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## A Phase 1, Open-label Study of Trebananib Combined With Sorafenib or Sunitinib in Patients With Advanced Renal Cell Carcinoma

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### Abstract

**Background**—Trebananib, an investigational peptibody, binds to angiotensin II type 2 receptor (Tie2), thereby blocking their interaction with Tie2.

**Patients and Methods**—This open-label phase 1 study examined trebananib 3 mg/kg or 10 mg/kg IV QW plus sorafenib 400 mg BID or sunitinib 50 mg QD in advanced renal cell carcinoma (RCC). Primary endpoints were adverse event incidence and pharmacokinetics.

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Trial registry and registration identification number: NCT00861419

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**Conflict of Interest Statement:** David Hong has research funding and Speakers Bureau support from Amgen. Razelle Kurzrock has research/grant funding from Amgen. Nicholas Vogelzang participates in a data safety and monitoring board for Amgen. Erik Rasmussen, Benjamin Wu, Michael Bass, Zhandong Zhong, and Gregory Friberg are employees of Amgen, and hold stocks or stock options in Amgen. Michael Gordon, Wolfram Samlowski, Nizar Tannir, David Friedland, David Mendelson, and Leonard Appleman have no conflicts to declare.

**Manufacturer Name:** The following companies manufactured products that were implemented in this study: Amgen Inc. (trebananib); Bayer HealthCare Pharmaceuticals Corporation and Onyx Pharmaceuticals (sorafenib [Nexavar<sup>®</sup>]); Pfizer (sunitinib [Sutent<sup>®</sup>]); and Pharsight (WinNonlin Professional, version 4.1e).

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**Results**—Thirty-seven patients were enrolled. During trebananib plus sorafenib administration ( $n = 17$ ), the most common treatment-related adverse events (TRAEs) included rash (71%), diarrhea (71%), hypertension (65%), and fatigue (65%); grade 3 TRAEs (41%); and 14% of patients had peripheral edema. During trebananib plus sunitinib administration ( $n = 19$ ), the most common TRAEs included diarrhea (74%), fatigue (68%), hypertension (58%), and decreased appetite (58%); grade 3 TRAEs (68%); and 42% of patients had peripheral edema. Trebananib did not appear to alter the pharmacokinetics of sorafenib or sunitinib. No patient developed anti-trebananib antibodies. Objective response rates were 29% (trebananib plus sorafenib) and 53% (trebananib plus sunitinib).

**Conclusions**—The toxicities of trebananib IV 3 mg/kg or 10 mg/kg plus sorafenib or sunitinib in RCC were similar to those of sorafenib or sunitinib monotherapy, with peripheral edema being likely specific to the combinations. Antitumor activity was observed.

### Keywords

Angiogenesis; Angiopoietins; Targeted therapies; Tie2 receptor; Vascular growth factor receptor

### Introduction

Simultaneous administration of multiple angiogenic inhibitors targeting the vascular endothelial growth factor (VEGF) pathway in patients with metastatic renal cell carcinoma (RCC) has not produced the expected additive therapeutic effects and has been associated with increased toxicity relative to therapies with single VEGF pathway inhibitors.<sup>1–3</sup> One treatment approach that may circumvent some of those limitations involves the combination of inhibitors targeting separate angiogenic pathways.

The angiopoietin pathway is a critically important contributor to angiogenesis.<sup>4–6</sup> The pathway ligands angiopoietin 1 and 2 (Ang1 and Ang2) bind to Tie2, a receptor tyrosine kinase primarily expressed in the vascular endothelium. Ang1 and Ang2 promote tumor angiogenesis through vessel remodeling and stabilization. Moreover, Ang2 elevations have been associated with various cancer types and worse clinical outcome.<sup>7–10</sup> Trebananib, an investigational peptide Fc–fusion protein (“peptibody”), suppresses tumor angiogenesis by binding to Ang1 and Ang2 and blocking their interaction with Tie2.<sup>11</sup> In tumor xenograft models, dual inhibition of Ang1 and Ang2 was associated with greater suppression of angiogenesis and tumor growth when compared with single inhibition of either ligand.<sup>11</sup> A first-in-human dose escalation study of patients with advanced solid tumors receiving trebananib monotherapy demonstrated antitumor activity and a specific and manageable toxicity profile.<sup>12</sup> In a phase 2 estimation study of patients with recurrent ovarian cancer, the combination of trebananib and paclitaxel was associated with a prolongation of progression-free survival (PFS).<sup>13</sup>

The objectives of the current study were to evaluate the tolerability, pharmacokinetic (PK) and biomarker profiles, and antitumor activity of trebananib in combination with the VEGF pathway inhibitors sorafenib and sunitinib in patients with advanced RCC.

## Patients and Methods

This open-label, phase 1b study evaluated trebananib combined with the VEGF pathway inhibitors sorafenib (Nexavar<sup>®</sup>; Bayer HealthCare Pharmaceuticals Corporation, Montville, NJ, USA; Onyx Pharmaceuticals, Emeryville, CA, USA), sunitinib (Sutent<sup>®</sup>; Pfizer, New York, NY, USA), bevacizumab (Avastin<sup>®</sup>; Genentech, Inc., South San Francisco, CA, USA), or motesanib. All patients receiving trebananib plus sorafenib or sunitinib had diagnoses of advanced RCC. Patients in the trebananib plus bevacizumab or motesanib treatment arms had diagnoses of advanced solid tumors across various tumor types. Because comparisons between the two patient groups (ie, patients with RCC and patients with solid tumors across various tumor types) would not be valid, the current report focuses only on the subset of patients with advanced RCC. The results related to patients with advanced solid tumors receiving trebananib plus bevacizumab or motesanib will be reported elsewhere. The study protocol was approved by independent institutional review boards, and the study was conducted in accordance with the Declaration of Helsinki. Patients (> 18 years) had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2; and adequate hematological, renal, and hepatic function. Patients with head and neck cancer were later excluded based on safety findings from one of the cohorts receiving trebananib and bevacizumab. Patients with a history of gastrointestinal disease were excluded as the disease may limit absorption of an oral agent. Patients with cardiovascular events during the year prior to enrollment were also excluded; those events included myocardial infarction, unstable or severe angina, coronary or peripheral artery bypass graft, unstable cardiac arrhythmia requiring medication, symptomatic congestive heart failure, and cerebrovascular accident or transient ischemic attack. Additional exclusion criteria included central nervous system metastasis; a recent anticancer therapy; therapies involving rifampin, phenobarbital, HIV protease or strong cytochrome P450 3A (CYP3A) suppressors, immune modulators, St. John's wort, or coumarin anticoagulants > 2 mg/day; previous treatment with radiation therapy, trebananib, bevacizumab, sorafenib (for the sorafenib cohorts), and sunitinib (for the sunitinib cohorts).

