Biological and Clinical Activity of Tivozanib (AV-951, KRN951), a Selective Inhibitor of Vascular Endothelial Growth Factor 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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Running title: Activity of VEGFR tyrosine kinase inhibitor tivozanib

Keywords: maximum tolerated dose, pharmacokinetics, solid tumors, tyrosine kinase inhibitor, vascular endothelial growth factor receptor

Research Support: Funding was provided by AVEO Pharmaceuticals, Inc.
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Conflicts of interest: Three authors (PB, MC, BE) are affiliated with AVEO Pharmaceuticals, Inc.; 2 authors (TI, KH) are affiliated with Kyowa Hakko Kirin Co Ltd, Tokyo, Japan.

Word count: 3,024 words
Total number of figures and tables: 2 figures, 4 tables

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.

The submission is original work not previously published in any substantial part, is not under consideration of publication elsewhere. The manuscript has been read and approved for submission by all authors.
Statement of Translational Relevance

Tivozanib is a potent and selective VEGFR tyrosine kinase inhibitor that inhibits angiogenesis and vascular permeability in tumor tissues and has demonstrated antitumor effects in a wide range of cancer types. This manuscript presents findings from a phase I and pharmacological 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 off 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 magnetic resonance imaging 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.
ABSTRACT

PURPOSE

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

PATIENTS AND METHODS

Dose levels of 1.0, 1.5, and 2.0 mg/day tivozanib for 28 days followed by 14 days off 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), one patient experienced DLT consisting of grade 3 hypertension. This dose was determined as the MTD. Of 10 additional patients treated at 1.5 mg, one patient each experienced grade 3 hypertension and grade 3 fatigue, and two 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 sVEGFR-2 showed dose-dependent increases and decreases, respectively. Dynamic contrast-enhanced magnetic resonance imaging 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 2 week off dosing regimen is 1.5 mg.
INTRODUCTION

Angiogenesis is required for tumor growth and metastasis, and vascular endothelial growth factor (VEGF) plays a critical role in tumor-induced angiogenesis. Various VEGF isoforms, of which VEGF165 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.\textsuperscript{1, 2}

Tivozanib (formerly AV-951, KRN 951) is a potent and selective VEGFR tyrosine kinase inhibitor (IC\textsubscript{50} 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.\textsuperscript{3} Tivozanib has demonstrated antitumor effects in human breast, colon, liver, lung, ovarian, pancreas, prostate, brain, and renal cell carcinoma xenograft models.\textsuperscript{3, 4}

A phase I and pharmacological 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 (PK), to analyze biomarkers of antiangiogenic activity in serum and tumor using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), and to study antitumor activity of tivozanib administered orally once daily for 28 days followed by 14 days off treatment.
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: aged ≥18 years; Eastern Cooperative Oncology Group Performance Status ≤2; estimated life expectancy ≥3 months; adequate bone marrow, hepatic, and renal function; 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 mmHg and/or antihypertensive treatment administered during the past 3 months]), proteinuria 4+ with dipstick or >3.5 g/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, Japan) and AVEO Pharmaceuticals, Inc. (Cambridge, MA, USA) 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 off medication, based on tivozanib toxicological 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 (AEs) grade ≥2 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 one patient experiencing drug-related DLT, an additional three patients were to be treated at that dose. The MTD was defined as the highest dose at which no more than one of six patients experience DLT during Cycle 1. Intrapatient dose escalation was not allowed. DLT was defined as neutrophils <0.5x10^9/L, hemoglobin <4.0 mmol/L, platelets <25x10^9/L, any grade 3 or 4 non-hematological 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: (1) no more than two different antihypertensive agents (either alone or in combination) required, (2) diastolic blood pressure reduced to <100 mmHg within 21 days of initiation of antihypertensive treatment confirmed by two consecutive measurements at least 24 hours apart, and (3) diastolic blood pressure not increasing by >20 mmHg 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 chest X-ray. Weekly evaluations during Cycle 1 and every other week thereafter included physical examination, AE assessment, and laboratory tests. Tumor measurements were performed prior to enrollment and every other cycle. Response was assessed using RECIST version 1.0. Patients were allowed to continue treatment in the absence of progressive disease or unacceptable toxicity.

Pharmacokinetic studies

PK samples were collected on Day 1 of Cycles 1 and 2 prior to dosing and 0.5, 1, 2, 4, 6, 8, 10, and 24 hours after dosing. On Day 28 of Cycle 1, samples were collected prior to 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 utilizing liquid-liquid extraction followed by high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS). Tivozanib and the internal standard KRN633 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 mM 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, Uppsala, Sweden.)
Pharmacodynamic studies

Serum levels of VEGF and soluble VEGFR-2 (sVEGFR-2) were analyzed prior to dosing in Cycle 1 on Days 0, 2, 15, 27, and 42. Validated Quantikine immunoassays (ELISAs) were used for quantitative analysis of VEGF-A (DVE00) and sVEGFR-2 (DVR200; R&D Systems Europe, Ltd. Abingdon, UK) according to manufacturer’s protocols.

