Phase I Trial of Pazopanib in Patients with Advanced Cancer

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Abstract

Purpose: The safety, pharmacokinetics, and clinical activity of pazopanib (GW786034), an oral angiogenesis inhibitor targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-Kit, were evaluated in patients with advanced-stage refractory solid tumors.

Experimental Design: Patients were enrolled into sequential dose-escalating cohorts (50 mg three times weekly to 2,000 mg once daily and 300-400 mg twice daily). Escalation or deescalation was based on toxicities observed in the preceding dose cohort. Pharmacokinetic and biomarker samples were obtained. Clinical response was assessed every 9 weeks.

Results: Sixty-three patients were treated (dose escalation, n = 43; dose expansion, n = 20). Hypertension, diarrhea, hair depigmentation, and nausea were the most frequent drug-related adverse events, the majority of which were of grade 1/2. Hypertension was the most frequent grade 3 adverse event. Four patients experienced dose-limiting toxicities at 50 mg, 800 mg, and 2,000 mg once daily. A plateau in steady-state exposure was observed at doses ≥ 800 mg once daily. The mean elimination half-life at this dose was 31.1 hours. A mean target trough concentration (C24) ≥ 15 μg/mL (34 μmol/L) was achieved at 800 mg once daily. Three patients had partial responses (two confirmed, one unconfirmed), and stable disease of ≥ 6 months was observed in 14 patients; clinical benefit was generally observed in patients who received doses of ≥ 800 mg once daily or 300 mg twice daily.

Conclusion: Pazopanib was generally well tolerated and showed antitumor activity across various tumor types. A monotherapy dose of 800 mg once daily was selected for phase II studies.

Tumor growth and metastasis depend on tumor angiogenesis and lymphangiogenesis. Vascular endothelial growth factor (VEGF) is one of several proangiogenic molecules that play a pivotal role in both of these processes. The biology of VEGF has been extensively reviewed (1, 2). Several anti-VEGF agents have shown efficacy in a range of tumor types (3, 4).

Increasing evidence suggests that platelet-derived growth factor receptor (PDGFR) signaling is also involved in tumor angiogenesis (5, 6). Specifically, signaling through PDGFR-β seems to play a critical role in the recruitment of tumor pericytes responsible for the development of functional capillaries and the production of VEGF by the tumor stroma (2, 5). Preclinical data suggest that simultaneously targeting VEGF and PDGF pathways may be more effective than targeting either pathway alone (7, 8). Thus, combined inhibition of multiple VEGFRs and PDGFRs could provide greater inhibition of both tumor angiogenesis and lymphangiogenesis, thereby more effectively inhibiting tumor growth and metastasis (7).

Pazopanib (GW786034) is an oral angiogenesis inhibitor targeting VEGF, PDGF, and c-Kit (9, 10). In vivo, pazopanib inhibited the growth of multiple human tumor xenografts in mice and basic fibroblast growth factor- and VEGF-induced angiogenesis in two different mouse models of angiogenesis (11). In preclinical models, the in vivo activity of pazopanib depended on achieving a steady-state concentration of ≥ 40 μmol/L (17.5 μg/mL; ref. 12).

This is the first phase I study of oral pazopanib in patients with cancer, designed to characterize the safety and pharmacokinetics of pazopanib after single-dose and multiple-dose administration, to evaluate the effect of pazopanib on biomarkers of angiogenesis and to describe any observed clinical activity.

Patients and Methods

Eligibility criteria. Patient inclusion criteria included: being ≥ 21 y old, histologically confirmed diagnosis of an advanced solid tumor refractory to standard therapy or a tumor type for which no standard therapy existed, a Karnofsky performance status ≥ 70%, and a life expectancy of ≥ 12 wk. Patient exclusion criteria included: hemoglobin concentration...
<9 g/dL (5 mmol/L), absolute granulocyte count <1,500/μm3 (1.5 × 10^9/L), platelet count <100,000/μm3 (100 × 10^9/L), aspartate aminotransferase or alanine aminotransferase >2 × the upper limit of normal, or uncontrolled hypertension (systolic <160 mm Hg; diastolic <100 mm Hg). All patients provided written informed consent in accordance with local institutional review boards. The study was conducted at Duke University Medical Center and Case Western Reserve University from December 2002 to September 2006 in accordance with the Declaration of Helsinki.

