ($AUC_{0–8}$ 23,077 vs 6,000–16,000 ng*h/mL) and might account for the higher toxicity rates we observed.[35] Sorafenib PK tended to correlate with toxicity and efficacy in some studies.[36] In our study, sorafenib exposure was higher among responding patients, but we did not observe definitive correlations with toxicity or survival.

Genetic variability of drug metabolism, transporters, or therapeutic targets may influence paclitaxel or sorafenib PK. Several genetic polymorphisms, including those affecting angiogenesis-related genes *VEGFA*, *VEGFR-1*, *VEGFR-2*, *VEGFR-3*, adenosine/endothelial nitric oxide synthase (eNOS) signaling (*SLC29A1* and *HSP90AB1)*, and immunomodulatory pathways have been previously correlated with safety and efficacy of anti-VEGF agents.[37–41] We observed no correlations between genotypes tested and toxicity in this study. *VEGFA* −2578 AA and −1154AA SNPs correlate with reduced VEGF-A expression. Contrary to prior reports in studies testing anti-VEGF monotherapies, *VEGFA* −1154AA vs −1154AG/GG (p=0.0148), *VEGFA*-7TT vs −7CT/CC (p=0.0010) and *VEGFA* −2578 AA vs −2578AC/CC (p=0.351) were associated with worse OS in our study. To date, no SNPs have been reliably correlated with outcomes from anti-VEGF therapies, to be used as biomarkers in clinical practice. Our observations in this small cohort are intriguing and hypothesis-generating.

VEGF blockade transiently normalizes tumor vasculature and improves blood perfusion, however high doses or continuous antiangiogenic therapy may reduce perfusion. Few patients underwent DCE-MRI in this study, precluding firm conclusions. Low baseline K^{trans} correlated with increased response to treatment, though not statistically significant. High baseline plasma VEGF levels confer increased vascular permeability and have been associated with worse outcomes for some, but not all cancers, after treatment with bevacizumab or VEGFR MKI.[42–44] Plasma VEGF levels significantly increased during treatment, as previously noted with bevacizumab, VEGFR MKIs,[43] and with dual anti-VEGF blockade,[4] but we observed a trend for less VEGF increase with treatment in responding vs non-responding patients. While VEGFR MKI decrease sVEGFR-2 levels,[43] sVEGFR2 levels were generally stable to slightly increased in our study, possibly due to the lower doses of sorafenib used.

Anti-VEGF therapies offer modest single-agent activity in hepatocellular, renal cell, gastric/gastroesophageal junction, thyroid, glioblastoma, and neuroendocrine tumors, and anti-VEGF antibodies such as bevacizumab or ramucirumab increase efficacy from paclitaxel chemotherapy in ovarian, cervical, lung and gastric/gastroesophageal cancers.[1,11–16] In recurrent ovarian cancer patients bevacizumab and sorafenib have single-agent activity, with ORR of 20%, PFS 4 months, and OS 17 months for bevacizumab, and ORR 3%, PFS 2 months, and OS 16 months with sorafenib, respectively; but resistance develops rapidly.[45,46]

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The AURELIA phase III trial in patients with recurrent platinum-resistant ovarian cancer demonstrated significant benefit with the addition of bevacizumab to chemotherapy, with ORR of 27.3% vs 11.8% (p=0.001), PFS 6.7 vs 3.4 months (p<0.001), but equivalent OS vs chemotherapy alone (16.6 vs 13.3 months, p=0.174).[13] Among the chemotherapy backbones, bevacizumab conferred the largest benefit when added to paclitaxel: ORR 53.3% vs 30.2%, PFS 10.4 vs 3.9 months, and OS 22.4 vs 13.2 months).[47] The TRIAS randomized phase II trial in platinum-resistant ovarian cancer patients treated with up to 2 prior therapies, demonstrated that sorafenib dosed sequentially with topotecan was safe and improved ORR (31% vs 12%), PFS (6.7 vs 4.4 months, p=0.002) and OS (17 vs 10 months, p=0.017), compared to topotecan alone.[17]