### Study Design and Treatment

Sorafenib and sunitinib are orally administered multikinase antagonists to the VEGF and platelet-derived growth factor receptors<sup>14,15</sup> and indicated for the treatment of advanced RCC.<sup>16,17</sup> Primary endpoints were the incidence of adverse events (AEs) and PK profiles. Secondary endpoints included tumor response and changes in biomarkers.

The following cohorts were enrolled: trebananib 3 mg/kg plus sorafenib 400 mg, trebananib 10 mg/kg plus sorafenib 400 mg, trebananib 3 mg/kg plus sunitinib 50 mg, and trebananib 10 mg/kg plus sunitinib 50 mg. Trebananib was administered intravenously (IV) once weekly (QW). Patients self-administered sorafenib orally twice daily (BID) and sunitinib (4 weeks on/2 weeks off) orally once daily (QD). Sorafenib and sunitinib dosing started on day 1 of week 1 followed by trebananib on day 1 of week 2. Trebananib doses were selected based on a previous monotherapy study in patients with advanced solid tumors; the half-life of trebananib at 3 mg/kg and 10 mg/kg in that study was approximately 4 and 6 days, respectively.<sup>12</sup> Recommended doses as indicated in the labeling approved by the Food and

Drug Administration as of December 2005 and February 2007 were selected for sorafenib and sunitinib, respectively.

A dose-limiting toxicity (DLT) was any grade 3 or greater toxicity, except for the following modifications: transient grade 3 infusion reactions lasting more than 2 hours; grade 3 fatigue or grade 4 neutropenia for more than 7 days; grade 3 or 4 nausea, diarrhea, vomiting, or neutropenia with fever above 38.5°C; grade 4 aspartate or alanine aminotransferase greater than 10 times the upper limit of normal; and grade 4 thrombocytopenia, anemia, or hypertension. The DLT had to occur during the initial 28 or 42 treatment days for the trebananib plus sorafenib or trebananib plus sunitinib cohorts, respectively.

Initially, three patients entered the trebananib 3 mg/kg plus sorafenib or sunitinib dose cohorts. If no DLT occurred in either cohort, up to six patients were enrolled in the trebananib 10 mg/kg plus sorafenib or sunitinib dose cohorts; three additional patients could also be enrolled at the investigator's discretion in the trebananib 3 mg/kg cohorts. If two or more patients out of the initial three patients in the trebananib 3 mg/kg cohorts had a DLT, no additional patients were enrolled; if one patient experienced a DLT, up to three additional patients were enrolled in that cohort. In this expanded cohort, if fewer than three patients experienced a DLT, up to six patients were enrolled in the trebananib 10 mg/kg cohorts. Finally, for one dose cohort of each treatment combination, an additional ten patients could be enrolled. A new patient was added for any patient with a trebananib dosing delay or sorafenib or sunitinib dose reduction for non-DLT-related toxicities during the DLT period. Patients who had a DLT during week 1 or withdrew during the first study month were replaced and excluded from the analyses.

### Adverse Events

Treatment-related AEs (ie, AEs possibly related to trebananib, sorafenib, or sunitinib administration) per clinical investigator assessment were recorded and graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI-CTCAE 3.0). Serum samples for evaluation of anti-trebananib antibodies were collected prior to dosing during weeks 1, 3, 5, and 8, and every 4 weeks thereafter. Anti-trebananib binding antibodies were detected with a validated electrochemiluminescence (ECL) assay and then further analyzed for neutralizing effects in an ECL receptor-binding neutralizing antibody assay.<sup>18</sup>

### Pharmacokinetics

Serum trebananib concentrations were measured using a validated enzyme-linked immunosorbent assay (MDS Pharma Services, Montreal, Canada; Tandem Labs, Trenton, NJ, USA).<sup>12</sup> Plasma concentrations of sorafenib, sunitinib, and sunitinib's active metabolite were analyzed with a validated liquid chromatography/mass spectrometry (LC-MS/MS) method at Covance Laboratories (Madison, WI, USA) for sorafenib, and at BASi Northwest Laboratory (McMinnville, OR, USA) for sunitinib. All PK parameters were estimated by implementing noncompartmental methods with WinNonlin Professional (version 4.1e; Pharsight, Mountain View, CA, USA). The schedule of PK assessments is detailed in the Supplementary Materials (Appendix S1).

## Biomarkers

A detailed description of the methodology for measurement of biomarkers has been described previously.<sup>19</sup> Serum samples were analyzed for placental growth factor (PLGF), soluble VEGF receptor 1 (sVEGFR-1 or sFlt-1) and 2 (sVEGFR-2), VEGF, soluble c-Kit (sKit), soluble intercellular adhesion molecule 1 (sICAM-1), and vascular cell adhesion molecule 1 (sVCAM-1). Plasma samples were analyzed for hepatocyte growth factor (HGF). Samples were collected according to the schedule described in the Supplementary Materials (Appendix S2).

## Tumor Response Evaluations

Tumor assessments were conducted using computer tomography or magnetic resonance imaging within 4 weeks before the treatment start and every 8 weeks thereafter. Tumor response was determined based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.0).<sup>20</sup> The denominator for calculating objective response rates (ORRs) was based on all patients receiving at least one dose of trebananib ( $n = 36$ ). Time to progression (TTP) per investigators' review was calculated as the number of weeks from the first administered dose of trebananib to disease progression; patients who completed the study without developing disease progression were censored. Because the study was not designed to follow patients until death, progression-free survival (PFS) was not estimated.

## Statistical Analysis

Responses in biomarkers were evaluated with a regression using an F-test comparing log-transformed analyte relative to baseline values. Descriptive statistics are provided for tolerability, toxicity, PK, and tumor response analyses.

