A Phase I Trial of Vatalanib (PTK/ZK) in Combination With Bevacizumab in Patients With Refractory and/or Advanced Malignancies

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Abstract: *Background:* Vatalanib is an orally active, small molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR). Bevacizumab is also an angiogenesis inhibitor, but it possesses a different mechanism of action. This phase I study was conducted to determine the dose-limiting toxicity, maximum-tolerated doses, and recommended phase II doses of the combination of vatalanib and bevacizumab. *Patients and Methods:* Treatment cycles were 4 weeks in length. Patients received oral vatalanib once or twice daily continuously. Bevacizumab was administered intravenously starting on day 15 of cycle 1, and dosing was repeated at 2-week intervals in patients with at least stable disease for 4 cycles. After 4 cycles, only patients with a partial or complete response continued treatment with the combination of vatalanib and bevacizumab. Patients with stable disease were allowed to continue single-agent vatalanib from cycle 5 until disease progression or intolerable toxicity. *Results:* A total of 27 patients received 93 cycles of treatment. Dose escalation was difficult due to enhanced toxicities (primarily proteinuria and hypertension) with the regimen that required numerous dose modifications. Interruption of vatalanib and bevacizumab dosing due to proteinuria occurred in 4 patients enrolled at dose level 3, with 1 of these patients developing grade 3 nephrotic range proteinuria. As a result, further dose escalation with the combination regimen was abandoned. *Conclusions:* Further development of bevacizumab and oral VEGF tyrosine kinase inhibitor combination regimens is questionable due to the additive toxicities that occur; future investigations should proceed with caution.

Introduction

Vascular endothelial growth factor (VEGF) and its receptors play a critical role in angiogenesis and tumor progression. Vatalanib (PTK/ZK, Bayer Schering/Novartis) is an orally active, small molecule tyrosine kinase inhibitor of all VEGF receptors (VEGFR). Early phase I trials administered single daily doses of vatalanib ranging from 50–2,000 mg/day

with no dose-limiting toxicities reported.[1] As a single agent administered twice daily in a phase I trial conducted by Thomas and colleagues, the maximum tolerated dose was 750 mg. Due to low-grade toxicities that could compromise compliance with continuous administration, the recommended daily dose for future studies is 1,000 mg/day (500 mg twice daily).[2] Dosing was limited in this study by reversible grade 3 lightheadedness, which occurred in patients who received a 1,000 mg twice daily vatalanib regimen. Other reported toxicities included nausea, fatigue, vomiting, diarrhea, elevated transaminases, and hypertension.

Bevacizumab (Avastin, Genentech) is also an angiogenesis inhibitor, but possesses a different mechanism of action. Bevacizumab is an intravenously administered humanized monoclonal antibody that is directed against VEGF. By binding to VEGF, bevacizumab blocks VEGF-A receptor binding. The initial phase I trial with bevacizumab explored doses ranging from 0.1–10.0 mg/kg, with no grade 3/4 treatment-related toxicities reported.[3] Bevacizumab is approved in combination with chemotherapy for the treatment of patients with colon, non-small cell lung, and breast cancers. The primary toxicities reported with bevacizumab include asymptomatic proteinuria and hypertension that is easily controlled with oral medications.

When administered as single agents, vatalanib and bevacizumab possess similar toxicity profiles. Mild, controllable hypertension and asymptomatic proteinuria are common side effects; thrombotic microangiopathy and wound dehiscence are reported less frequently. Due to the different mechanisms of action of the 2 agents, it is hoped that a combination regimen incorporating both compounds will produce increased activity without enhanced toxicity.

