Clinical Cancer Research

Biologic and Clinical Activity of Tivozanib (AV-951, KRN-951), a Selective Inhibitor of VEGF Receptor-1, -2, and -3 Tyrosine Kinases, in a 4-Week-On, 2-Week-Off Schedule in Patients with Advanced Solid Tumors

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Abstract

Purpose: To assess the maximum tolerated dose (MTD)/dose-limiting toxicities (DLT), safety, pharmacokinetics, and pharmacodynamics of tivozanib, a potent and selective oral VEGF receptor (VEGFR) tyrosine kinase inhibitor.

Experimental Design: Dose levels of 1.0, 1.5, and 2.0 mg/d tivozanib for 28 days followed by 14 days of medication were explored in patients with advanced solid tumors.

Results: Forty-one patients were enrolled. Animal data incorrectly predicted toxicity, resulting in DLTs at the starting dose (2.0 mg) consisting of grade 3 proteinuria and hypertension and grade 3 ataxia. At 1.0 mg, no DLT was observed. At an intermediate dose (1.5 mg), 1 patient experienced DLT consisting of grade 3 hypertension. This dose was determined as the MTD. Of 10 additional patients treated at 1.5 mg, 1 patient each experienced grade 3 hypertension and grade 3 fatigue, and 2 patients experienced grade 3 and 4 transaminase elevation. In 12 additional patients treated at 1.0 mg, no DLT was observed. Pharmacokinetics displayed long absorption time, dose proportional exposure, and a half-life of 4.7 days. Plasma levels of VEGF-A and soluble VEGFR-2 showed dose-dependent increases and decreases, respectively. Dynamic contrast-enhanced MRI indicated reduction in tumor perfusion. Clinical activity was observed in renal cell cancer, colorectal cancer, and other tumors.

Conclusion: Tivozanib was well tolerated with manageable side effects. The pharmacokinetics profile revealed that tivozanib was suitable for once-daily dosing. Encouraging and durable clinical activity was observed. The recommended daily dose of tivozanib in a 4-week-on and 2-week-off dosing regimen is 1.5 mg. *Clin Cancer Res; 17(22); 7156–63. ©2011 AACR.*

Introduction

Angiogenesis is required for tumor growth and metastasis, and VEGF plays a critical role in tumor-induced angiogenesis. Various VEGF isoforms, of which $VEGF_{165}$ is predominant, bind to high-affinity receptors VEGF receptor (VEGFR)-1, -2, and -3, resulting in a signal transduction cascade that results in formation of new blood vessels (VEGFR-1 and -2) and lymphangiogenesis (VEGFR-3), respectively. Increased VEGF expression in human cancers correlates with poor clinical outcome, irrespective of tumor grade or stage (1, 2).

Tivozanib (formerly AV-951, KRN-951) is a potent and selective VEGFR tyrosine kinase inhibitor (IC_{50} value of 0.21, 0.16, and 0.24 nmol/L for VEGFR-1, -2, and -3, respectively) and inhibits angiogenesis and vascular permeability in tumor tissues (3). Tivozanib has shown antitumor effects in human breast, colon, liver, lung, ovarian, pancreas, prostate, brain, and renal cell carcinoma (RCC) xenograft models (3, 4).

A phase I and pharmacologic study of tivozanib was conducted in patients with advanced solid tumors to determine maximum tolerated dose (MTD) and dose-limiting toxicity (DLT), to characterize single and multiple dose pharmacokinetics, to analyze biomarkers of antiangiogenic activity in serum and tumor with dynamic contrast-enhanced MRI (DCE-MRI), and to study antitumor activity of tivozanib administered orally once daily for 28 days followed by 14 days of treatment.

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Parts of these materials were presented at the 2006 ASCO annual meeting: Journal of Clinical Oncology, Proceedings Part I. Vol 24, No. 18S, 2006: (abstract 2034), and at the 2008 AACR annual meeting: Proceedings AACR, LBA 201.