DCE-MRI examinations were performed using a 1.5-T unit (Philips Medical Systems, Best, The Netherlands). Scan sequences included single-shot fast spin-echo with varying echo times for lesion characterization, fat-suppressed T2-weighted fast spin echo, T2-weighted black-blood echo planar imaging, and T1-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 (Magnevist [gadopentetate dimeglumine], Schering, Berlin, Germany), the main dynamic gadolinium-enhanced sequence was routinely performed based on T1-weighted 2D or 3D breath hold gradient-echo sequences. The following phases were acquired: (1) pre-contrast sequence; (2) arterial phase timed based on timing-bolus information; (3) portal phase at 45 seconds after completion of the arterial phase; and (4) a delayed sequence at 120 seconds after injection of contrast medium. Scans were performed at baseline and in Cycle 1 at Days 2 and 27.

Statistical methods

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

PK calculations were performed by a non-compartmental analysis using model 200 (extravascular administration) of WinNonlin Professional Edition version 4.1.b (Pharsight Corporation, Mountain View, CA, USA). Pre-dose 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 PK parameters were presented and summarized by descriptive statistics.

Paired Student’s t tests were employed to calculate a $P$ value for comparison of means and to define any statistically significant changes in biomarker levels. Spearman’s 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.
Most commonly reported AEs related to tivozanib are summarized in Table 2. Hypertension was most frequently observed, was seemingly dose dependent, and occurred in 7/18, 10/16, and 7/7 patients in the 1.0-mg, 1.5-mg, and 2.0-mg groups, respectively. Other commonly observed AEs were fatigue, hoarseness, and diarrhea. Proteinuria was only observed in the 2-mg group. The only grade 3 AE related to tivozanib reported in more than two patients in any treatment group was 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 listed in Table 3.

Dose-limiting toxicity 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 six patients, no DLT was observed. It was then decided to evaluate an intermediate dose of 1.5 mg. In the first three patients, one DLT (uncontrollable hypertension) was observed and, according to the protocol, three 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 two episodes of asymptomatic and reversible grade 3 and 4 transaminase elevation, respectively, and one episode of uncontrollable hypertension; one 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 Figure 1. Median observed time of maximum observed serum concentration ($t_{\text{max}}$) was 2 to 24 hours with substantial individual variability (Table 4). Due to the occurrence of secondary peaks in the concentration versus time profiles indicating possible enterohepatic recirculation, $t_{\text{max}}$ was variable.

Although inter-patient variability was high, mean maximum observed serum concentration ($C_{\text{max}}$) and area under the serum concentration versus time curve during a 24-hour dosing interval (AUC$_{0-24}$) after single and multiple doses was 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 due to expected accumulation (Table 4). In the majority of patients, pre-dose 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 off 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 off medication, concentrations were still decreased by 23% on Day 42.

DCE-MRI analysis was considered to be exploratory, and only eight patients underwent scanning at the pre-specified time points. Overall there was a trend to diminishing internal vascularisation of tumors over time, and in one patient with renal cell carcinoma (RCC) there was a decrease in tumor vascularization accompanied by a decrease in tumor size, suggesting antiangiogenic effects underlying an observed clinical response.

**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 (SD). Overall, 35% of patients
demonstrated tumor shrinkage during treatment (Figure 2), and the majority of
patients (55.2%) had a best overall response of SD (10 patients in the 1.0-mg group,
four patients in the 1.5-mg group, and two patients in the 2.0-mg group). Nine patients
had SD lasting for ≥3 cycles (≥18 weeks), including three patients in the 1.0-mg group
with SD in ≥6 cycles (≥36 weeks). There was no apparent relationship between dose
and clinical response. Several patients received prolonged duration of treatment, with
eight patients (20%) receiving treatment for ≥9 months and five patients (12%)
receiving treatment for ≥12 months (Figure 2). One patient with acinar cell pancreatic
carcinoma and hepatic metastases received 1.0 mg, with SD lasting approximately 25
cycles (approximately 3 years).

**DISCUSSION**

The treatment schedule of oral tivozanib once daily for 28 days followed by 14 days off
treatment explored in this study was based upon results in murine xenograft models
demonstrating antitumor activity and a manageable toxicity pattern that suggested
intermittent treatment to allow recovery from observed toxicities. In addition, clinical
and pharmacological data of 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. Based upon subnanomolar target inhibitory activity
and preclinical efficacy data, it was anticipated that tivozanib would exert profound
biological 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 MTD and yielded various DLTs with a spectrum of on-target AEs 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. In studies with some of the currently available multi-kinase inhibitors targeting VEGFR and other kinases (eg, sorafenib, 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 biological activity of tivozanib.