Study design and treatment. VEG10003 was a multicenter, open-label, nondramonized, dose-finding phase I study (trial registration number NCT00060151). Pazopanib (monohydrochloride salt; GlaxoSmithKline) was supplied as 50-mg, 100-mg, 400-mg, and 500-mg tablets for oral administration.

Patients received a single dose of pazopanib on day 1 followed by 96 h of pharmacokinetic sampling before multiple daily doses were administered. Dose-escalation decisions were based on the safety profile observed after all patients in the preceding cohort completed ≥1 treatment cycle consisting of 21 consecutive days. In the first cycle, pharmacokinetic sampling occurred after the single dose on day 1, and continuous dosing started the day after pharmacokinetic sampling. Doses were escalated until the maximum dose level of pazopanib was reached (2,000 mg once daily) or the maximum-tolerated dose (MTD) was achieved. Patients received doses of 50 mg and 100 mg three times weekly, 50 to 2,000 mg once daily, and 300 mg and 400 mg twice daily.

MTD and dose-limiting toxicities. The MTD was defined as the highest dose of pazopanib administered at which no more than 1 of 6 patients experienced a dose-limiting toxicity (DLT), defined as a grade 3/4 clinically significant nonhematologic toxicity; a hematologic toxicity including grade 4 granulocytopenia lasting ≥3 d, febrile neutropenia, or grade 3/4 thrombocytopenia; or a treatment delay of ≥14 d because of unresolved toxicity, each occurring within cycle 1. Toxicities that occurred after cycle 1 were classified as DLTs if the investigator and sponsor concluded that the toxicity was dose-limiting. Grade 3 hypertension controlled with antihypertensive medication was not considered dose limiting.

Planned enrollment included a minimum of two patients at each dose level. After observation of grade 2 toxicities in two patients per dose cohort, dose escalation was continued with a minimum of three patients per dose level. If one of three patients in a cohort developed a DLT, up to three additional patients were to be enrolled, for a total of six patients. Up to 15 patients were enrolled in each expanded cohort.

Patients remained on study until disease progression, withdrawal of consent, unacceptable toxicities, investigator discretion, or a treatment delay of >14 d. Intrapatient dose escalation was permitted beyond cycle 1 if the patient had not experienced DLT or disease progression and the new dose did not exceed the last well-tolerated dose in other patients.

Safety assessments. Adverse events were graded using the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0. A complete medical history, physical examination, and laboratory tests were done within 72 h of the first dose of pazopanib, throughout the study, and after the last dose of pazopanib.

All patients were provided with a home blood pressure monitor (Omron, model HEM-712C) and instructed to do at least twice-daily monitoring between clinic visits. Baseline blood pressure was compared with the maximum blood pressure measured at any point during the study, before dose escalations. Median change in systolic, diastolic, and mean arterial blood pressure was analyzed for each dose cohort. To avoid an underestimate of the incidence of hypertension, a study-specific definition of hypertension was used based on NCI CTC version 2.0 criteria for grade 3 hypertension (elevated blood pressure requiring therapy or more intensive treatment than previously) with the inclusion of a ≥15-mm-Hg rise from baseline in mean arterial blood pressure on at least three separate occasions.