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doi: 10.1158/1078-0432.CCR-11-0411

Translational Relevance

Tivozanib is a potent and selective VEGF receptor tyrosine kinase inhibitor that inhibits angiogenesis and vascular permeability in tumor tissues and has shown antitumor effects in a wide range of cancer types. This article presents findings from a phase I and pharmacologic study of tivozanib that was conducted in patients with advanced solid tumors to determine maximum tolerated dose and dose-limiting toxicity, to characterize single and multiple dose pharmacokinetics, and to study antitumor activity of tivozanib administered orally once daily for 28 days followed by 14 days of treatment. Overall, tivozanib was well tolerated with a manageable pattern of side effects, and the pharmacokinetics profile revealed that tivozanib was suitable for once-daily dosing. In addition, dynamic contrast-enhanced MRI indicated reduction in tumor perfusion, and encouraging clinical activity was observed in renal cell carcinoma, colorectal cancer, and other tumors. The recommended daily dose of tivozanib is 1.5 mg.

Patients and Methods

Eligibility criteria

The study enrolled patients from March 2004 to June 2007. Patients with histologically or cytologically confirmed solid tumors for whom no established therapy existed or who were not amenable to established treatments were eligible. Additional criteria included: age of 18 years or older; Eastern Cooperative Oncology Group (ECOG) performance status of 2 or lower; estimated life expectancy of 3 months or more; adequate bone marrow, hepatic, and renal function; and no chemotherapy, immunotherapy, radiotherapy, or hormonal therapy within 28 days excluding luteinizing hormone–releasing hormone agonists or hormones taken for breast cancer. Other exclusion criteria included cardiac abnormalities [myocardial infarction in the past 3 months, symptomatic left ventricular failure, or active hypertension (diastolic blood pressure >100 mm Hg and/or antihypertensive treatment administered during the past 3 months)], proteinuria 4+ with dipstick or >3.5 g per 24 hours, symptomatic central nervous system metastases, or unhealed wounds.

The local ethics committee approved the study, and all patients provided written informed consent prior to any study-related investigation.

Study design

Tivozanib was supplied by Kyowa Hakko Kirin (formerly Kirin Pharma) and AVEO Pharmaceuticals, Inc., as capsules containing 1.0, 1.5, or 2.0 mg of active study drug. Capsules were taken in the morning 1 hour before food intake. A cycle was defined as 28 days on treatment followed by 14 days of medication, based on tivozanib toxicologic studies and the clinical regimen used for sunitinib, another anti-VEGF tyrosine kinase inhibitor, at the time this study was designed.

The starting dose, 2.0 mg, corresponded with one third of the no-observed-adverse-effect level (NOAEL) in rats and monkeys and the no-observed-effect level (NOEL) in monkeys. Doses for successive cohorts were planned to be doubled until observation of drug-related adverse events of grade 2 or higher according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 2.0 in one or more patients in the first cycle. Thereafter, escalation steps of no more than 50% were anticipated. Initially, 3 evaluable patients per dose level were planned, and in case of 1 patient experiencing drug-related DLT, an additional 3 patients were to be treated at that dose. The MTD was defined as the highest dose at which no more than 1 of 6 patients experience DLT during cycle 1. Intrapatient dose escalation was not allowed. DLT was defined as neutrophils less than 0.5×10^9 per liter; hemoglobin less than 4.0 mmol/L; platelets less than 25×10^9 per liter; any grade 3 or 4 nonhematologic toxicity, except controllable grade 3 hypertension; and grade 2 nausea or vomiting requiring chronic 5-hydroxytryptamine antagonist treatment. Grade 3 hypertension was regarded as controllable if the following criteria were met: (i) no more than 2 different antihypertensive agents (either alone or in combination) required; (ii) diastolic blood pressure reduced to less than 100 mm Hg within 21 days of initiation of antihypertensive treatment confirmed by 2 consecutive measurements at least 24 hours apart; and (iii) diastolic blood pressure not increasing by more than 20 mm Hg subsequent to the start of antihypertensive treatment.