Patients and Methods

Patient Selection

Patients 18 years of age or older who had histologically proven, advanced solid tumors that were refractory to conventional therapy (or for which no standard therapy exists), and who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were enrolled in the study. Patients had to have completed previous radiotherapy at least 4 weeks prior, previous chemotherapy at least 3 weeks prior, and previous biologic or immunotherapy at least 2 weeks prior to treatment; they must have recovered from any therapy-related toxicities as well. Patients were not allowed to receive any prior anti-VEGF therapy (including vatalanib and bevacizumab) and could not have received investigational drugs within 4 weeks of treatment. The following baseline laboratory values were required for enrollment: absolute neutrophil count (ANC) of 1,500/L; platelet count of 100,000/L; hemoglobin 9 g/dL or higher; serum creatinine and serum bilirubin less than or equal to 1.5 times the upper limit of normal; serum glutamic oxaloacetic transaminase and/or serum glutamate pyruvate transaminase less than 3 times the upper limit of normal; and international normalized ratio (INR) less than 2. Patients were also required to have negative or trace protein by urine dipstick. If a reading of 1+ was obtained at baseline, patients were then required to have a 24-hour urine collection with a total urine protein less than or equal to 500 mg, and a measured creatinine clearance 50 mL/min or greater. Patients with a history or presence of central nervous system disease were excluded from the study. Patients who had major surgery within 4 weeks of treatment or minor surgery within 2 weeks of treatment were also excluded. Patients with any of the following concurrent severe and/or uncontrolled medical conditions were excluded: uncontrolled high blood pressure (>160/100 mmHg on medication); unstable angina pectoris; symptomatic congestive heart failure; myocardial infarction within the previous 6 months; serious uncontrolled cardiac arrhythmia; uncontrolled diabetes; active infections; interstitial pneumonia or fibrosis; chronic renal or liver disease; impaired gastrointestinal function (due to oral vatalanib); nonhealing wounds; coagulopathy; hemoptysis or hematemesis within 3 months; or stroke within 6 months. Patients were also excluded if they were taking therapeutic warfarin doses, chronic daily aspirin or non-steroidal anti-inflammatory agents, or chronic steroid therapy. Female patients who were pregnant or lactating were ineligible for the study. The study was approved by the local institutional review board, and written informed consent was obtained from all patients prior to enrollment.

Treatment Plan

This was a single center, phase I, dose escalation trial. The proposed combination dose levels are outlined in Table 1. Vatalanib was administered orally as a single agent once daily on days 1–14 of cycle 1. The day-14 morning dose of vatalanib was administered in the clinic with limited pharmacokinetic samples obtained before and after the dose. The initial dose of bevacizumab was administered on day 15 in combination with the morning vatalanib dose. Vatalanib was then given continuously once daily. Intravenous bevacizumab dosing was subsequently repeated at 2-week intervals in patients with at least stable disease for 4 cycles of treatment (16 weeks). After 4 cycles, only patients with a partial or complete response continued treatment with the combination of vatalanib and bevacizumab. Patients with stable disease were allowed to continue single agent vatalanib from cycle 5 until disease progression or intolerable toxicity warranted drug discontinuation. On day 1 of cycle 2, the lim-

Table 1. Proposed Vatalanib and Bevacizumab Dose Levels

Dose Level	Vatalanib Daily Dose	Bevacizumab QOW Dose
1	750 mg once daily	1.0 mg/kg
2	1,000 mg once daily	1.0 mg/kg
3	1,000 mg (500 mg bid)	2.5 mg/kg
4	1,250 mg (500 mg qam and 750 mg qpm)	2.5 mg/kg
5	1,250 mg (500 mg qam and 750 mg qpm)	5.0 mg/kg

bid=twice daily; qam=every morning;
QOW=every other week; qpm=every evening.

ited pharmacokinetic samples were repeated before and after the oral vatalanib and intravenous bevacizumab doses. Each treatment cycle was defined as 28 days or 4 weeks of treatment. Toxicity assessments were conducted throughout the study and disease assessments were repeated every 8 weeks.

In an attempt to improve tolerability, the protocol was amended after the second dose level to modify the initial lead-in period of single-agent vatalanib and to divide the dosing into twice daily administration. Instead of starting at full dose, the vatalanib dose was gradually escalated over a 3-week period to the prescribed total dose (250 mg twice daily for 1 week, 250 mg every morning and 500 mg every evening for 1 week, and 500 mg twice daily for 1 week) prior to adding bevacizumab to the regimen. Due to the gradual dose escalation, the pharmacokinetic samples following single-agent vatalanib were eliminated from the protocol, and only the first cycle of treatment was extended to 5 weeks. Patient enrollment post-amendment started at dose level 3.