Pharmacokinetic assessments. Blood samples (4 mL) were collected for determination of plasma pazopanib concentrations on days 1 and 22. On day 1, blood samples were collected before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 96 h postdose. On day 22, blood samples were collected before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h postdose. A single blood sample was collected within 1 h before the morning dose on days 8 and 15 to determine trough plasma pazopanib concentrations, which, in the context of daily dosing, is identical to the plasma pazopanib concentration at 24 hours (C_{24}). Plasma samples were analyzed using a high-performance liquid chromatography tandem mass spectrometry method. Pazopanib was extracted from 50 μL of human plasma by protein precipitation. Extracts were analyzed by high-performance liquid chromatography tandem mass spectrometry using a Turbo-IonSpray interface and positive-ion, multiple-reaction monitoring. The lower limit of quantitation for pazopanib was 10.0 ng/mL.

WinNonlin Professional software (Pharsight Corporation) and standard noncompartmental methods were used to calculate area under the plasma pazopanib concentration-time curve to 12 h or 24 h postdose (AUC_{0-12} or AUC_{0-24}, respectively), maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration, and elimination half-life.

Pharmacodynamic assessments. Blood samples were collected for pharmacodynamic assessments before dosing on day 1; 1 to 2 h postdose on days 8, 15, and 22; and every 3 wk thereafter. Platelet-poor plasma was collected at baseline and on days 8, 15, and 22, and every 3 wk thereafter. Briefly, 4.5 mL of whole blood was collected in a sodium-citrate Vacutainer tube, gently inverted 6 times to mix, and centrifuged at 2,500 × 15 min. The plasma supernatant was transferred to a fresh tube and centrifuged again (2,500 × 15 min) to ensure depletion of platelets. The resultant platelet-poor plasma was frozen until assayed. Changes in biomarkers compared with baseline were listed by patient and compared by cohort. Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) scans were planned for the dose-escalation and expansion phases of the study among patients with measurable liver lesions. Two baseline scans were done within the 7 d before the first dose, and scans were repeated on day 8 and day 22. T1 maps were created to enable DCE-MRI series to convert into Gd-diethylenetriaminepentaacetic acid maps on a pixel-by-pixel basis. For each pixel, the initial area under the gadolinium concentration-time curve (IAUC) was calculated as the integral over the first 60–s postarrival. The median lesion IAUC_{0-30} was determined in addition to a region of interest in normal liver; giving a single liver

Translational Relevance

Multikinase angiogenesis inhibitors have shown clinical activity in multiple tumor types. Pazopanib is a multikinase angiogenesis inhibitor targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-Kit. This first-in-man, phase I biomarker study evaluated the pharmacokinetics and pharmacodynamics of pazopanib, including dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and serial blood pressure measurements. As expected, pazopanib showed treatment-related changes in tumor perfusion and permeability as measured by DCE-MRI and increases in blood pressure. Changes in blood pressure and clinical benefit in the subset of patients with renal cell carcinoma correlated with trough concentrations at steady state. These translational studies support both the dose selection for pazopanib and the use of DCE-MRI and serial blood pressure measurements as pharmacodynamic markers of antivascular endothelial growth factor receptor activity.

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IAUC_{liver} for each patient visit. IAUC_{lesion} was normalized to IAUC_{liver}, providing IAUC_{60}.

### Evaluation of clinical activity

Disease assessments were done \( \geq 28 \) d before the first pazopanib dose (baseline) and every 9 wk thereafter until withdrawal from the study. Response was evaluated according to the Response Evaluation Criteria in Solid Tumors guidelines (13).

## Results

### Patient characteristics

Sixty-three patients with relapsed or refractory solid tumors (dose escalation, 43; dose expansion, 20) were treated with pazopanib (Table 1). The median duration of exposure to pazopanib was 10 weeks (range, 0.7-103.4 weeks).