Pretreatment and follow-up studies

Pretreatment evaluations included a complete medical history and physical examination, laboratory tests, electrocardiogram, and radiography. Weekly evaluations during cycle 1 and every other week thereafter included physical examination, adverse event assessment, and laboratory tests. Tumor measurements were conducted prior to enrollment and every other cycle. Response was assessed with Response Evaluation Criteria in Solid Tumors version 1.0 (5). Patients were allowed to continue treatment in the absence of progressive disease or unacceptable toxicity.

Pharmacokinetic studies

Pharmacokinetic samples were collected on day 1 of cycles 1 and 2 before dosing and 0.5, 1, 2, 4, 6, 8, 10, and 24 hours after dosing. On day 28 of cycle 1, samples were collected before dosing and 0.5, 1, 2, 4, 6, 8, 10, 24, and 48 hours after dosing.

Tivozanib serum concentrations were determined by a validated method using liquid–liquid extraction followed by high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS-MS). Tivozanib and the internal standard KRN-633 were extracted from 100 μL serum with acetonitrile. The supernatant was injected onto a reversed-phase HPLC column. The mobile phase

consisted of acetonitrile and 5 mmol/L ammonium acetate buffer with a flow rate of 0.2 mL/min. Detection was with MS-MS. The method was validated in the range of 0.089 to 89.3 ng/mL. All serum samples were stored at −20°C until analysis. (Method AS M-118 and Validation Q-23131, Quintiles AB Analytical Services).

Pharmacodynamic studies

Serum levels of VEGF and soluble VEGFR-2 (sVEGFR-2) were analyzed before dosing in cycle 1 on days 0, 2, 15, 27, and 42. Validated Quantikine immunoassays (ELISA) were used for quantitative analysis of VEGF-A (DVE00) and sVEGFR-2 (DVR200; R&D Systems Europe Ltd.) according to manufacturer's protocols.

DCE-MRI examinations were conducted with a 1.5-T unit (Philips Medical Systems). Scan sequences included single shot fast spin echo with varying echo times for lesion characterization, fat-suppressed T_2-weighted fast spin echo, T_2-weighted black-blood echo planar imaging, T_1-weighted chemical shift imaging, and a dynamic gadolinium-enhanced sequence. After administration of 0.4 mL/kg body weight of non–liver-specific gadolinium chelate (gadopentetate dimeglumine; Magnevist), the main dynamic gadolinium-enhanced sequence was routinely carried out on the basis of T_1-weighted 2-dimensional or 3-dimensional breath hold gradient echo sequences. The following phases were acquired: (i) precontrast sequence; (ii) arterial phase timed on the basis of timing bolus information; (iii) portal phase 45 seconds after completion of the arterial phase; and (iv) a delayed sequence 120 seconds after injection of contrast medium. Scans were conducted at baseline and in cycle 1 at days 2 and 27.

Statistical methods

Data were analyzed by either counts of patients displaying distinctive characteristics for categorical data or, for continuous measures, by descriptive statistical summaries such as mean, SD, median, and range. Results were displayed within each dose group and overall, irrespective of cohort.

Pharmacokinetic calculations were conducted by a noncompartmental analysis with model 200 (extravascular administration) of WinNonlin Professional Edition version 4.1.b (Pharsight Corporation). Predose samples, taken before the first dose administration in a single-dose profile or before the last dose in a multiple-dose profile, were assigned an actual sampling time of 0 hours. Otherwise, individual serum concentration data from each patient and the exact time points for blood sampling were used throughout the analysis. Samples with serum concentrations below the lower limit of quantification (LLOQ) in early time points (lag-time) were treated as zero. Serum levels below the LLOQ appearing in terminal samples were omitted from the analysis. Individual serum concentrations and individual pharmacokinetic parameters were presented and summarized by descriptive statistics.

Paired Student *t* tests were used to calculate a *P* value for comparison of means and to define any statistically significant changes in biomarker levels. The Spearman rank correlation coefficients were used to assess correlations among the biomarker levels.