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

The PK profile of tivozanib demonstrated oral bioavailability, slow absorption, and t1/2 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 tmax. Generally, maximum serum concentrations and exposure increased with increasing doses, both after single and chronic administration. The PK of tivozanib allows for continuous serum exposure, even during the 2-week break in dosing for most patients.
All PK parameters displayed moderate to high variability, similar to what is seen with other orally administered tyrosine kinase inhibitors. The high inter-patient 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 while 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," ie, transcriptional up-regulation of positive regulators such as VEGF-A and down-regulation 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 is 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 six of the remaining seven patients with RCC had SD lasting ≥3 months. Given the relatively small numbers of patients in this study...
and the fact that responses were observed throughout the three dose levels studied, it is not possible to correlate clinical activity to PK or pharmacodynamic variables such as hypertension (that occurred in virtually all patients in this study). Currently available data of tivozanib in a larger cohort of patients with RCC, however, point at a correlation between the occurrence of hypertension and clinical efficacy.\textsuperscript{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 biological and clinical activity. The recommended dose for further studies using this schedule is 1.5 mg.

**Acknowledgments**

We thank all of the patients, investigators, and staff who participated in the study. Funding for this study was provided by AVEO Pharmaceuticals, Inc.
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Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Total, N</th>
<th>41</th>
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</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>27/14</td>
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<tr>
<td>Mean age, years</td>
<td>56</td>
</tr>
<tr>
<td>Range, years</td>
<td>28-73</td>
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<tr>
<td>ECOG Performance Status, n</td>
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<tr>
<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Prior therapy, n</td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>32</td>
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</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>10</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>9</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>6</td>
</tr>
<tr>
<td>Non–small cell lung cancer</td>
<td>3</td>
</tr>
<tr>
<td>Esophageal carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>2</td>
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<tr>
<td>Miscellaneous</td>
<td>7</td>
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<table>
<thead>
<tr>
<th>Number of patients (total no. of cycles)</th>
<th>Number of patients with DLT in Cycle 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mg</td>
<td>18 (72)</td>
</tr>
<tr>
<td>1.5 mg</td>
<td>16 (6)</td>
</tr>
<tr>
<td>2.0 mg</td>
<td>7 (35)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; DLT, dose-limiting toxicity.

<sup>a</sup>One additional patient with DLT in Cycle 3.

<sup>b</sup>One additional patient with DLT in Cycle 2.
Table 2. Most frequently occurring adverse effects in evaluable patients

<table>
<thead>
<tr>
<th>Drug-related adverse event</th>
<th>1.0 mg (n = 18)</th>
<th>1.5 mg (n = 16)</th>
<th>2.0 mg (n = 7)</th>
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<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
<td>Grade 1-2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11%</td>
<td>28%</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>55%</td>
<td>6%</td>
<td>44%</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>33%</td>
<td>--</td>
<td>56%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44%</td>
<td>--</td>
<td>31%</td>
</tr>
<tr>
<td>Nausea</td>
<td>44%</td>
<td>--</td>
<td>19%</td>
</tr>
<tr>
<td>Rash</td>
<td>22%</td>
<td>--</td>
<td>25%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>28%</td>
<td>--</td>
<td>13%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>22%</td>
<td>--</td>
<td>19%</td>
</tr>
<tr>
<td>Dry skin</td>
<td>28%</td>
<td>--</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>--</td>
<td>31%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22%</td>
<td>--</td>
<td>13%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>11%</td>
<td>--</td>
<td>6%</td>
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Table 3. Grade 3 or 4 laboratory abnormalities observed during the study

<table>
<thead>
<tr>
<th>Laboratory test, n</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<th>Grade 4</th>
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<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
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<td>4</td>
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<tr>
<td>Alanine transaminase</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
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<tr>
<td>Aspartate aminotransferase</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Gamma-glutamyltransferase</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>4</td>
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<td>0</td>
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<tr>
<td>Glucose</td>
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<td>Lymphocytes</td>
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<td>1</td>
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<tr>
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<td>Potassium</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Total bilirubin</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
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</table>
Table 4. Mean (± SD) pharmacokinetic parameters of tivozanib on Cycle 1, Days 1 and 28 and Cycle 2, Day 1