## Results

Between September 2006 and April 2010, 36 of 37 enrolled patients received at least one dose of trebananib. Demographic and clinical characteristics are summarized in Table 1; duration of study participation is depicted in Supplementary Figure 1.

## Tolerability

No patient in the trebananib 3 mg/kg plus sorafenib and sunitinib cohorts ( $n = 3$  and 5, respectively) experienced a DLT. Consequently, six patients were enrolled in both trebananib 10 mg/kg cohorts (sorafenib and sunitinib), which were later expanded to include fourteen patients in each cohort. Two patients in the trebananib 10 mg/kg plus sorafenib cohort experienced a DLT (grade 3 decreased blood phosphorus and grade 3 diarrhea); one patient in the trebananib 10 mg/kg plus sunitinib cohort developed a DLT (grade 3 hypertension).

Unless otherwise noted, the AEs summarized here represent treatment-related AEs (ie, AEs possibly related to trebananib, sorafenib, or sunitinib administration) per clinical investigator assessment. Across both trebananib plus sorafenib cohorts, the most common treatment-related AEs were rash (71%), diarrhea (71%), hypertension (65%), and fatigue (65%; Table 2). Two patients (14%) in the 10 mg/kg cohort experienced peripheral edema. Two patients

(67%) in the 3 mg/kg cohort and 5 patients (36%) in the 10 mg/kg cohort had grade 3 treatment-related AEs. Two grade 4 AEs (12%; pulmonary embolism,  $n = 1$ ; hyperuricemia,  $n = 1$ ) occurred on study, but they were not considered to be related to treatment. No patients died or developed anti-trebananib antibodies.

In the trebananib plus sunitinib cohorts, the most frequent treatment-related AEs included diarrhea (74%), fatigue (68%), hypertension (58%), and decreased appetite (58%; Table 3). Two patients (40%) in the 3 mg/kg cohort and six patients (43%) in the 10 mg/kg cohort had peripheral edema. Two patients (40%) in the 3 mg/kg cohort and eleven patients (79%) in the 10 mg/kg cohort experienced grade 3 treatment-related AEs. One patient (7%) in the 10 mg/kg cohort had two grade 4 AEs (congestive cardiac failure and myocardial infarction); four patients (29%) in the 10 mg/kg cohort died (metastatic RCC, renal failure, cerebral ischemia, and sepsis; all  $n = 1$ ). None of the grade 4 AEs or deaths were considered to be related to treatment. One patient in each of the cohorts had pre-existing anti-trebananib binding antibodies. However, no patient developed anti-trebananib antibodies on study.

### Pharmacokinetics

The mean serum concentration-time profiles of trebananib plus sorafenib and sunitinib at week 4 were similar to those reported in an earlier phase 1 monotherapy study of trebananib (Table 4, Figure 1A).<sup>12</sup> Coadministration of trebananib did not appear to alter the PK of sorafenib or sunitinib (Table 5; Figures 1B, C, & D).

### Biomarkers

In the current report, only the analyses pertaining to PLGF, sVEGFR-2, VEGF, and sKit are presented. No pharmacodynamic effect was observed for sVEGFR-1 or sFlt-1, sICAM-1, sVCAM-1, and HGF. Relative to baseline, PLGF significantly increased and sVEGFR-2 significantly decreased by day 1 of week 4 in both cohorts of trebananib plus sunitinib (Supplementary Figure 2A & B). A significant increase in PLGF ( $P < 0.01$ ) was also observed in the trebananib 10 mg/kg plus sorafenib cohort. Serum VEGF concentrations significantly increased in the trebananib 10 mg/kg plus sunitinib cohort after day 1 of week 2 ( $P < 0.01$ ; Supplementary Figure 2C). Steady decreases in sKit levels were significant at the end of study for the trebananib 3 mg/kg plus sorafenib and both trebananib plus sunitinib cohorts (all  $P < 0.01$ ; Supplementary Figure 2D).

### Tumor Response

Tumor response was evaluated in 32 patients (Figure 2). Three patients did not have postbaseline tumor measurements (treatment was terminated for two patients after they developed AEs during the first month; technical problems prevented tumor response measurement for another patient). In the trebananib plus sorafenib cohorts, the ORR was 29%. No patient achieved a complete response. Five patients (29%; 3 mg/kg cohort,  $n = 1$ ; 10 mg/kg cohort,  $n = 4$ ) had a partial response with a median time to response of 28.6 weeks. Eight patients (47%; 3 mg/kg cohort,  $n = 2$ ; 10 mg/kg cohort,  $n = 6$ ) had stable disease as their best response, four of whom (24%) had stable disease > 6 months. Four patients with a partial response or stable disease did not develop progressive disease before

the data analysis cutoff date. Up until treatment week 8, tumor size decreased a median of 16.58% and 14.46% in the 3 mg/kg and 10 mg/kg cohorts, respectively. The median TTP (95% CI) was 40.3 weeks (22.9 weeks – 127.4 weeks) for patients across both trebananib plus sorafenib dose cohorts ( $n = 17$ ).

In the trebananib plus sunitinib cohorts, the ORR was 53%. One patient (5%) in the 10 mg/kg cohort had a complete response. Nine patients (47%; 3 mg/kg cohort,  $n = 3$ ; 10 mg/kg cohort,  $n = 6$ ) had a partial response. The median time to complete or partial response was 22.6 weeks. Five patients (26%; 3 mg/kg cohort,  $n = 2$ ; 10 mg/kg cohort,  $n = 3$ ) had stable disease. One patient (5%) had stable disease > 6 months. The patient with the complete response and five patients with a partial response or stable disease did not progress by the data cutoff date. Up until treatment week 12, tumor size decreased a median of 18.70% and 23.81% in the 3 mg/kg and 10 mg/kg cohorts, respectively. Across the trebananib plus sunitinib dose cohorts ( $n = 19$ ), the median TTP (95% CI) was 48.0 weeks (30.6 weeks – 98.3 weeks).

## Discussion

In this study, we showed that trebananib IV QW at 3 mg/kg or 10 mg/kg could be combined with sorafenib or sunitinib at full–recommended doses per package insert of these two VEGFR tyrosine kinase inhibitors (TKIs). Toxicities were largely similar in nature, severity, and frequency to those observed with sorafenib or sunitinib as single agents (eg, grade 3 hypertension). Peripheral edema has been previously identified as an AE specific to trebananib treatment.<sup>12,13</sup> In this study, peripheral edema (all grade 2) occurred more frequently in patients receiving trebananib plus sunitinib compared with patients receiving trebananib plus sorafenib. From a tolerability standpoint, the combinations of trebananib plus sorafenib or sunitinib are suitable for further study in the phase 2 and 3 setting. The PK results also were consistent with this conclusion; no drug–drug interactions were observed when trebananib was coadministered with sorafenib or sunitinib.