Results

Forty-one patients were enrolled. Their characteristics are summarized in Table 1. Dose levels studied were 2 mg ($n = 7$), 1 mg ($n = 18$), and 1.5 mg ($n = 16$). Patients received a total of 153 cycles (median: 2; range: 1–22). One patient with acinar pancreatic carcinoma received 25 cycles of tivozanib at 1.0 mg.

The most commonly reported adverse events related to tivozanib are summarized in Table 2. Hypertension was most frequently observed, was seemingly dose dependent, and occurred in 7 of 18, 10 of 16, and 7 of 7 patients in the 1.0-mg, 1.5-mg, and 2.0-mg groups, respectively. Other commonly observed adverse events were fatigue, hoarseness, and diarrhea. Proteinuria was only observed in the 2-mg group. The only grade 3 adverse event related to tivozanib reported in more than 2 patients in any treatment group was

Table 1. Patient characteristics

Total, *N*		41
Male/female, *n*		27/14
Mean age, y		56
Range, y		28–73
ECOG performance status, *n*		
0		13
1		26
2		2
Prior therapy, *n*		
Prior chemotherapy		32
Prior radiotherapy		14
Prior immunotherapy		4
No prior systemic therapy		9
Tumor type, *n*		
Colorectal carcinoma		10
Renal cell carcinoma		9
Pancreatic carcinoma		6
Non–small cell lung cancer		3
Esophageal carcinoma		2
Melanoma		2
Hepatocellular carcinoma		2
Miscellaneous		7
Dose cohort, mg		
	Patients, *n* (total cycles)	Patients with DLT in cycle 1, *n*
1.0	18 (72)	0
1.5	16 (6)	4[a]
2.0	7 (35)	2[b]

[a]One additional patient with DLT in cycle 3.
[b]One additional patient with DLT in cycle 2.

Table 2. Most frequently occurring adverse effects in evaluable patients

Drug-related adverse event	1.0 mg ($n = 18$)		1.5 mg ($n = 16$)		2.0 mg ($n = 7$)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Hypertension	11%	28%	—	62%	29%	71%
Fatigue	55%	6%	44%	6%	29%	—
Hoarseness	33%	—	56%	—	57%	—
Diarrhea	44%	—	31%	—	29%	—
Nausea	44%	—	19%	—	43%	—
Rash	22%	—	25%	—	43%	—
Anorexia	28%	—	13%	—	43%	—
Stomatitis	22%	—	19%	—	43%	—
Dry skin	28%	—	6%	—	29%	—
Headache	6%	—	31%	—	29%	—
Vomiting	22%	—	13%	—	14%	—
Myalgia	11%	—	6%	—	29%	—

hypertension (5/18 patients, 1 mg; 10/16 patients, 1.5 mg; and 5/7 patients, 2 mg). A summary of all grade 3 and 4 laboratory abnormalities is provided in Table 3.

DLT and cohort expansion

In the 2.0-mg cohort, DLTs in cycle 1 consisted of grade 3 asymptomatic proteinuria coinciding with hypertension and grade 3 ataxia coinciding with hypertension (Table 1). In one additional patient, grade 4 intracerebral hemorrhage was observed in cycle 2; however, this event was not considered a protocol-defined DLT because it did not occur during cycle 1. In the 1.0-mg cohort consisting of 6 patients, no DLT was observed. It was then decided to evaluate an intermediate dose of 1.5 mg. In the first 3 patients, one DLT (uncontrollable hypertension) was observed and, according to the protocol, 3 more patients were enrolled, none of whom experienced DLT. Therefore, 1.5 mg was determined to be the MTD, and 10 additional patients were enrolled for an expanded safety assessment. In these patients, DLTs consisted of 2 episodes of asymptomatic and reversible grade 3 and 4 transaminase elevation, respectively, and 1 episode of uncontrollable hypertension; 1 additional patient experienced an episode of grade 3 fatigue and dyspnea during cycle 3 that was not considered a protocol-defined DLT (Table 1). Based upon the number of DLT episodes observed at 1.5 mg, 12 additional patients were enrolled at 1.0 mg, none of whom experienced DLT.