Sorafenib dosing in this trial was sub-standard due to toxicity, and the schedule was intermittent with RP2D of 200 mg BID 5/7 starting dose followed by 200 mg QD 5/7 for long-term dosing, after a median of 3 cycles. With low intermittently dosed sorafenib added to bevacizumab and paclitaxel, the ORR of 48%, CBR of 78% and median duration of response of 8.3 months were high in the ITT population. Sorafenib dose reductions did not seem detrimental to efficacy, as 16 of 21 patients (76%) who remained on study for ≥ 4 months had sorafenib dose reductions, and two-thirds of responders received sorafenib QD long-term with good tolerability. Previous reports of sorafenib plus bevacizumab noted ORR of 47% and CBR of 59% among refractory ovarian cancer patients.[4,5] With the addition of paclitaxel in this study, refractory ovarian cancer patients (n=14, median 5 prior chemotherapy regimens, all previously treated with paclitaxel) had ORR of 64%, CBR of 86%, and median PFS and OS of 8.5 and 21.3 months, respectively. In addition, promising activity was seen in patients with endometrial (1 CR 30 cycles, 1 PR 8 cycles), prostate (1 PR 26 cycles, 1 SD 7 cycles), paraganglioma (1 SD 24 cycles), cervical (2 SD, 4 and 5 cycles), and bladder cancers (1 PR 6 cycles, 1 SD 4 cycles) (Figure 1).

Despite having multiple VEGF and VEGFR inhibitors available in the clinic, the optimal patient subgroups benefiting from these agents have not yet been defined. It is assumed that antiangiogenic agents affect the structure and function of tumor vasculature and improve chemotherapy delivery,[48] and conversely, chemotherapy cytotoxicity synergizes with VEGF/R inhibitors.[49] It has also been postulated that while short-term anti-VEGF therapy improves tumor perfusion and chemotherapy delivery, high-dose or chronic VEGF inhibition may have detrimental effects,[50] therefore lower doses or intermittent exposure to anti-VEGF therapy may be desirable for long-term treatment. It is likely that vertical axis inhibition of related VEGF/R targets leads to additive or synergistic effects while allowing lower drug dosing. Consistent with previous reports of dual VEGF inhibition and clinical trials of sorafenib plus chemotherapy [4,17,48] continuous low dose (200 mg BID 7/7) or intermittent standard dose (400 mg po BID 5/7) of sorafenib were not tolerable, but intermittent low-dose (200 mg BID 5/7 followed by 200 mg QD 5/7) in combination with paclitaxel plus bevacizumab was tolerable long-term. Chemotherapy plus bevacizumab is currently the standard first-line treatment for ovarian cancer, therefore there is high need to develop effective regimens for recurrence after bevacizumab-containing first-line treatment. Given the effects of angiogenesis modulation on tumor microenvironment and DNA repair, there is high interest for exploring novel strategies in advanced ovarian cancer patients and other

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tumor types with anti-angiogenic agents in combination with poly (ADP-ribose) polymerase inhibitors, immunotherapy, and chemotherapy.

In conclusion, the combination of paclitaxel with bevacizumab and intermittent low-dose sorafenib is highly active and should be further explored in larger clinical trials, especially in patients with recurrent ovarian cancers, where clinical activity was impressive. It is possible that novel strategies, such as targeting non-overlapping pro-angiogenic and tumor microenvironment pathways, may be highly effective and better tolerated.