### Safety and tolerability

Four patients experienced DLTs. At the 50-mg once-daily dose level, two patients experienced DLTs (grade 3 gastrointestinal hemorrhage and grade 3 extrapyramidal involuntary movements) that led to discontinuation of treatment. As a result of these DLTs, seven patients were enrolled at a lower dose level of 50 mg three times weekly. Once this dose level was determined to be safe, six additional patients were enrolled at a dose of 50 mg once daily before

### Table 1. Patient baseline characteristics and disposition

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>56.5 (12.1)</td>
</tr>
<tr>
<td>Prior chemotherapy regimens</td>
<td>57 (90)</td>
</tr>
<tr>
<td>( \geq 4 ) regimens</td>
<td>37 (59)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>28 (44)</td>
</tr>
<tr>
<td>Primary disease site</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Colon</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Breast</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Rectal</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Lung</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Liver</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Stomach</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Prostate</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Other*</td>
<td>11 (18)</td>
</tr>
</tbody>
</table>

**Disposition n**

- Dose-escalation phase (n = 43)
  - 100 mg three times weekly: 2
  - 50 mg once daily: 9
  - 50 mg three times weekly: 7
  - 100 mg once daily: 3
  - 200 mg once daily: 3
  - 400 mg once daily: 4
  - 800 mg once daily: 3
  - 1,400 mg once daily: 3
  - 2,000 mg once daily: 3
  - 1,000 mg once daily: 3
  - 600 mg once daily: 3

- Dose-expansion phase (n = 20)
  - 800 mg once daily: 11
  - 300 mg twice daily: 6
  - 400 mg twice daily: 3

*Other tumor types included angiosarcoma (\( n = 1 \)), endometrium (\( n = 1 \)), fibrous histiocytoma (\( n = 1 \)), gastrointestinal stromal tumor (\( n = 1 \)), head and neck (\( n = 1 \)), hepatobiliary carcinoma (\( n = 1 \)), Hürthle cell cancer (\( n = 1 \)), melanoma (\( n = 1 \)), mesothelioma (\( n = 1 \)), ovarian (\( n = 1 \)), and carcinoma unknown primary (\( n = 1 \)).

## Table 2. Summary of drug-related adverse events and laboratory abnormalities in \( \geq 5 \)% of patients, per NCI CTC version 2.0 criteria for toxicity grading (\( N = 63 \))

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All grades Patients, n (%)</th>
<th>Grades 3-4* Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>21 (33)</td>
<td>16 (25)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21 (33)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Hair depigmentation</td>
<td>20 (32)</td>
<td>No grading</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (32)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>16 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (24)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusis</td>
<td>8 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>8 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5 (8)</td>
<td>No grading</td>
</tr>
<tr>
<td>Skin hypopigmentation</td>
<td>5 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>4 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>3 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>3 (5)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory abnormality</th>
<th>Patients, n (%)</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>22 (35)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19 (30)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>12 (19)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Anemia</td>
<td>10 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13 (21)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTT</td>
<td>16 (25)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>INR</td>
<td>9 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>24 (38)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>21 (33)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>17 (27)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>21 (33)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>13 (21)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>11 (17)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>10 (16)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>7 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>5 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>8 (13)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>24 (38)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>ALT</td>
<td>15 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin, total</td>
<td>8 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipstick or 24-hour</td>
<td>33 (52)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

*Abbreviations: PTT, partial thromboplastin time; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

*All were limited to grade 3 only except creatinine (\( n = 2 \)) and hypoglycemia (\( n = 2 \)).

*Includes blurred vision.
further dose escalation. At the 800-mg once-daily dose level, one patient with a preexisting history of well-controlled hypertension experienced acute onset of severe, asymptomatic, grade 3 hypertension. This was first documented on day 2, with maximum blood pressure on day 3 (227/114 mm Hg) that required interruption of pazopanib treatment and the addition of antihypertensive medications to the patient’s baseline regimen. After hypertension was controlled, pazopanib was resumed at a lower dose and gradually escalated back to 800 mg once daily. The patient subsequently developed grade 3 proteinuria that occurred despite dose reductions and was withdrawn from the study because of grade 3 proteinuria. At the maximum dose level (2,000 mg once daily), two patients experienced fatigue that required dose reductions. One patient experienced grade 2 fatigue in cycle 5 that was managed by dose reduction to 1,000 mg once daily.