Three patients were initially enrolled at each dose level. In order for a patient to be evaluable for dose-limiting toxicity, the patient had to receive treatment with the combination of vatalanib and bevacizumab. Any patient who discontinued the study during the single-agent vatalanib lead-in dosing was considered unevaluable for dose-limiting toxicity and was replaced (even if the patient was discontinued due to toxicity). If dose-limiting toxicities were observed in 1 of the 3 patients, the dose level was expanded to 6 patients. If more than 2 of the 6 patients experienced a dose-limiting toxicity, the next lower dose was considered the recommended phase II dose.

For the purposes of this study, acute dose-limiting toxicity was defined as any of the following: ANC nadir less than 500/L or platelets less than 25,000/L; any grade 3/4 nonhematologic toxicity due to treatment, with the exception of alopecia, nausea, and vomiting; grade 3/4 nausea or vomiting while receiving an optimal antiemetic regimen for prophylaxis and treatment; an inability to administer all doses in the first 8 weeks of treatment at full dose (no doses omitted or reduced for toxicity); or a treatment delay of more than 2 weeks due to treatment-related toxicity. The National Cancer Institute Common Toxicity Criteria Version 3.0 was used to grade treatment-related toxicities, and responses were assessed based on the response evaluation criteria in solid tumors (RECIST).

Drug Dosing and Administration

Vatalanib was dosed on a flat scale of mg per day and not by weight or body surface area. The drug was provided by Novartis Pharmaceuticals as a 250-mg tablet and was administered with or without food once or twice (post-amendment) daily. Antiemetics were utilized at the discretion of the treating physician.

Bevacizumab was dosed on a mg per kg basis based on actual body weight. The dose of bevacizumab was calculated at the beginning of the study and was only re-calculated if the patient's weight changed by 10% or more. Commercial product was purchased and provided for the patients enrolled in the trial. The drug was diluted in 100 mL of normal saline and administered initially as a 90-minute infusion. Subsequent doses were administered over 60 and 30 minutes, respectively, if tolerated by the patient.

Dose Modification/Reduction Guidelines

Treatment cycles were repeated at 28-day intervals if toxicity permitted. Vatalanib dosing was interrupted for any of the following reasons: blood pressure elevations requiring urgent management; grade 3 ataxia or dizziness; grade 4 neutropenia or thrombocytopenia; grade 3 or higher transaminase or bilirubin values; grade 2 or higher proteinuria on dip stick confirmed by a 24-hour urine collection with a protein of 1.0 gram or greater; grade 2 or higher hematuria; serum creatinine equal to or greater than 2 times the upper limit of normal; or any other treatment-related toxicity of grade 3 or higher. Once the toxicities resolved to grade 1 or baseline, vatalanib treatment could be resumed at the next lowest dose level. Patients requiring a dose reduction below 750 mg/day or a treatment delay of more than 3 weeks were removed from the study due to poor tolerability.

Bevacizumab doses were held for any of the following reasons: grade 2 or higher proteinuria on dip stick confirmed by a 24-hour urine collection with a protein of 1.0 gram or greater; any evidence of serious bleeding; blood pressure elevations requiring urgent management; or any treatment-related toxicity of grade 3 or higher.

Patients who developed an arterial thromboembolic event, a gastrointestinal perforation, or wound dehiscence were not allowed to continue bevacizumab treatment. No bevacizumab dose reductions were allowed.

Pharmacokinetics

In order to evaluate the effect of bevacizumab administration on the pharmacokinetics of vatalanib, blood samples were collected prior to dosing and at 1, 2, 3, 4, 6, 8, and 24 hours after dosing on day 14 of cycle 1 and on day 1 of cycle 2. On day 1 of cycle 2, the bevacizumab infusion was started at the same time the oral vatalanib dose was administered. Weekly trough samples were also obtained throughout cycles 1 and 2. When both drugs were administered, the plasma samples were split into 2 separate aliquots so that concentrations of vatalanib and bevacizumab could be determined. Following the approval of amendment 1, the single-agent vatalanib sampling done prior to bevacizumab dosing was eliminated from the protocol. Vatalanib pharmacokinetic samples were analyzed by AAI Development Services in Shawnee, Kansas. Bevacizumab plasma concentrations were measured via a quantitative indirect enzyme-linked immunosorbent assay developed and validated at ALTA Analytical Laboratory in San Diego, California.