While trebananib dose levels up to 10 mg/kg weekly combined with sorafenib 400 mg or sunitinib 50 mg were found to be tolerable in this study, the potential effects of higher doses of trebananib on toxicity and antitumor activity are unknown. In an open–label phase 2 study of patients with metastatic RCC, results indicated that trebananib at 10 mg/kg or 15 mg/kg plus sunitinib 50 mg was tolerable and associated with ORRs of 58% and 59%, respectively, similar to the current response rate of 53%.<sup>21</sup> A randomized phase 2 study of trebananib at 3 mg/kg or 10 mg/kg plus sorafenib in patients with metastatic RCC found that the addition of trebananib did not prolong PFS.<sup>22</sup> The present study was not designed to assess PFS. TTP appeared to suggest efficacy of the treatment regimens in this study, possibly indicating a benefit of trebananib treatment combinations at higher doses up to 15 mg/kg without additional toxicity. A randomized phase 2 study of trebananib at 3 mg/kg and 10 mg/kg or placebo plus weekly paclitaxel in patients with advanced ovarian cancer found a trend toward improved PFS and response rate with increasing doses of trebananib.<sup>13</sup> PK analysis uncovered a trend toward improved PFS with increasing exposure to trebananib, and further modeling suggested that doses greater than 10 mg/kg may have an additional impact on PFS.<sup>23</sup> Taken together, the findings of recent studies and the current results



suggest that the relationship between trebananib exposure and clinical response in metastatic RCC requires more study.

Metastatic RCC eventually escapes VEGF pathway inhibitors, but the mechanisms leading to this resistance are complex and poorly understood.<sup>24</sup> Because the vasculature is a target of antiangiogenic treatment, resistance may involve adaptive changes to the host rather than exclusive changes in tumor cells that have been seen in response to treatment with TKIs in other tumors.<sup>25</sup> Some data suggest a role of the angiotensin pathway in resistance development to VEGF pathway inhibition. Studies with a murine neuroendocrine tumor model found that Ang1 is upregulated in response to VEGFR antibody blockade.<sup>26</sup> Both the VEGF and angiotensin pathways induce endothelial cell proliferation, and it is possible that combined treatments with trebananib plus sorafenib or sunitinib provide a more efficient blockade. Overexpression of Ang1 in an Ewing's sarcoma xenograft model prevented tumor regression in response to treatment with a soluble VEGFR (VEGF–Trap, aflibercept).<sup>27</sup> In another report, Ang1 was shown to mediate the transient pericyte recruitment occurring during the initial response of tumor vasculature to VEGF blockade.<sup>28</sup> Plasma levels of Ang2 were proportional to tumor burden in a cohort of patients with metastatic RCC, and sunitinib treatment decreased levels of Ang2 and soluble Tie2.<sup>29</sup> A case–control study found that plasma levels of Ang2 were increased in patients with metastatic RCC compared with matched controls and patients with stage I RCC; Ang2 levels in the patients with metastatic disease decreased by 80% with sunitinib treatment and increased again when resistance developed.<sup>10</sup> These observations suggest a functional interaction between the Ang/Tie2 and VEGF signaling pathways.

Efforts are underway to identify circulating biomarkers with prognostic and predictive value in patients receiving antiangiogenic therapies for RCC. Treatment of patients with advanced RCC with sunitinib has been associated with increased levels of VEGF and PLGF and decreased soluble VEGFR–2.<sup>30,31</sup> In the current study, we observed a similar pattern: increased levels of plasma VEGF and PLGF and decreased levels of sVEGFR–2 with the combination treatment of trebananib and sunitinib or sorafenib, suggesting a pharmacodynamic effect on these markers. Kit is a tyrosine kinase transmembrane receptor for stem cell factor (SCF) that is inhibited by both sorafenib and sunitinib. Kit is proteolytically cleaved in vivo to produce sKit, which binds and neutralizes SCF.<sup>32</sup> Plasma levels of sKit are abnormally elevated in patients with gastrointestinal stromal tumor (GIST), and levels decrease with treatment using both imatinib and sunitinib, whereas they rise in patients treated with placebo.<sup>33,34</sup> To assess sKit as a pharmacodynamic biomarker in this study, we measured levels of sKit in serum at baseline and on day 1 of week 4. We observed a decline in sKit with treatment using trebananib plus sunitinib or sorafenib, in concordance with the imatinib and sunitinib studies. In this study, the baseline sKit levels did not appear prognostic for TTP. The study design prevented evaluating whether sKit is a predictive marker for trebananib. In the study of sunitinib in GIST, a correlation between the degree of decline in sKit and increased PFS was observed.<sup>34</sup> The biological roles and prognostic significance of sKit in metastatic RCC is not well understood, nor is the predictive value of declining sKit levels with trebananib plus sorafenib or sunitinib treatment. A recent pathologic study found a correlation between Kit overexpression on RCC tumors and response of metastatic disease to sorafenib.<sup>35</sup> Further investigation to

define the role of Kit and sKit in metastatic RCC is needed. Preclinical models provide evidence that PLGF may play a role in tumor escape from antiangiogenic therapies targeting the VEGF axis.<sup>36</sup> The study of blood biomarkers in RCC may lend insight into mechanisms of resistance against antiangiogenic treatments.

In sum, weekly IV infusion of trebananib at 3 mg/kg or 10 mg/kg combined with sorafenib or sunitinib had an acceptable toxicity profile in patients with metastatic RCC. This finding is consistent with other studies of trebananib combined with sunitinib or sorafenib in metastatic RCC.<sup>21,22</sup> Data from other combination studies suggest that higher doses of trebananib may be more effective,<sup>13,23</sup> an approach that may merit further investigation of trebananib in combination with sorafenib or sunitinib. The role of the angiotensin pathway in resistance to VEGF pathway inhibition requires further preclinical and clinical study. Plasma and tissue biomarker studies will likely make an important contribution to these investigations.