Pharmacokinetics

After single and multiple dosing, the overall rate of absorption was slow. Tivozanib serum concentration versus time curves by dose level are shown in Fig. 1. Median observed time of maximum observed serum concentration (t_{max}) was 2 to 24 hours with substantial individual variability (Table 4). Because of the occurrence

Table 3. Grade 3 or 4 laboratory abnormalities observed during the study

Laboratory test, *n*	1.0 mg ($n = 18$)		1.5 mg ($n = 16$)		2.0 mg ($n = 7$)		Total ($n = 41$)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Alkaline phosphatase	1	0	2	0	1	0	4	0
Alanine transaminase	1	0	3	0	0	0	4	0
Aspartate aminotransferase	1	0	3	0	1	0	5	0
γ-Glutamyltransferase	4	1	1	4	1	0	6	5
Glucose	0	0	2	0	0	0	2	0
Hemoglobin	0	0	0	1	0	0	0	1
Lymphocytes	2	0	1	0	0	0	3	0
Phosphate	3	0	0	0	0	0	3	0
Potassium	0	0	0	0	1	0	1	0
Total bilirubin	1	0	1	0	0	0	2	0

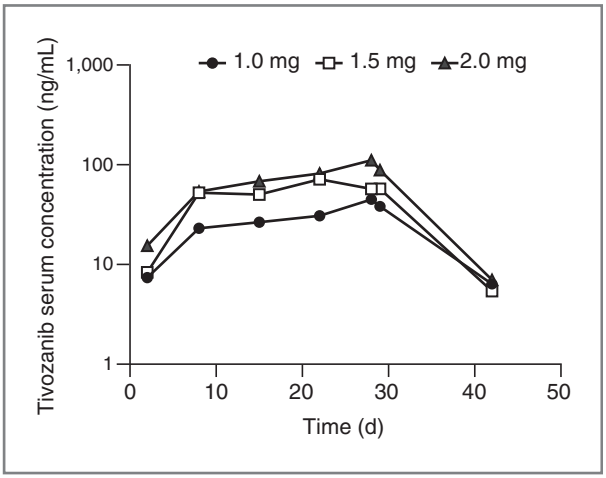

Figure 1. Tivozanib serum concentrations versus time per dose level.

of secondary peaks in the concentration-versus-time profiles indicating possible enterohepatic recirculation, t_{max} was variable.

Although interpatient variability was high, mean maximum observed serum concentration (C_{max}) and area under the serum concentration versus time curve during a 24-hour dosing interval (AUC_{0-24}) after single and multiple doses were close to dose proportional (Table 4). Mean half-life ($t_{1/2}$) of tivozanib across all dose levels was 4.7 days (112 hours), range 1.3 to 9.7 days (31–233 hours; data not included in tables). Sufficient time points to characterize the terminal phase were not available from all patients.

AUCs on day 28 were higher than those on day 1 because of expected accumulation (Table 4). In the majority of patients, predose samples collected prior to the first dose of cycle 2 still had measurable tivozanib levels. Thus, for the majority of patients, there was continuous systemic drug exposure even during the 14-day dosing break at the end of cycle 1.

Pharmacodynamics

Serum levels of VEGF-A increased in an apparent dose-dependent manner and tended to return to near-baseline values after 14 days of medication. The increase was apparent at day 2 and most pronounced at day 27. At doses of 2.0, 1.5, and 1.0 mg, a 5.0 ± 9.1-, 2.6 ± 2.8-, and 1.9 ± 1.0-fold relative increase in levels at day 27 was observed. Notably, this correlation was only noted for normalized levels.