The plasma concentration versus time data was subjected to non-compartmental analysis for the purpose of determining pharmacokinetic data. The time to (t_{max}) and value of the maximum plasma concentration (C_{max}) were determined by visual inspection of the plasma concentration versus time data for each analyte of interest. The area under the plasma concentration versus time curve at steady-state (AUC_{ss}) was determined for the duration of the dosing interval at steady-state using the linear trapezoidal rule. The steady-state plasma concentration ($C_{ss,\ avg}$) was determined by dividing the AUC by the dosing interval (24 hours). The terminal phase rate constant (λz) and half-life ($t_{1/2}$) was obtained by applying linear regression to the natural log-transformed concentration versus time data in the terminal phase. The clearance (CL) was calculated by dividing the daily dose by the AUC over the 24-hour dosing interval; for vatalanib, the clearance was oral clearance (CL/F). The area volume of distribution (Vz) after oral dosing was calculated as the quotient $CL/\lambda z$; the volume of distribution was oral Vz (Vz/F).

Results

A total of 27 patients were enrolled in the study between November 2004 and May 2006. The patient demographics are outlined in Table 2. A total of 93 cycles of treatment were administered, with a median number of 2 cycles and a range of 1–6 cycles per patient.

Nine patients received 33 cycles of treatment on dose level 1 (vatalanib 750 mg orally once daily + bevacizumab 1 mg/kg every other week), with 6 of 9 patients evaluable for dose-limiting toxicity. One patient developed a bowel obstruction prior to starting bevacizumab and was removed from the study; a second patient was unevaluable due to rapidly progressing disease, which resulted in study removal at the end of cycle 1; the third patient had treatment held at the beginning of cycle 2 at the discretion of the treating physician due to decreased appetite and weight loss that was not considered dose-limiting. Of the 6 evaluable patients treated at dose level 1, 1 patient required interruption of dosing with vatalanib and bevacizumab on day 15 of cycle 2 due to grade 2 proteinuria and grade 3 hypertension (dose-limiting toxicity). This patient had hypertension at baseline, but required the addition of a second antihypertensive agent for blood pressure control during the first 8 weeks of treatment. The patient remained in the study, but was removed from treatment at the end of cycle 4 due to continued hypertension and an inability to tolerate treatment. One additional patient at this dose level also experienced grade 3 mucositis and grade 3 hypertension during cycle 3 of treatment (beyond the DLT assessment period) and was also removed from study at the end of cycle 4 due to an inability to tolerate treatment.

Nine patients received 35 cycles of treatment on dose level 2 (vatalanib 1,000 mg orally once daily + bevacizumab 1 mg/kg every other week), with 7 of 9 patients evaluable for dose-limiting toxicity. One patient developed intermittent shortness of breath during cycle 2 and treatment was held after cycle 2 day 15 due to a decreased ejection fraction. The patient was removed from the study at the end of cycle 2 due to progressive disease and the ventricular dysfunction was deemed not to be study drug related by the treating physician. A second patient at this dose level was removed from study at the end of cycle 1 in order to undergo hip surgery. Two of the remaining 7 evaluable patients experienced treatment-related dose-limiting toxicities: grade 3 mucositis that occurred on day 15 of cycle 1 in 1 patient and grade 3 dizziness/ataxia on day 8 of cycle 1 that warranted a dose reduction to 750 mg/day. One additional patient had the vatalanib dose decreased to 500 mg/day at the beginning of cycle 2 due to dizziness/ataxia that was not considered dose limiting (grade 3).

In an attempt to improve the tolerability of vatalanib, the protocol was amended after dose level 2 to incorporate an initial lead-in period of single-dose vatalanib—in which the dose is gradually escalated over a 3-week period prior to administration of the first dose of bevacizumab—and to divide the vatalanib dose into twice daily dosing. Nine patients received

Table 2. Patient Demographics (N=27)

	Number of Patients
Median Age (range)	57 years (19–83 years)
Sex	
Female	13
Male	14
Race	
Caucasian	23
African American	3
Asian	1
ECOG performance status	
0	22
1	5
Number of prior chemotherapy regimens	
Unknown	1
0	3
1	4
2	6
3	13
Prior radiation	15
Tumor type	
Breast	6
Colorectal	4
Renal	4
NSCLC	3
Esophageal	2
Sarcoma	2
Other (pancreas, prostate, ovarian, thyroid, neuroendocrine, melanoma)	6

ECOG=Eastern Cooperative Oncology Group; NSCLC=non-small cell lung cancer.