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Conflicts of Interest

E. Gabriela Chiorean: research funding (institution) Roche/Genentech/Ignyta; research funding (institution) Onyx/Bayer

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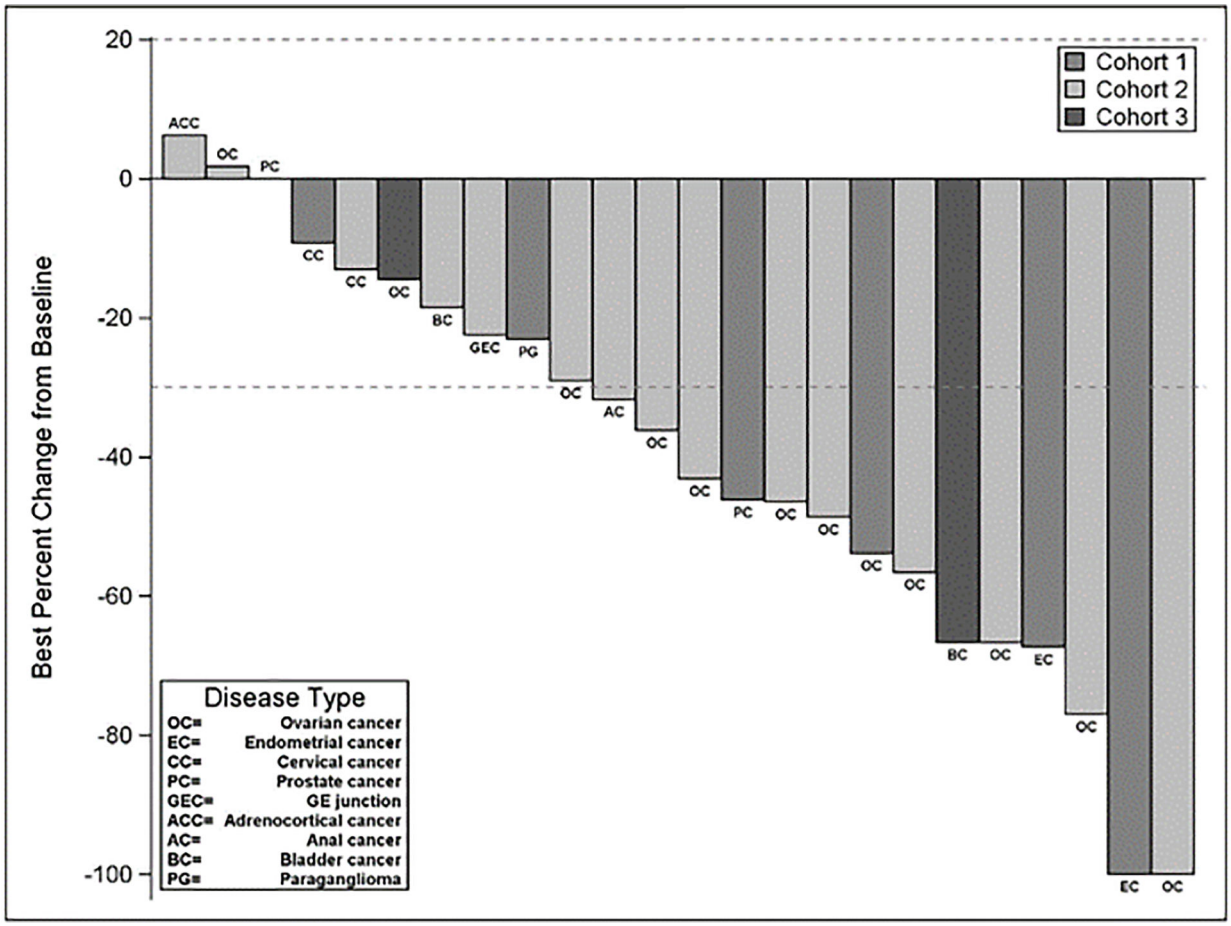

Figure 1: Waterfall Plot of Best Tumor Response

Best tumor response is shown in 24 response-evaluable patients based on treatment cohorts. Dotted line at −30% represents the mark for 30% tumor shrinkage and partial response.

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Table 1:

Characteristics of 27 Enrolled Patients

Characteristic	Number	%
Age (years)		
Median (range)	53 (29–75)	
Gender		
Female	20	74
Male	7	26
ECOG performance status		
0	18	67
1	9	33
Tumor type		
Ovarian	14	52
- Serous	11	41
- Endometrioid	1	4
- Mixed serous/endometrioid	1	4
- Unspecified	1	4
Cervical	2	7
Endometrial	2	7
Bladder	2	7
Prostate	2	7
Gastroesophageal Junction	2	7
Adrenocortical	1	4
Anus	1	4
Paraganglioma	1	4
Nr of prior chemotherapies		
Median (range)	3 (0–11)	
Prior anti-VEGF therapies	6	22
Prior paclitaxel	19	70
Nr prior chemotherapies in ovarian cancer patients		
Median (range)	5 (1–11)	
Prior anti-VEGF therapies in ovarian cancer patients	4	28
Prior paclitaxel in ovarian cancer patients	14	100

Abbreviations: ECOG, Eastern Cooperative Oncology Group

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Table 2:

Treatment-Related Toxicities in ≥ 10% of Patients (NCI-CTCAE v3.0)

Adverse Event	All grades Nr (%)	Grade 3/4 Nr (%)
HFSR	20 (74)	8 (30)
Hypertension	19 (70)	9 (33)
Alopecia	17 (63)	0
Mucositis	16 (59)	3 (11)
Fatigue	13 (48)	0
Sensory neuropathy	11 (41)	0
Hemorrhage-nose	8 (30)	0
Anorexia	8 (30)	0
Neutropenia	7 (26)	4 (15)
Voice alteration	7 (26)	0
Nausea	7 (26)	0
Diarrhea	7 (26)	0
Pain – limb	5 (19)	3 (11)
Dyspnea	5 (19)	0
Vomiting	5 (19)	0
Rash-desquamation	5 (19)	0
Headache	4 (15)	0
Cough	3 (11)	0
Dysgeusia	3 (11)	0
Nail changes	3 (11)	0
Pruritus	3 (11)	0
Constipation	3 (11)	0