Serum levels of sVEGFR-2 decreased in an apparent dose-dependent manner. The decrease was not evident at day 2, but highly manifest at days 15 and 27 for all dose levels. Actual levels at day 27 at doses of 2.0, 1.5, and 1.0 mg were decreased by 52% (2.0-fold), 39% (1.6-fold), and 28% (1.4-fold), respectively. Although there was a trend that levels were returning to baseline after 14 days of medication, concentrations were still decreased by 23% on day 42.

DCE-MRI analysis was considered to be exploratory, and only 8 patients underwent scanning at the prespecified time points. Overall, there was a trend to diminishing internal vascularization of tumors over time, and in 1 patient with RCC, there was a decrease in tumor vascularization accompanied by a decrease in tumor size, suggesting antiangiogenic effects underlying an observed clinical response (Supplementary Fig. 1).

Table 4. Mean (± SD) pharmacokinetic parameters of tivozanib on cycle 1, days 1 and 28, and cycle 2, day 1

Pharmacokinetic parameter	Tivozanib dose					
	1 mg	*n*	1.5 mg	*n*	2 mg	*n*
Cycle 1, day 1						
t_{max}, h	6.015 (1.00–24.03)	18	6.000 (1.00–24.00)	16	24.00 (2.02–24.00)	7
C_{max}, ng/mL	9.293 (6.386)	18	10.19 (4.934)	16	17.65 (6.861)	7
$AUC_{(0-24)}$, h ng/mL	131.2 (52.6)	18	159.2 (69.4)	16	274.3 (83.6)	7
Cycle 1, day 28						
$t_{max,ss}$, h	4.010 (0.38–24.00)	16	2.000 (0.50–24.00)	13	24.00 (2.02–24.08)	5
$C_{max,ss}$, ng/mL	50.03 (21.17)	16	67.46 (45.55)	13	110.0 (61.43)	5
$AUC_{(0-24)}$, h ng/mL	856.0 (396.6)	15	1,180.2 (813.4)	13	1,997.2 (1,054.6)	5
Cycle 2, day 1						
t_{max}[a], h	4.000 (0.50–24.00)	19	23.970 (1.00–24.05)	9	4.000 (2.07–24.00)	3
C_{max}, ng/mL	14.40 (8.090)	19	13.35 (5.355)	9	24.97 (15.03)	3
$AUC_{(0-24)}$, h ng/mL	245.4 (116.4)	19	236.6 (100.5)	9	400.2 (244.4)	3

Abbreviations: C_{max}, maximum observed serum concentration; $C_{max,ss}$, maximum observed serum concentration during a dosing interval at steady state; $C_{min,ss}$, maximum observed serum concentration during a dosing interval at steady state; $t_{max,ss}$, observed time to reach $C_{max,ss}$.

[a] t_{max} values are presented as the median and the range.

Antitumor activity

One patient with RCC at 2.0 mg had a confirmed partial response (PR) from cycle 4 to cycle 22. One patient with clear cell RCC at 1.5 mg had an unconfirmed PR in cycle 2 with a best overall response of stable disease. Overall, 35% of patients showed tumor shrinkage during treatment (Fig. 2), and the majority of patients (55.2%) had a best overall response of stable disease (10 patients in the 1.0-mg group, 4 patients in the 1.5-mg group, and 2 patients in the 2.0-mg group). Nine patients had stable disease lasting for 3 cycles or more (≥18 wk), including 3 patients in the 1.0-mg group with stable disease in 6 cycles or more (≥36 wk). There was no apparent relationship between dose and clinical response. Several patients received prolonged duration of treatment, with 8 patients (20%) receiving treatment for 9 months or more and 5 patients (12%) receiving treatment for 12 months or more (Fig. 2). One patient with acinar cell pancreatic carcinoma and hepatic metastases received 1.0 mg, with stable disease lasting approximately 25 cycles (approximately 3 years).