## Conclusion

The study was prompted by the idea that in patients with RCC, coadministration of two angiogenic inhibitors may provide improved efficacy when compared with treatments relying on a single angiogenic inhibitor. Current evidence suggests that this approach may not be very successful when combining inhibitors targeting the same pathway, partially as a result of unacceptable toxicities. Furthermore, efficacy gains have been modest, which has been attributed to the development of resistance mechanisms. Our results show that adding trebananib to sorafenib or sunitinib does not appear to exacerbate toxicities typically observed with sorafenib or sunitinib monotherapies. Results also suggest evidence of antitumor activity. Those results are important in view of studies showing only moderate efficacy, but increased toxicity, of combination therapies relying on agents all targeting the same angiogenic pathway compared with single angiogenic inhibitors. Yet, many patients' disease progresses while receiving treatment with only a single angiogenic inhibitor. Thus, innovative treatment strategies are needed. We believe that the results from the current study will encourage physicians to more closely investigate the combination of antiangiogenic inhibitors targeting separate angiogenic pathways in patients with RCC.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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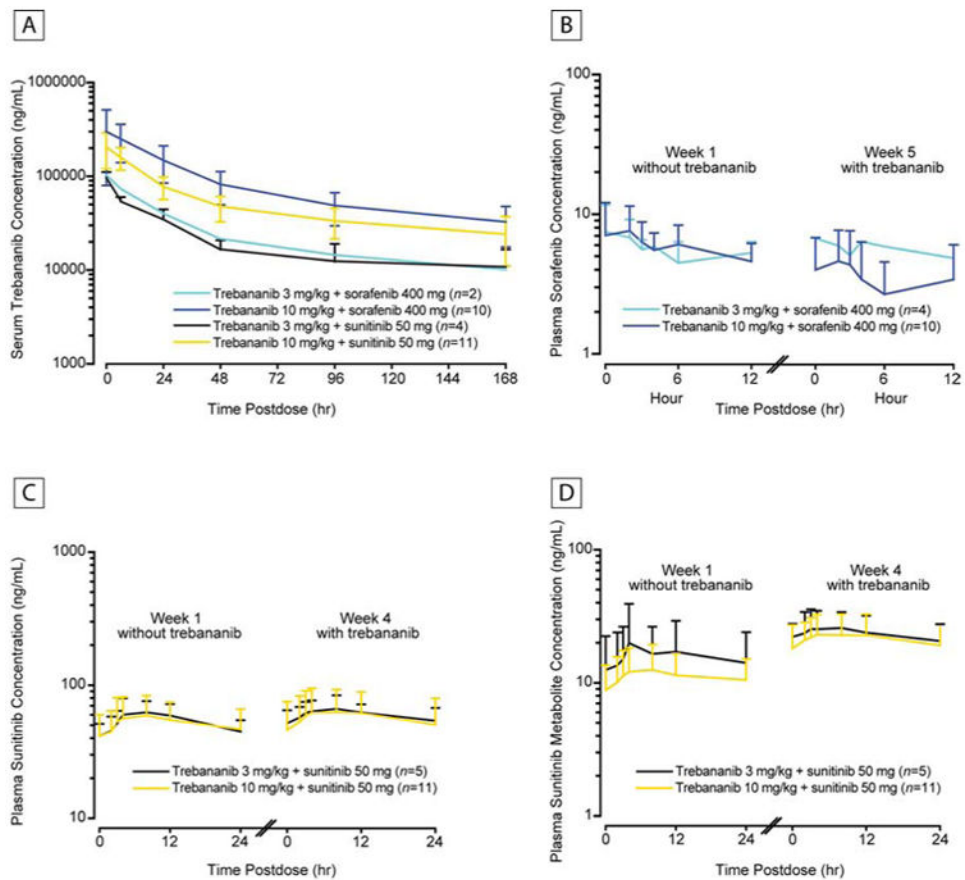
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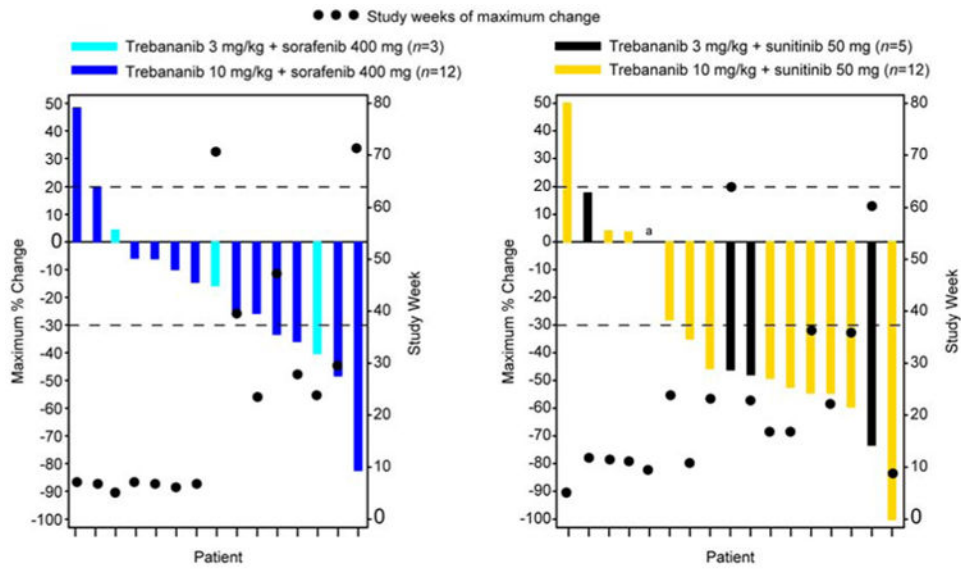
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### Clinical Practice Points

Although antiangiogenic monotherapies targeting the VEGF pathway have demonstrated efficacy in RCC, many patients will experience disease progression. Attempts to slow progression have focused on simultaneous administration of multiple agents targeting the VEGF pathway. Results from those studies, however, suggest that efficacy gains are only moderate and toxicities are difficult to tolerate. In this phase 1b study of patients with advanced RCC, we evaluated the combination of two agents targeting distinct angiogenic pathways. Trebananib suppresses tumor angiogenesis by binding to Ang1 and Ang2, thereby preventing their interaction with the Tie2 receptor. Trebananib 3 mg/kg and 10 mg/kg was combined with the VEGF pathway inhibitors sorafenib or sunitinib to investigate AEs, PK, biomarkers, and tumor response. The results suggest that combining trebananib with sorafenib or sunitinib does not exacerbate toxicities typically associated with monotherapies involving VEGF pathway inhibitors. The data also provide evidence of antitumor activity. The current study may provide oncologists further impetus for investigating antiangiogenic combination therapies targeting separate angiogenic pathways for the treatment of advanced RCC.