25 cycles of treatment on dose level 3 (vatalanib 500 mg orally twice daily + bevacizumab 2.5 mg/kg every other week) following approval of the protocol amendment. Four patients were removed from study prior to the completion of cycle 1: 1 due to the development of an obstruction on day 8 of cycle 1, 1 due to rapidly progressing liver disease on day 15 of cycle 1, and 2 due to patient request (day 15 of cycle 1 and day 19 of cycle 1, respectively). None of these patients were ever dosed with bevacizumab. Interruption of vatalanib and bevacizumab dosing was required in 4 of the 5 remaining patients at this dose level due to proteinuria (2 patients during cycle 2 of treatment and 2 patients during subsequent treatment cycles), with 1 of these patients developing grade 3 nephrotic range proteinuria. As a result, further dose escalation with the combination regimen was abandoned. The treatment-related toxicities are described in Table 3.

Dose interruptions were frequent for both vatalanib and bevacizumab. Thirteen patients (48%) had vatalanib dosing held intermittently due to the following toxicities: proteinuria (n=5); mucositis (n=2); proteinuria/hypertension (n=1); fatigue/weakness (n=1); weight loss/decreased appetite (n=1); gastrointestinal toxicity (n=1); grade 3 thrombocytopenia (n=1); and decreased ejection fraction (n=1). Two additional patients required dose reductions for ataxia/dizziness. Five patients never started bevacizumab dosing due to underlying illness (n=3) or poor vatalanib tolerability warranting study discontinuation (n=2). Nine of the remaining 22 patients (41%) had bevacizumab doses held due to the following toxicities: proteinuria (n=5), proteinuria/hypertension (n=1), fatigue/weakness (n=1), weight loss/decreased appetite (n=1), and decreased ejection fraction (n=1). Only 1 patient required bevacizumab discontinuation due to toxicity. This patient was a 66-year-old, heavily pretreated patient with metastatic breast cancer who developed grade 3 proteinuria by urine dipstick on day 15 of cycle 2 that was confirmed with a 24-hour urine total protein of 5,015 mg/24 hours (grade 3). A renal consult was obtained and the patient was diagnosed with drug-induced nephrotic range proteinuria. Her serum creatinine remained normal, and the 24-hour urine protein gradually decreased over the following 6 weeks to grade 1. At that point, the patient was re-evaluated with scans and tumor markers and appeared to be responding to treatment (26% decrease in tumor measurements; CA 15.3 decreased from 144 to 90.1 U/mL). Thus, the decision was made to re-initiate treatment with single-agent vatalanib, as the benefits of continued treatment appeared to outweigh the risks. The patient remained on vatalanib for 5 additional months before discontinuing at her request due to a planned prolonged vacation and what was believed to be maximum benefit. Per protocol, patients with stable disease would discontinue bevacizumab at the end of cycle 4 and continue treatment with single-agent vatalanib. Five patients met these criteria and continued vatalanib for 1 (n=1), 2 (n=2), 4 (n=1), and 12 (n=1) subsequent cycles, respectively. The patient who discontinued bevacizumab due to proteinuria received 5 cycles of single-agent vatalanib prior to withdrawing from the study.

Twenty-one patients were evaluable for response. The patient with heavily pretreated metastatic breast cancer who discontinued bevacizumab due to proteinuria experi-

Table 3. Treatment-Related Hematologic and Non-Hematologic Toxicities (N=27)

	No. of patients (%)	No. of patients (%)	No. of patients (%)
Treatment-Related Toxicity	**Grade 1**	**Grade 2**	**Grade 3**
Proteinuria (by dipstick)	5 (19%)	6 (22%)	7 (26%)
Proteinuria (24-hour collection)	10 (37%)	3 (11%)	1 (4%)
Hypertension	7 (26%)	2 (7%)	2 (7%)
Mucositis	9 (33%)	1 (4%)	2 (7%)
Dizziness/ataxia	---	1 (4%)	1 (4%)
Anorexia	12 (44%)	1 (4%)	---
Nausea	13 (48%)	4 (15%)	---
Vomiting	7 (26%)	4 (15%)	---
Diarrhea	7 (26%)	---	---
Edema	3 (11%)	1 (4%)	---
Fatigue	9 (33%)	3 (11%)	---
Peripheral neuropathy	4 (15%)	2 (7%)	---
Rash	4 (15%)	---	---
Anemia	2 (7%)	2 (7%)	1 (4%)
Neutropenia	---	1 (4%)	---
Thrombocytopenia	---	---	1 (4%)