Sixty-one (97%) patients experienced at least one adverse event, and 48 (76%) patients experienced drug-related adverse events. The most frequently reported drug-related event, and 48 (76%) patients experienced drug-related adverse events. The most frequently reported drug-related adverse events (all grades) were hypertension (33%), diarrhea (33%), hair depigmentation (32%), and nausea (32%; Table 2).

Additional grade 3 treatment-related adverse events included proteinuria (n = 2), diarrhea (n = 1 each for 50 mg, 800 mg, and 2,000 mg once daily), nausea (n = 1 for 1,400 mg once daily), fatigue (n = 1 for 2,000 mg once daily), increased aspartate aminotransferase (n = 1), extrapyramidal disorder (n = 1), pelvic

<table>
<thead>
<tr>
<th>Table 3. Mean (percent coefficient of variation) pazopanib pharmacokinetic parameters after single and repeat daily doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td><strong>AU0-24 (µg h/mL)</strong></td>
</tr>
<tr>
<td>22</td>
</tr>
<tr>
<td><strong>AU0-12 (µg h/mL)</strong></td>
</tr>
<tr>
<td><strong>Cmax (µg/mL)</strong></td>
</tr>
<tr>
<td>22</td>
</tr>
<tr>
<td><strong>t1/2 (h)</strong></td>
</tr>
<tr>
<td>22</td>
</tr>
<tr>
<td><strong>Cmax (µg/mL)</strong></td>
</tr>
<tr>
<td>22</td>
</tr>
</tbody>
</table>

**NOTE:** There were three patients per cohort unless otherwise noted. Abbreviations: t1/2, elimination half-life; tmax, time to maximum observed plasma concentration; NC, not calculated.

n = 8.

n = 4.

n = 5.

n = 2.

n = 1.

**n = 9.

†† Median tmax.
venous thrombosis (n = 1), tumor hemorrhage (n = 1), and deep vein thrombosis (n = 1 for 300 mg twice daily). All grade 3 treatment-related adverse events resolved after treatment with routine medications or dose reductions. Grade 3 diarrhea was not considered clinically significant because procedures for optimal clinical support of this adverse event had not been implemented.

One grade 4 adverse event (pulmonary embolism) was reported in a patient with metastatic adenocarcinoma of the lung after dose escalation from 100 mg once daily to 200 mg once daily. No treatment-related deaths occurred.

Hair depigmentation was observed in 20 (32%) patients, sometimes associated with skin depigmentation. All of these events were reversible on treatment discontinuation.

No grade 4 hematologic toxicities were observed, and grade 3 cytopenias, observed in two or more patients, were limited to lymphopenia (21%) and neutropenia (3%) patients. Grade 3/4 lymphopenia was reported in 9 (14%) patients; however, no infections were reported in these patients. In addition, 6 (10%) patients had grade 2 lymphopenia at baseline.

Two patients experienced grade 3 proteinuria, both with renal cell carcinoma. One of these patients was eventually withdrawn from the study because of recurrent proteinuria after dose interruption/reduction. Proteinuria was not associated with azotemia. Serial adrenocorticotropic hormone stimulation test results were analyzed in 25 patients. Data were available for ≥24 weeks in eight patients and ≥52 weeks in five patients. No evidence of primary adrenal insufficiency was observed. In addition, two patients experienced a grade 4 increase in creatinine. In one patient with colorectal cancer, the creatinine increase was observed in the follow-up period and was not associated with either proteinuria or diarrhea. The other patient experienced a transient increase in creatinine levels and experienced grade 2 diarrhea during the same treatment cycle. These events were not considered to be related to pazopanib.

Treatment interruptions and/or dose reductions because of pazopanib-related toxicities occurred in 10 patients: hypertension (n = 3), fatigue (n = 2), proteinuria (n = 1), diarrhea (n = 1), nausea (n = 1), changes in electrocardiography and bradycardia (n = 1), and nausea, anorexia, and taste disturbance (n = 1). In 8 of 10 patients, the treatment interruption/dose reduction occurred at doses of 800 to 2,000 mg once daily. As noted, two patients had pazopanib permanently discontinued for DLTs in cycle 1.