**Figure 1.** Pharmacokinetic Concentration–Time Profiles. (A) Mean ( $\pm$  SD) Serum Concentration–Time Profiles of Trebananib at Week 4 or 5 Following Weekly IV Infusions of Trebananib in Combination With Sorafenib or Sunitinib. (B) Mean ( $\pm$  SD) Plasma Concentration–Time Profiles of Sorafenib at Week 1 Without Trebananib and at Week 5 With IV Infusions of Trebananib 3 mg/kg or 10 mg/kg. (C) Mean ( $\pm$  SD) Plasma Concentration–Time Profiles of Sunitinib at Week 1 Without Trebananib and at Week 4 With IV Infusions of Trebananib 3 mg/kg or 10 mg/kg. (D) Mean ( $\pm$  SD) Plasma Concentration–Time Profiles of Sunitinib Metabolite at Week 1 Without Trebananib and at Week 4 With IV Infusions of Trebananib 3 mg/kg or 10 mg/kg. Abbreviations: SD = standard deviation.



\*One patient receiving trebananib 3 mg/kg plus sunitinib 50 mg had a maximum tumor size change of 0% during study treatment.

**Figure 2.** Antitumor Effect of Trebananib (3 mg/kg and 10 mg/kg) Plus Sorafenib or Sunitinib for Each Patient. Best Response Measured by Using Modified RECIST 1.0.<sup>20</sup> Abbreviations: RECIST = Response Evaluation Criteria in Solid Tumors.

**Table 1**

**Demographic and Clinical Characteristics<sup>a</sup>**

	Trebananib 3 mg/kg + Sorafenib (n = 3)	Trebananib 10 mg/kg + Sorafenib (n = 14)	Trebananib 3 mg/kg + Sunitinib (n = 5)	Trebananib 10 mg/kg + Sunitinib (n = 14)	All Cohorts Combined (n = 36)
<b>Sex, n (%)</b>					
Female	2 (67)	7 (50)	1 (20)	4 (29)	14 (39)
Male	1 (33)	7 (50)	4 (80)	10 (71)	22 (61)
<b>Race/Ethnicity, n (%)</b>					
Caucasian	2 (67)	14 (100)	5 (100)	9 (64)	30 (83)
African American	1 (33)	0 (0)	0 (0)	1 (7)	2 (6)
Hispanic	0 (0)	0 (0)	0 (0)	4 (29)	4 (11)
Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Age, median (range), years ECOG Score, n (%)</b>	64 (61 – 70)	59 (47 – 72)	49 (44 – 65)	63 (42 – 76)	61 (42 – 76)
0	2 (67)	8 (57)	2 (40)	11 (79)	23 (64)
1	1 (33)	6 (43)	3 (60)	3 (21)	13 (36)
2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Disease Stage at Enrollment, n (%)</b>					
II	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
III	0 (0)	1 (7)	1 (20)	2 (14)	4 (11)
IV	3 (100)	13 (93)	4 (80)	12 (86)	32 (89)
<b>Lines of Prior Chemotherapy, n (%)</b>					
0	0 (0)	2 (14)	1 (20)	8 (57)	11 (31)
1	3 (100)	5 (36)	1 (20)	5 (36)	14 (39)
2	0 (0)	1 (7)	1 (20)	0 (0)	2 (6)
3	0 (0)	6 (43)	2 (40)	1 (7)	9 (25)
<b>Any Prior Radiotherapy, n (%)</b>					
Yes	0 (0)	2 (14)	2 (40)	1 (7)	5 (14)
No	3 (100)	12 (86)	3 (60)	13 (93)	31 (86)
<b>Any Prior Cancer-Related Surgery, n (%)</b>					
Yes	3 (100)	14 (100)	5 (100)	14 (100)	36 (100)
No	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)



Reason for Study Discontinuation, n (%) <sup>b</sup>	Trebananib 3 mg/kg + Sorafenib (n = 3)	Trebananib 10 mg/kg + Sorafenib (n = 14)	Trebananib 3 mg/kg + Sunitinib (n = 5)	Trebananib 10 mg/kg + Sunitinib (n = 14)	All Cohorts Combined (n = 36)
Disease progression	1 (25)	10 (71)	4 (80)	4 (29)	19 (53)
Withdrawal of consent	1 (25)	2 (14)	0 (0)	1 (7)	4 (11)
Adverse events	2 (50)	1 (7)	0 (0)	1 (7)	4 (11)
Death	0 (0)	0 (0)	0 (0)	3 (21) <sup>c</sup>	3 (8)
Noncompliance	0 (0)	1 (7)	0 (0)	0 (0)	1 (3)
Requirement for alternative therapy	0 (0)	0 (0)	0 (0)	1 (7)	1 (3)
Other	0 (0)	0 (0)	1 (20)	0 (0)	1 (3)

Abbreviation: ECOG = Eastern Cooperative Oncology Group

<sup>a</sup> Demographic and clinical characteristics are presented for all patients who received 1 dose of trebananib.

<sup>b</sup> Reasons for study discontinuation are presented for all patients who provided informed consent.

<sup>c</sup> Four patients died in the trebananib 10 mg/kg plus sunitinib cohort. For one of those patients, the reason for study discontinuation was categorized as an adverse event. The adverse event was sepsis, which led to the patient's death.