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Tivozanib dose</th>
<th>1 mg</th>
<th>n</th>
<th>1.5 mg</th>
<th>n</th>
<th>2 mg</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle 1, Day 1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>6.015 (1.00-24.03)</td>
<td>18</td>
<td>6.000 (1.00-24.00)</td>
<td>16</td>
<td>24.00 (2.02-24.00)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)*</td>
<td>9.293 (6.386)</td>
<td>18</td>
<td>10.19 (4.934)</td>
<td>16</td>
<td>17.65 (6.861)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>131.2 (52.6)</td>
<td>18</td>
<td>159.2 (69.4)</td>
<td>16</td>
<td>274.3 (83.6)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>AUC&lt;sub&gt;(0-24)&lt;/sub&gt; (h•ng/mL)</td>
<td>131.2 (52.6)</td>
<td>18</td>
<td>159.2 (69.4)</td>
<td>16</td>
<td>274.3 (83.6)</td>
<td>7</td>
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<tr>
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<td>4.010 (0.38-24.00)</td>
<td>16</td>
<td>2.000 (0.50-24.00)</td>
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<td>24.00 (2.02-24.08)</td>
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<tr>
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<td>t&lt;sub&gt;max,ss&lt;/sub&gt; (h)</td>
<td>50.03 (21.17)</td>
<td>16</td>
<td>67.46 (45.55)</td>
<td>13</td>
<td>110.0 (61.43)</td>
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<tr>
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<td>C&lt;sub&gt;max,ss&lt;/sub&gt; (ng/mL)</td>
<td>856.0 (396.6)</td>
<td>15</td>
<td>1180.2 (813.4)</td>
<td>13</td>
<td>1997.2 (1054.6)</td>
<td>5</td>
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<tr>
<td></td>
<td>AUC&lt;sub&gt;(0-24)&lt;/sub&gt; (h•ng/mL)</td>
<td>856.0 (396.6)</td>
<td>15</td>
<td>1180.2 (813.4)</td>
<td>13</td>
<td>1997.2 (1054.6)</td>
<td>5</td>
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<tr>
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<td>Cycle 2, Day 1</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>4.000 (0.50-24.00)</td>
<td>19</td>
<td>23.970 (1.00-24.05)</td>
<td>9</td>
<td>4.000 (2.07-24.00)</td>
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<tr>
<td></td>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)*</td>
<td>14.40 (8.090)</td>
<td>19</td>
<td>13.35 (5.355)</td>
<td>9</td>
<td>24.97 (15.03)</td>
<td>3</td>
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<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>245.4 (116.4)</td>
<td>19</td>
<td>236.6 (100.5)</td>
<td>9</td>
<td>400.2 (244.4)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>AUC&lt;sub&gt;(0-24)&lt;/sub&gt; (h•ng/mL)</td>
<td>245.4 (116.4)</td>
<td>19</td>
<td>236.6 (100.5)</td>
<td>9</td>
<td>400.2 (244.4)</td>
<td>3</td>
</tr>
</tbody>
</table>

*<sup>t<sub>max</sub></sup> values are presented as the median and the range

<sup>1</sup>t<sub>max</sub>, observed time of C<sub>max</sub>; t<sub>max,ss</sub>, observed time to reach C<sub>max,ss</sub>; C<sub>max</sub>, maximum observed serum concentration; C<sub>max,ss</sub>, maximum observed serum concentration during a dosing interval at steady state; AUC<sub>(0-24)</sub>, area under the serum concentration versus time curve during a 24-hour dosing interval.
FIGURE LEGENDS

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

Figure 2. (A) Waterfall plot showing maximum tumor change from baseline and (B) duration of treatment in all patients.

PR, partial response; SD, stable disease; PD, progressive disease; N/A, not applicable; ECOG, Eastern Cooperative Oncology Group; DLT, dose-limiting toxicity.
Figure 1.

![Graph showing Tivozanib serum concentration (ng/ml) over time (days) for doses of 1.0 mg, 1.5 mg, and 2.0 mg.](image-url)
Figure 2.

A

B

Cohorts

- 2 mg (2 doses of 10 mg [n = 1])
- 2 mg (n = 5)
- 1.5 mg (n = 14)
- 1 mg (n = 16)

Maximum target lesion change from baseline (%)

Time (months)

-100 -80 -60 -40 -20 0 20 40 60 80 100

n = 12 (35%)

2.0 mg
n = 8

1.5 mg
n = 16

1.0 mg
n = 18

PR PD Patient 102 received two doses of 10 mg instead of 2 mg

SD Missing or N/A

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Patient 102 received two doses of 10 mg instead of 2 mg
Clinical Cancer Research

Biological and Clinical Activity of Tivozanib, 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

Ferry ALM Eskens, Maja JA de Jonge, Pankaj Bhargava, et al.

Clin Cancer Res  Published OnlineFirst October 5, 2011.

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