Pharmacokinetics. Plasma pazopanib concentrations were observed in all patients. Overall, mean Cmax and AUC0-24 on day 1 increased as the pazopanib dose increased, with the highest mean values observed in the 2,000-mg dose group (Table 3). Mean AUC0-24 and plasma pazopanib concentration at 24-hour (C24) values on day 22 of daily pazopanib administration were approximately 1.2- to 4.5-fold greater than values after single doses. Although the greatest mean exposure to pazopanib after a single dose was observed in the 2,000-mg dose group, steady-state exposure to pazopanib seemed to plateau in the 800-mg once-daily dose group (Fig. 1).
Administration of pazopanib 300 mg or 400 mg twice daily resulted in similar mean C_{max} and AUC_{0-12} values on day 22. Mean C_{max} values in both twice-daily dose groups were less than the mean C_{max} values in the 800-mg and 1,000-mg once-daily cohorts. However, mean C_{24} values on day 22 were similar in all four dosing regimens (800 mg once daily, 1,000 mg once daily, 300 mg twice daily, and 400 mg twice daily). Overall, no unexpected accumulation of pazopanib in plasma was observed.

Clinical activity. Three patients achieved a partial response; two patients with renal cell carcinoma (Fig. 2) had a confirmed partial response, and one patient with neuroendocrine tumor had an unconfirmed partial response. Fourteen patients achieved prolonged stable disease of ≥6 months (Table 4). Of 12 patients with renal cell carcinoma, in addition to the two patients with confirmed partial response, stable disease was observed in four patients, progressive disease was observed in four patients, and two patients were withdrawn from study because of toxicity (doses of 50 mg once daily and 800 mg once daily) before the first disease assessment. Patients with renal cell carcinoma who experienced partial response or stable disease received doses of 300 mg twice daily or 400 mg twice daily; patients with progressive disease received ≤400 mg once daily. No patients with renal cell carcinoma who experienced partial response had received prior antiangiogenic therapy.

Pharmacodynamic and biomarker assessments. Analysis of circulating biomarkers in the 43 patients in the dose-escalation phase showed no significant changes between the predose and postdose levels of D-dimer, VCAM-1, E-selectin, thrombin, or factor VIII. A ≥3-fold increase in plasma VEGF concentrations (from baseline) was observed on at least one occasion during the first 22 days of pazopanib administration in 22 of 45 patients from whom evaluable plasma VEGF concentration data were available. In addition, in the subset of patients who received pazopanib 300 mg twice daily, 400 mg twice daily, or ≥800 mg once daily, a ≥3-fold increase in plasma VEGF concentrations was observed in 17 of 30 patients. Baseline plasma VEGF concentrations ranged from below the limit of quantitation (15.3 pg/mL) to 205 pg/mL. The maximum evaluable plasma VEGF concentration observed during the study was 2,602 pg/mL.

Evaluation of DCE-MRI data obtained in patients from the dose-escalation cohorts was confounded because of various inconsistencies in data acquisition, including lack of a standardized MR sequence protocol and standardized administration of contrast. DCE-MRI scans were obtained in 12 patients enrolled in the expanded cohorts (4 patients at 300 mg twice daily, 2 patients at 400 mg twice daily, and 6 patients at 800 mg twice daily) after amendment to the protocol to standardize not only data acquisition but also to carry out the data analysis at a single center. In 10 of these patients with a total of 16 lesions, the reproducibility (assessed as the median variation, i.e. the absolute value of the difference in the repeatability pairs over the sum of the repeatability pairs) was 33% (range, 14-86%). Data were grouped together irrespective of dose because the dose range across the 12 patients was minimal. Seven of the 12 patients (58%) had a ≥50% reduction in tumor blood flow after treatment with pazopanib as determined by the initial area under the gadolinium concentration-time curve at 60 seconds (IAUGC_{60}) on day 8. Ten of the 11 patients (91%) with day 22 DCE-MRI data had ≥50% reduction in IAUGC_{60}.