**Table 2**  
**Patient Incidence of Treatment-Related Adverse Events<sup>a</sup> in the Trebananib Plus Sorafenib Cohorts<sup>b</sup>**

	Trebananib 3 mg/kg + Sorafenib (n = 3)		Trebananib 10 mg/kg + Sorafenib (n = 14)		Trebananib + Sorafenib Cohorts Combined (n = 17)	
	All grades	Grade 3	All grades	Grade 3	All grades	Grade 3
<b>Patients With Any Treatment-Related Adverse Event, n (%)</b>						
Grade 3		3 (100)		14 (100)		17 (100)
Grade 4		2 (67)		5 (36)		7 (41)
Grade 5		0 (0)		0 (0)		0 (0)
		0 (0)		0 (0)		0 (0)
<b>Treatment-Related Adverse Events Occurring in &gt; 10% of Patients in one or More Treatment Arms, n (%)</b>						
Rash	2 (67)	0 (0)	10 (71)	1 (7)	12 (71)	1 (6)
Diarrhea	2 (67)	0 (0)	10 (71)	1 (7)	12 (71)	1 (6)
Hypertension	3 (100)	1 (33)	8 (57)	0 (0)	11 (65)	1 (6)
Fatigue	3 (100)	0 (0)	8 (57)	0 (0)	11 (65)	0 (0)
Decreased appetite	2 (67)	0 (0)	6 (43)	0 (0)	8 (47)	0 (0)
Nausea	1 (33)	0 (0)	7 (50)	0 (0)	8 (47)	0 (0)
Alopecia	2 (67)	0 (0)	5 (36)	0 (0)	7 (41)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	0 (0)	0 (0)	6 (43)	0 (0)	6 (35)	0 (0)
Decreased weight	2 (67)	1 (33)	3 (21)	0 (0)	5 (29)	1 (6)
Dysgeusia	1 (33)	0 (0)	3 (21)	0 (0)	4 (24)	0 (0)
Headache	1 (33)	0 (0)	3 (21)	0 (0)	4 (24)	0 (0)
Vomiting	1 (33)	0 (0)	3 (21)	0 (0)	4 (24)	0 (0)
Oral pain	0 (0)	0 (0)	3 (21)	0 (0)	3 (18)	0 (0)
Increased aspartate aminotransferase	1 (33)	0 (0)	2 (14)	0 (0)	3 (18)	0 (0)
Peripheral neuropathy	2 (67)	0 (0)	1 (7)	0 (0)	3 (18)	0 (0)
Dysphonia	1 (33)	0 (0)	2 (14)	0 (0)	3 (18)	0 (0)
Erythema	0 (0)	0 (0)	3 (21)	0 (0)	3 (18)	0 (0)
Skin exfoliation	0 (0)	0 (0)	3 (21)	0 (0)	3 (18)	0 (0)
Hypophosphatemia	1 (33)	0 (0)	1 (7)	1 (7)	2 (12)	1 (6)
Dry mouth	0 (0)	0 (0)	2 (14)	0 (0)	2 (12)	0 (0)
Peripheral edema	0 (0)	0 (0)	2 (14)	0 (0)	2 (12)	0 (0)

	Trebananib 3 mg/kg + Sorafenib (n = 3)	Trebananib 10 mg/kg + Sorafenib (n = 14)	Trebananib + Sorafenib Cohorts Combined (n = 17)
Mucosal inflammation	1 (33)	1 (7)	2 (12)
Arthralgia	1 (33)	1 (7)	2 (12)
Pain in extremity	1 (33)	1 (7)	2 (12)
Proteinuria	2 (67)	0 (0)	2 (12)
Skin fissures	1 (33)	1 (7)	2 (12)

<sup>a</sup>Treatment-related adverse events include all adverse events that were considered to be possibly related to any of the study treatments per clinical investigator assessment.

<sup>b</sup>The analysis set for the evaluation of treatment-related adverse events includes all patients who received 1 dose of trebananib.

**Table 3**  
**Patient Incidence of Treatment-Related Adverse Events<sup>a</sup> in the Trebananib Plus Sunitinib Cohorts<sup>b</sup>**

	Trebananib 3 mg/kg + Sunitinib (n = 5)		Trebananib 10 mg/kg + Sunitinib (n = 14)		Trebananib + Sunitinib Cohorts Combined (n = 19)	
	All grades	Grade 3	All grades	Grade 3	All grades	Grade 3
<b>Patients With Any Treatment-Related Adverse Event, n (%)</b>						
	5 (100)		14 (100)		19 (100)	
Grade 3	2 (40)		11 (79)		13 (68)	
Grade 4	0 (0)		0 (0)		0 (0)	
Grade 5	0 (0)		0 (0)		0 (0)	
<b>Treatment-Related Adverse Events Occurring in &gt; 10% of Patients in 1 or More Treatment Arms, n (%)</b>						
Diarrhea	4 (80)	0 (0)	10 (71)	1 (7)	14 (74)	1 (5)
Fatigue	3 (60)	1 (20)	10 (71)	2 (14)	13 (68)	3 (16)
Hypertension	4 (80)	0 (0)	7 (50)	2 (14)	11 (58)	2 (11)
Decreased appetite	2 (40)	0 (0)	9 (64)	0 (0)	11 (58)	0 (0)
Thrombocytopenia	2 (40)	1 (20)	6 (43)	1 (7)	8 (42)	2 (11)
Peripheral edema	2 (40)	0 (0)	6 (43)	0 (0)	8 (42)	0 (0)
Dysgeusia	2 (40)	0 (0)	6 (43)	0 (0)	8 (42)	0 (0)
Dry skin	3 (60)	0 (0)	5 (36)	0 (0)	8 (42)	0 (0)
Hypothyroidism	3 (60)	0 (0)	4 (29)	0 (0)	7 (37)	0 (0)
Periorbital edema	1 (20)	0 (0)	6 (43)	0 (0)	7 (37)	0 (0)
Mucosal inflammation	3 (60)	0 (0)	4 (29)	0 (0)	7 (37)	0 (0)
Stomatitis	1 (20)	0 (0)	5 (36)	2 (14)	6 (32)	2 (11)
Nausea	2 (40)	1 (20)	4 (29)	0 (0)	6 (32)	1 (5)
Neutropenia	1 (20)	1 (20)	4 (29)	4 (29)	5 (26)	5 (26)
Increased blood creatinine	1 (20)	0 (0)	5 (36)	0 (0)	6 (32)	0 (0)
Increased alanine aminotransferase	0 (0)	0 (0)	4 (29)	1 (7)	4 (21)	1 (5)
Increased aspartate aminotransferase	0 (0)	0 (0)	4 (29)	1 (7)	4 (21)	1 (5)
Oral pain	1 (20)	0 (0)	3 (21)	0 (0)	4 (21)	0 (0)
Dehydration	2 (40)	0 (0)	2 (14)	0 (0)	4 (21)	0 (0)
Arthralgia	2 (40)	0 (0)	2 (14)	0 (0)	4 (21)	0 (0)
Pain in extremity	1 (20)	0 (0)	3 (21)	0 (0)	4 (21)	0 (0)