Abbreviations: HFSR, hand-foot skin reaction

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Table 3:

All Grade 3/4 Treatment Related Toxicities

Cohort **Sorafenib Dose / Schedule**	**Adverse Event**	**Grade 3/4*** **nr (%)**
Cohort 1 (n=6) 200 mg BID 5/7	HTN	2 (33)
	Neutropenia	1 (17)
	Vascular catheter thrombosis	1 (17)
	Osteonecrosis jaw	1 (17)
Cohort 2/2 expansion (n=19) 200 mg BID 7/7	HTN	6 (32)
	HFSR	6 (32)
	Mucositis	3 (16)
	Pain-limb	3 (16)
	Neutropenia	2 (11)
	CNS cerebrovascular ischemia (CVA)	1 (5)
	Colon/bladder perforation	1 (5)
	Enterocutaneous fistula	1 (5)
	Paclitaxel infusion reaction	1 (5)
Cohort 3 (n=2) 400 mg BID 5/7	HFSR	2 (100)
	HTN	1 (50)
	Neutropenia	1 (50)

Abbreviations: HFSR, hand-foot skin reaction; HTN, hypertension

* all toxicities were grade 3 except grade 4 colon/bladder perforation and grade 4 CNS cerebrovascular ischemia (CVA, cerebrovascular accident)

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Table 4:

Summary Pharmacokinetic Parameters for Paclitaxel and Sorafenib

Sorafenib dose, schedule	Parameter (units) mean (SD)	Paclitaxel C1D1	Paclitaxel C1D15	Sorafenib C1D7	Sorafenib C1D15
200 mg BID 5/7 cohort 1	n	6	6	3[a]	5[b]
	C_{max} (ng/mL)	3,553 (1,304)	4,350 (1157)	2,755 (1506)	8,815 (11636)
	$t_{1/2}$ (h)	11.6 (2.8)	10.3 (5.3)	7.2 (2.3)	4 (-)
	AUC_{0-8} (ng*hr/mL)	6,105 (2,055)	6,872 (2,159)	14,911 (8,174)	48,469 (66,889)
200 mg BID 7/7 cohorts 2/2 expansion	n	19	13	19[c]	14[d]
	C_{max} (ng/mL)	3,035 (2148)	3,485 (1974)	4,539 (2,333)	3,213 (1691)
	$t_{1/2}$ (h)	15.1 (11.4)	19.5 (8.6)	19.7 (23.3)	6.5 (2.2)
	AUC_{0-8} (ng*hr/mL)	6,992 (4827)	8,415 (4,029)	23,077 (11,959)	19,353 (10,823)
400 mg BID 5/7 cohort 3	n	2	2	2[e]	0
	C_{max} (ng/mL)	2,241 (1,007)	3,804 (1306)	3,825 (624)	-
	$t_{1/2}$ (h)	13.4 (2.5)	12.1 (0.4)	7.8 (-)	-
	AUC_{0-8} (ng*hr/mL)	3,867 (388)	6,097 (1,617)	22,951 (3,065)	-

Abbreviations: C_{max}, maximum concentration; N, number patients; SD, standard deviation; $t_{½}$, half-life;

[a] n=2 for cohort 1 $t_{1/2}$

[b] n=1 for cohort 1 $t_{1/2}$

[c] n=9 for cohort 2/2 expansion $t_{1/2}$

[d] n=13 for cohort 2/2 expansion C_{max} and n=5 for $t_{1/2}$

[e] n=1 for cohort 3 $t_{1/2}$

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Table 5:

Summary Pharmacodynamic Parameters

Sorafenib dose, schedule	Timepoint	n	plasma VEGF-A (pg/mL) mean (SD)	n	plasma sVEGFR-2 (pg/mL) mean (SD)
200 mg BID 5/7 cohort 1	C1D1	5	30.7 (57.5)	5	1659.2 (250.1)
	C1D15	5	100.0 (49.1)	5	1955.3 (285.8)
	C2D1	4	75.6 (17.1)	4	1972.9 (358.7)
200 mg BID 7/7 cohorts 2 / 2 expansion	C1D1	10	20.3 (42)	19	1584.9 (372.8)
	C1D15	14	82.2 (30.6)	14	1740.4 (315.9)
	C2D1	8	73.1 (21.6)	8	1601.4 (389.7)
400 mg BID 5/7 cohort 3	C1D1	2	6.4 (0.3)	2	1886.7 (151.4)
	C1D15	2	94.9 (14.1)	2	1973.9 (46.1)
	C2D1	2	84.8 (6.5)	2	2006.5 (30.4)