Twenty (77%) of the 26 patients with C_{24} values of ≥15 μg/mL on day 22 developed hypertension, whereas hypertension developed in only 11 (39%) of the 28 patients who had a C_{24} value of <15 μg/mL on day 22. A relationship between development of hair depigmentation and systemic pazopanib exposure could not be determined because of insufficient data. Of the 6 patients with renal cell carcinoma that had either a partial response or stable disease as the best response, 5 (83%) achieved a steady-state C_{24} of ≥15 μg/mL. All 4 (100%)

### Table 4. Patients receiving pazopanib with partial response or stable disease of ≥6 months’ duration

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Starting dose (mg)</th>
<th>Final dose (mg)</th>
<th>Response*</th>
<th>Duration of response or stable disease (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell carcinoma</td>
<td>300 twice daily</td>
<td>300 twice daily</td>
<td>PR</td>
<td>12.8</td>
</tr>
<tr>
<td>Pancreatic islet cell tumor</td>
<td>1,000 once daily</td>
<td>1,000 once daily</td>
<td>PR</td>
<td>7.3</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>1,400 once daily</td>
<td>800 once daily</td>
<td>PR</td>
<td>6.0</td>
</tr>
<tr>
<td>Melanoma</td>
<td>30 times weekly</td>
<td>800 once daily</td>
<td></td>
<td>9.0</td>
</tr>
<tr>
<td>Hürthle cell</td>
<td>50 once daily</td>
<td>800 once daily</td>
<td>SD</td>
<td>26.6</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>50 once daily</td>
<td>800 once daily</td>
<td>SD</td>
<td>9.0</td>
</tr>
<tr>
<td>Non–small cell lung cancer</td>
<td>200 once daily</td>
<td>800 once daily</td>
<td>SD</td>
<td>13.6</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>400 once daily</td>
<td>800 once daily</td>
<td>SD</td>
<td>7.6</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>300 twice daily</td>
<td>300 twice daily</td>
<td>SD</td>
<td>17.1</td>
</tr>
<tr>
<td>Pancreatic islet cell tumor</td>
<td>300 twice daily</td>
<td>800 once daily</td>
<td>SD</td>
<td>18.3</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>600 once daily</td>
<td>800 once daily</td>
<td>SD</td>
<td>6.8</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor</td>
<td>600 once daily</td>
<td>800 once daily</td>
<td>SD</td>
<td>15.8</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>800 once daily</td>
<td>800 once daily</td>
<td>SD</td>
<td>7.8</td>
</tr>
<tr>
<td>Rectal carcinoid</td>
<td>800 once daily</td>
<td>800 once daily</td>
<td>SD</td>
<td>19.0</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>800 once daily</td>
<td>400 once daily</td>
<td>SD</td>
<td>15.6</td>
</tr>
<tr>
<td>Prostate</td>
<td>800 once daily</td>
<td>800 once daily</td>
<td>SD</td>
<td>10.0</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>2,000 once daily</td>
<td>800 once daily</td>
<td>SD</td>
<td>19.8</td>
</tr>
</tbody>
</table>

Abbreviations: PR, partial response; SD, stable disease.
*Response was summarized by the dose to which the patient was originally assigned. Dose adjustments were permitted; therefore, patients in the lower-dose groups may also have received higher doses of pazopanib during the course of their treatment.

† Unconfirmed PR.
patients with renal cell carcinoma and progressive disease achieved a steady-state \( C_{24} \) of <15 \( \mu \)g/mL.