	Trebananib 3 mg/kg + Sunitinib (n = 5)	Trebananib 10 mg/kg + Sunitinib (n = 14)	Trebananib + Sunitinib Cohorts Combined (n = 19)
Rash	1 (20)	3 (21)	4 (21)
Vomiting	2 (40)	1 (7)	3 (16)
Increased lacrimation	1 (20)	2 (14)	3 (16)
Abdominal pain	1 (20)	2 (14)	3 (16)
Face edema	1 (20)	2 (14)	3 (16)
Dysphonia	2 (40)	1 (7)	3 (16)
Palmar-plantar erythrodysesthesia syndrome	2 (40)	1 (7)	3 (16)
Skin fissures	1 (20)	2 (14)	3 (16)
Anemia	0 (0)	2 (14)	2 (11)
Asthenia	0 (0)	2 (14)	2 (11)
Peripheral neuropathy	0 (0)	2 (14)	2 (11)
Erythema	1 (20)	1 (7)	2 (11)
Leukopenia	0 (0)	2 (14)	2 (11)
Abdominal distension	1 (20)	1 (7)	2 (11)
Constipation	0 (0)	2 (14)	2 (11)
Flatulence	0 (0)	2 (14)	2 (11)
Gastroesophageal reflux disease	1 (20)	1 (7)	2 (11)
Glossodynia	1 (20)	1 (7)	2 (11)
Generalized edema	2 (40)	0 (0)	2 (11)
Temperature intolerance	2 (40)	0 (0)	2 (11)
Hyperbilirubinemia	0 (0)	2 (14)	2 (11)
Decreased ejection fraction	0 (0)	2 (14)	2 (11)
Myalgia	1 (20)	1 (7)	2 (11)
Headache	0 (0)	2 (14)	2 (11)
Proteinuria	0 (0)	2 (14)	2 (11)
Genital rash	2 (40)	0 (0)	2 (11)
Epistaxis	1 (20)	1 (7)	2 (11)
Nasal dryness	1 (20)	1 (7)	2 (11)
Hyperkeratosis	1 (20)	1 (7)	2 (11)
Pruritus	1 (20)	1 (7)	2 (11)
Skin exfoliation	1 (20)	1 (7)	2 (11)

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	Trebananib 3 mg/kg + Sunitinib (n = 5)	Trebananib 10 mg/kg + Sunitinib (n = 14)	Trebananib + Sunitinib Cohorts Combined (n = 19)
Blister	1 (20)	0 (0)	2 (11)
			0 (0)

<sup>a</sup>Treatment-related adverse events include all adverse events that were considered to be possibly related to any of the study treatments per clinical investigator assessment.

<sup>b</sup>The analysis set for the evaluation of treatment-related adverse events includes all patients who received 1 dose of trebananib.

**Table 4**  
**Pharmacokinetics of Trebananib**

Descriptive Statistics	$T_{\max}$ (hr) <sup>a</sup>	$C_{\max}$ (µg/mL)	$AUC_{0-T}$ (hr·µg/mL)	CL (µg/mL)
<b>Trebananib 3 mg/kg + Sorafenib 400 mg</b>				
<i>n</i>	2	2	2	2
Mean	0.64	102	4400	0.552
%CV	NA	NA	NA	NA
<b>Trebananib 10 mg/kg + Sorafenib 400 mg</b>				
<i>n</i>	9	9	8	7
Mean	38	343	15900	0.566
%CV	190	42.3	30.4	29.3
<b>Trebananib 3 mg/kg + Sunitinib 50 mg</b>				
<i>n</i>	4	4	4	4
Mean	0.57	96.6	3540	0.799
%CV	13	14.8	29.4	33.1
<b>Trebananib 10 mg/kg + Sunitinib 50 mg</b>				
<i>n</i>	11	11	11	11
Mean	0.52	214	9490	0.927
%CV	160	25.4	31.0	39.6

Abbreviations:  $AUC_{0-T}$  = Area under the concentration-time curve from time zero to the time of the dosing interval;  $C_{\max}$  = Maximum observed concentration after IV infusion of trebananib; CL = Clearance; CV = coefficient of variation; NA = Not applicable;  $T_{\max}$  = Time of maximum concentration after IV infusion of trebananib.

<sup>a</sup> $T_{\max}$  is reported as median and range.

**Table 5**  
**Pharmacokinetic Parameters of Sorafenib, Sunitinib, and Sunitinib Metabolite With and Without Trebananib**

Trebananib Dose	Sorafenib		Sunitinib		Sunitinib Metabolite		Sunitinib Metabolite	
	Without	With	Without	With	Without	With	Without	With
<b>T<sub>max</sub> (hr)<sup>a</sup></b>								
Mean	1.1	1.0	1.0	8.0	8.0	8.0	8.0	8.0
%CV	100	200	37	24	46	35	34	64
<b>C<sub>max</sub> (µg/mL)</b>								
Mean	0.466	0.507	0.559	0.0642	0.0703	0.0618	0.0676	0.0133
%CV	75.9	40.6	53.2	25.9	20.2	42.9	47.0	51.6
<b>AUC<sup>a</sup> (hr·µg/mL)</b>								
Mean	2.58	3.18	3.13	1.30	1.337	1.25	1.41	0.268
%CV	68.1	89.7	12.2	23.4	24.5	40.4	49.6	48.1
<b>CL (µg/mL)</b>								
Mean	20.9	173	14.2	44.8	54.3	46.6	50.7	10.5
%CV	79.6	159	50.7	21.7	24.6	42.1	57.6	44.1

Abbreviations: AUC = Area under the concentration-time curve; C<sub>max</sub> = Maximum observed concentration after IV infusion of trebananib; CL = Clearance; CV = coefficient of variation; NA = Not applicable; T<sub>max</sub> = Time of maximum concentration after IV infusion of trebananib.

<sup>a</sup>Sorafenib AUC<sub>0-12</sub>; sunitinib AUC<sub>0-24</sub>.