Table 4. Summary of Pharmacokinetics for Vatalanib 1,000 mg/day Alone or With Bevacizumab

Pharmacokinetic Parameter	Vatalanib Alone (n=8)	With Bevacizumab 1 mg/kg (n=5)	With Bevacizumab 2.5 mg/kg (n=4)
$T_{1/2}$ (h)	5.56±2.72	6.56±2.85	7.59±2.75
T_{max} (h)*	2.0 (1.0-6.0)	1.0 (1.0-4.0)	3.0 (1.0-4.0)
$C_{ss,\ max}$ (ng/mL)	3,326±2,144	4585±4188	2438±1656
AUC_{ss} (ng·h/mL)	20,391±11,870	23,057±23781	13,386±3,454
$C_{ss,avg}$ (ng/mL)	825±462	961±991	558±144
CL/F (L/h)	66.0±34.4	150±152	77.9±16.5
Vz/F (L)	591±542	1,794±2,103	847±373

*Median (range) data based on plasma concentration data. The standard deviation is included for each parameter.
AUC_{ss}=area under the concentration time at steady state; CL/F=clearance after oral dosing; $C_{ss,avg}$=average concentration at steady state; $C_{ss,max}$=maximum concentration at steady state; $T_{1/2}$=half life; T_{max}=time to $C_{ss,max}$; Vz/F=volume of distribution/fraction of dose available.

enced a partial response to treatment at the end of cycle 6, but this was not confirmed with subsequent scans. The patient removed herself from the study at the end of cycle 8 (prior to scans) in order to take a prolonged vacation. The patient had marked progression of disease on scans obtained upon her return 6 weeks later. A second patient with previously treated renal cell cancer experienced a partial response to treatment at the end of cycle 2, but repeat scans at the end of cycle 4 demonstrated progressive disease. Ten patients had stable disease as their best response to treatment. The median duration of stable disease was 4.5 cycles, with a range of 3–16 cycles (maximum of 16 cycles experienced by a pancreatic neuroendocrine tumor patient). Nine patients had disease progression as their best response to treatment and 6 patients were unevaluable for disease response.

There was a high degree of variability in the pharmacokinetic parameters for vatalanib. At the 750 mg and 1,000 mg dose levels the pharmacokinetic parameters of single-agent vatalanib were similar to those obtained when bevacizumab was concurrently administered. In general, the mean measures of plasma concentrations were lower in the presence of bevacizumab, although variability was high and the differences did not appear to be significant. Table 4 is the pharmacokinetic summary table for vatalanib after 1,000 mg/day, given alone or with bevacizumab.

Compared to vatalanib, the variability for bevacizumab was much lower. The concentration as measured by C_{max} and AUC increased in an approximately dose-proportional manner between the 1 and 2.5 mg/kg dose levels. The CL, Vz, and $t_{1/2}$ were all very similar between the 2 dose groups. Table 5 is the pharmacokinetic summary table (mean ± SD unless indicated) for bevacizumab when given with vatalanib 1,000 mg per day.

Table 5. Summary of Pharmacokinetics for Bevacizumab When Given With Vatalanib 1,000 mg/day

PK Parameter	1 mg/kg (n=5)	2.5 mg/kg (n=4)
$T_{1/2}$ (h)	155±70.1	196.8±115.3
T_{max} (h)*	2.0 (1.0–2.0)	4.0 (1.5–6.0)
C_{max} (mg/L)	33.1±1.5	89.0±8.3
AUC_{0-24} (mg·h/L)	583±75	1,576±270
AUC_{ss} (mg·h/L)	4,213±798	11,959±1,666
$C_{ss, avg}$ (mg/L)	12.5±2.4	35.6±5.0
CL (mL/h/kg)	0.2457±0.0556	0.2116±.0.0277
Vz (L/kg)	0.05261±0.01801	0.0623±0.0427

*Median (range) data based on plasma concentration data. The standard deviation is included for each parameter.
AUC_{ss}=area under the concentration time curve at steady state; AUC_{0-24}= area under the concentration time curve from 0 to 24 h; $C_{ss,avg}$=average concentration at steady state; C_{max}=maximum concentration; CL=clearance; $T_{1/2}$=half life; T_{max}=time to $C_{ss,max}$; PK=pharmacokinetic; Vz=volume of distribution.