**Discussion**

Pazopanib was generally well tolerated in this phase I study with continuous daily dosing of pazopanib \( \geq 2,000 \) mg once daily. A MTD was not determined, although the final cohort (2,000 mg once daily pazopanib) was not fully evaluated because the steady-state exposure to pazopanib seemed to be saturated at doses of 800 to 2,000 mg once daily. In addition, two patients experienced fatigue that required dose reductions in cycles 1 (grade 3, DLT) and 5 (grade 2). In four patients who experienced DLTs, fatigue and hypertension were observed at the 2,000-mg and the 800-mg once-daily dose, respectively. Grades 1/2 hypertension, diarrhea, hair depigmentation, and nausea were the most frequent drug-related toxicities. In general, grade 3 or 4 toxicities were uncommon. Although the toxicities reported with pazopanib are similar to those reported for other multikinase angiogenesis inhibitors (14–18), there are some differences. Drug-related rash (≤50% of patients), epistaxis (≤5% of patients), mouth ulceration and stomatitis (≤2% of patients), and asthenia (≤2% of patients) were uncommon in this study, and none exceeded grade 2. Furthermore, hand-foot syndrome was not observed.

Hypertension, the most frequent grade 3 toxicity reported in this study, has also been observed with other angiogenesis inhibitors (14–20). In this study, hypertension was controlled with antihypertensive medications or pazopanib dose reductions, and no patients were withdrawn from the study because of hypertension. Patients without a history of hypertension were as likely to develop hypertension as patients with a history of hypertension. The association of hypertension with day-22 \( C_{24} \) values suggests that hypertension may represent a general pharmacodynamic marker of pazopanib activity; however, these data are too limited to define any association of hypertension with clinical benefit.

The greatest mean \( C_{\text{max}} \) and \( C_{24} \) values after a single dose of pazopanib were observed in the 2,000-mg once-daily dose cohort. However, steady-state exposure to pazopanib seemed to plateau at doses of \( \geq 800 \) mg once daily, and therefore, the 2,000-mg dose was not fully explored. Mean plasma pazopanib \( AUC_{0-24} \), \( C_{\text{max}} \), and \( C_{24} \) values were similar after daily administration of doses of 800 to 2,000 mg. These results suggest that increasing the pazopanib dose to \( \geq 800 \) mg once daily is not likely to result in consistently greater plasma concentrations with a once-daily schedule.

Pazopanib showed evidence of clinical activity in patients with refractory malignancies. In patients with renal cell carcinoma, clinical activity seemed to correlate with day-22 \( C_{24} \) values of \( \geq 15 \) \( \mu \)g/mL. Interestingly, optimal inhibition of tumor angiogenesis was observed in preclinical studies when plasma pazopanib concentrations of \( \geq 17.5 \) \( \mu \)g/mL (40 \( \mu \)mol/L) were maintained over the entire dosing interval (12). Therefore, maintaining a minimum threshold concentration may be relevant for observing optimal benefit with pazopanib. A threshold concentration of 15,000 ng/mL also correlates with the pharmacodynamic effect of hypertension.

Although an MTD was not determined in this trial, no further increase in exposure occurred with increasing dose of \( \geq 800 \) mg once daily. At 800 mg once daily, 93% of patients achieved day-22 \( C_{24} \) values of \( \geq 15 \) \( \mu \)g/mL, a dose that correlated with the pharmacodynamic effect of hypertension. Several patients in this trial received pazopanib 800 mg once daily after dose escalations or reductions and, therefore, additional information on the safety, tolerability, and clinical activity at this dose was obtained. The 800-mg once-daily dose was recommended for evaluation in future studies based on a tolerable safety profile, saturation in exposure, changes in DCE-MRI consistent with significant changes in tumor perfusion, and achievement of a threshold concentration that seems to correlate with clinical activity in patients with renal cell carcinoma and with the pharmacodynamic effect of hypertension. Phase II and III trials in a variety of malignancies have been initiated (21–25).

**Disclosure of Potential Conflicts of Interest**

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Pazopanib: Safety, Pharmacokinetics, Clinical Activity


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