Discussion

The treatment schedule of oral tivozanib explored in this study, once daily for 28 days followed by 14 days of treatment, was based on results in murine xenograft models showing antitumor activity and a manageable toxicity pattern that suggested intermittent treatment to allow recovery from observed toxicities. In addition, clinical and pharmacologic data on sunitinib, which was the angiogenesis inhibitor in most advanced clinical development at the time this study was designed, also prompted the incorporation of a drug-free period. On the basis of subnanomolar target inhibitory activity and preclinical efficacy data, it was anticipated that tivozanib would exert profound biologic activity through inhibition of VEGFRs and, therefore, based upon normally applied assumptions such as the NOAEL in animal models and in particular the NOEL in monkeys, a starting dose of 2.0 mg was thoughtfully selected and expected to be devoid of relevant toxicities. However, and unexpectedly, this starting dose turned out to exceed the

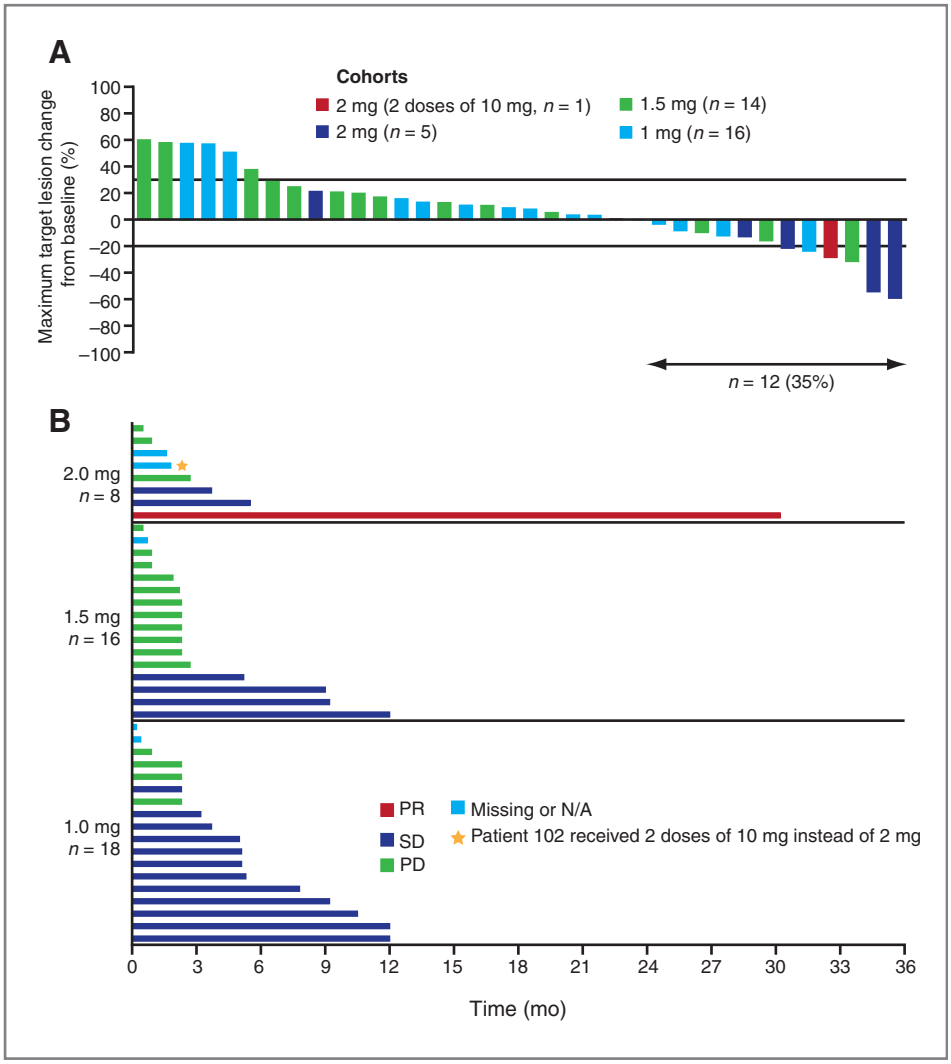

Figure 2. A, waterfall plot showing maximum tumor change from baseline and (B) duration of treatment in all patients. N/A, not applicable; PD, progressive disease; SD, stable disease.