Conclusions

This study was conducted with the hypothesis that targeting different segments of the VEGF pathway would result in additive or synergistic activity with an acceptable toxicity profile. Unfortunately, this was not the case with the combination of vatalanib and bevacizumab. Dose escalation was difficult due to enhanced toxicities (primarily proteinuria and hypertension) with this regimen, which required numerous dose modifications. The enhanced toxicity does not appear to be related to a pharmacologic interaction between the 2 drugs, as pharmacokinetic parameters obtained for single-agent and combination dosing do not appear to be significantly different. It is also worth noting that, despite an inability to administer previously established optimal therapeutic doses of both agents and a revised dosing schedule for vatalanib, toxicities associated with VEGFR inhibition were still manifested by a majority of patients. Thus, it is unlikely that the dose escalation plan was overly aggressive, given that all dose concentrations and schedules of administration were below previously established limits in other combinations with vatalanib.

In the phase I trial of twice daily single-agent vatalanib, DCE-MRI and pharmacokinetic data indicated that doses of 1,000 mg/day or higher were biologically active with dosing limited by reversible grade 3 lightheadedness. In the current trial, the first 2 vatalanib dose levels (750 and 1,000 mg) were administered as a single daily dose in combination with bevacizumab doses of 1 mg/kg every other week (1/5 of the FDA-approved doses for colorectal cancer). Dose-limiting hypertension, mucositis, and dizziness were encountered at these first 2 dose levels. In an attempt to improve tolerability (in case the toxicities were peak concentration related), vatalanib dosing was changed to twice daily and the bevacizumab dose was escalated to 2.5 mg/kg (dose level 3). The increased bevacizumab dose intensified the VEGF-receptor toxicities of proteinuria and hypertension, with 5 patients requiring dose modifications due to proteinuria and 1 patient developing grade 3 nephrotic range proteinuria warranting bevacizumab discontinuation at the highest dose level explored. If we choose to accept the recommended doses for these agents

that have been established in previous studies, it would appear that only subtherapeutic doses of bevacizumab, and possibly of vatalanib, can be administered in combination. However, one could argue that the optimal dose of any targeted therapy remains to be determined. It is possible that further exploration of vatalanib as a single agent could yield a more refined, attenuated dosing regimen, which would increase safety and be more attractive to clinicians as part of a combination regimen.

A recent trial published by investigators at the National Cancer Institute reported similar difficulties with enhanced toxicities for the combination of oral sorafenib (Nexavar, Bayer/Onyx), a Raf kinase and VEGF receptor inhibitor, and bevacizumab.[4] In contrast to our trial, this study demonstrated significant antitumor activity in the large subset of ovarian cancer patients that were enrolled at the lower-than-recommended doses of sorafenib and bevacizumab. However, the investigators urged that the data be handled cautiously due to the additive toxicities of the combination. Furthermore, in July 2008, Genentech issued a warning letter to healthcare providers based on the results of a phase I dose escalation trial combining bevacizumab and sunitinib (Sutent, Pfizer), another oral tyrosine kinase inhibitor of VEGF.[5] In this trial, 5 of the 12 patients treated at the highest dose level exhibited laboratory findings consistent with microangiopathic hemolytic anemia (MAHA). Additional phase II studies with the combination of bevacizumab, sunitinib, and chemotherapy were also closed due to poor tolerability of the regimen (eg, diarrhea, anorexia, dehydration, and stomatitis) and the potential for developing MAHA with the combination. Based on the above data and the results of this trial, the feasibility of further development of bevacizumab and oral VEGF tyrosine kinase inhibitor combination regimens is questionable; due to the additive toxicities that occur, further investigations should proceed with caution.

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