MTD and yielded various DLTs with a spectrum of on-target adverse events well recognizable for VEGFR-inhibiting agents. It is interesting to note that a similar phenomenon was observed in a phase I study of AG-013736 (axitinib), which also displays subnanomolar inhibitory activity against VEGFR tyrosine kinases (6). In studies with some of the currently available multikinase inhibitors targeting VEGFR and other kinases (e.g., sorafenib and sunitinib), starting doses, however, turned out to be completely safe. Whether high target affinity of tivozanib explains this phenomenon or whether these observations are examples of poor predictive value of preclinical models for the human situation cannot be completely assessed. In our view, however, these observations underscore the profound biologic activity of tivozanib.

The most frequently observed drug-related adverse event was dose-related manageable hypertension. Other frequently occurring adverse events, such as fatigue, hoarseness, and diarrhea were not dose related. Of note in this study was the low incidence of proteinuria.

The pharmacokinetic profile of tivozanib showed oral bioavailability, slow absorption, and $t_{1/2}$ suitable for once-daily dosing. Concentration–time profiles from the majority of patients showed secondary peaks indicating that tivozanib may undergo enterohepatic recirculation, which would likely be a contributing factor in the observed long t_{max}. Generally, maximum serum concentrations and exposure increased with increasing doses, after both single and chronic administration. The pharmacokinetics of tivozanib allows for continuous serum exposure, even during the 2-week break in dosing for most patients. All pharmacokinetic parameters displayed moderate to high variability, similar to what is seen with other orally administered tyrosine kinase inhibitors. The high interpatient variability may have resulted from several factors, such as a mixed population of advanced cancer patients with different tumor types, varied prior therapies, concomitant medications, and altered gastrointestinal anatomy.

Tivozanib induced significant modulations of serum levels of proteins involved in VEGF signaling. Our data suggest that VEGF-A levels rapidly increase whereas concomitantly sVEGFR-2 levels decrease in response to tivozanib exposure. Apparently, inhibition of the complex system of VEGFR signaling induces activation of a "compensation mechanism," that is, transcriptional upregulation of positive regulators such as VEGF-A and downregulation of negative regulators such as sVEGFR-2. The latter is a truncated soluble form of membrane-bound VEGFR-2 that binds VEGF-A and may thereby function as a "decoy." Serum VEGF-A and in particular sVEGFR-2 levels may be of value as (surrogate) biomarkers of tivozanib activity. These preliminary effects on serum levels of VEGF-A and sVEGFR-2 are in concordance with data from phase I/II studies with the VEGFR inhibitors sunitinib, telatinib, pazopanib, cediranib, and linifanib (7–11).

Encouraging clinical activity was observed in patients with RCC. One patient exposed to 2.0-mg tivozanib had a confirmed PR lasting 22 cycles after which the patient had to be taken off-study due to the onset of an acute coronary syndrome. A second patient with RCC had an unconfirmed PR, and 6 of the remaining 7 patients with RCC had stable disease lasting 3 months or more. Given the relatively small numbers of patients in this study and the fact that responses were observed throughout the 3 dose levels studied, it is not possible to correlate clinical activity to pharmacokinetic or pharmacodynamic variables such as hypertension (that occurred in virtually all patients in this study). Currently available data on tivozanib in a larger cohort of patients with RCC, however, point at a correlation between the occurrence of hypertension and clinical efficacy (12).

In summary, tivozanib is a novel selective VEGFR tyrosine kinase inhibitor. When given daily for 4 weeks every 6 weeks, tivozanib is well tolerated with a recognizable and manageable pattern of side effects and reproducible biologic and clinical activity. The recommended dose for further studies using this schedule is 1.5 mg.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors thank all of the patients, investigators, and staff who participated in the study.

Grant Support

The funding was provided by AVEO Pharmaceuticals, Inc.

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Received February 15, 2011; revised August 23, 2011; accepted September 11, 2011; published OnlineFirst October 5, 2011.

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