Phase I Dose-Finding Study of Pazopanib in Hepatocellular Carcinoma: Evaluation of Early Efficacy, Pharmacokinetics, and Pharmacodynamics

Thomas Yau, Pei-Jer Chen, Pierre Chan, C. Martin Curtis, Philip S. Murphy, A. Benjamin Suttle, Jennifer Gauvin, Jeffrey P. Hodge, Mohammed M. Dar, and Ronnie T. Poon

Abstract

Background: A phase I dose-escalating study of pazopanib was conducted to determine the maximum tolerated dose (MTD), pharmacokinetic/pharmacodynamic relationships, and clinical activity in patients with advanced hepatocellular carcinoma (HCC).

Experimental Design: Asian patients (N = 28) were dose escalated on pazopanib (200–800 mg) once daily (QD) on 21-day cycles, with MTD as the primary endpoint using a modified 3 + 3 design. Changes in tumor vasculature were evaluated by dynamic contrast-enhanced MRI (DCE—MRI).

Results: Two of five patients at the 800-mg dose level experienced dose-limiting toxicities [grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevations and grade 3 malaise]. The MTD in patients with HCC (Child–Pugh class A) was 600 mg QD. Diarrhea, skin hypopigmentation, and AST elevation were the most commonly reported adverse events at the MTD. Mean Cmax and area under the concentration-time curve (AUCO–6) of pazopanib and its metabolites did not increase dose proportionally across the 200 to 800 mg range. Reductions in IAUGC and Ktrans were shown at all pazopanib doses evaluated, with the greatest reductions at 600 and 800 mg. Although larger DCE-MRI parameter decreases were associated with larger C24 and Cmax values, there was no constant relationship between tumor perfusion decreases measured by DCE-MRI and plasma pazopanib pharmacokinetic parameters. Overall, 19 patients (73%) had either partial response or stable disease.

Conclusion: Pazopanib has a manageable safety profile in patients with advanced HCC, and 600 mg was chosen for further development of pazopanib in advanced HCCs. Moreover, pazopanib reduced tumor vessel leakage, as shown by DCE-MRI, indicating a direct effect on HCC vasculature that might be associated with its antitumor activity. Clin Cancer Res; 17(21); 6914–23. ©2011 AACR.
Patients and Methods

This phase I, open-label, dose-finding study (VEG107200; clinicaltrials.gov identifier NCT00370513) was conducted in 2 phases: a dose-escalation and a cohort-expansion phase, at 3 international centers. The study complied with the Helsinki Declaration principles; study protocol and amendments were reviewed and approved by the appropriate national, regional, or investigational center Ethics Committee or Institutional Review Board. All patients provided written informed consent.

Patients

Eligible patients were at least 18 years of age, satisfied European Association for the Study of the Liver diagnostic criteria for diagnosis of HCC (14), and had advanced (local unresectable and/or metastatic) disease not amenable to surgery or local therapy. Prior systemic or local therapy was permitted, provided it was completed within the protocol-specified time frame as follows: >4 weeks since prior systemic therapy, radiotherapy, or major surgery; >6 weeks since administration of nitrosoureas, mitomycin, or prior local-ablative therapy; >60 days since completion of prior radiofrequency ablation. Patients who received prior therapy had to show evidence of disease progression and must have fully recovered from previous therapy. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1; at least 1 target lesion according to Response Evaluation Criteria for Solid Tumors (RECIST; ref. 15); adequate hematologic and renal function; and Child–Pugh class A cirrhosis with adequate hepatic parameters [serum albumin ≥ 2.8 g/dL, serum bilirubin < 2.0 mg/dL; aspartate aminotransferase (AST) ≤ 2.0 × upper limit of normal; and alanine aminotransferase [ALT] ≤ 2.0 × upper limit of normal].

Major exclusion criteria included underlying malabsorption syndrome, any condition that interfered with oral administration of the study drug, Child–Pugh class B or C cirrhosis, previous therapy with any VEGF-directed angiogenesis inhibitor, and previous history of portal vein thrombosis or bleeding esophageal varices. Additional exclusion criteria included poorly controlled hypertension; QTc prolongation (defined as a QTc interval > 470 msec); previous class III or IV heart failure; history of cerebrovascular events within 6 months; history of myocardial infarction, hospitalization for unstable angina, or cardiac angioplasty or stenting within 6 months; or untreated venous thrombosis.

Study design and treatment

Dose-escalation phase. Pazopanib dose escalation ranged from 200 to 800 mg QD during the dose-escalation phase, with a minimum of 3 patients enrolled in each cohort; a modified 3 + 3 design specified that at least 3 to 6 patients could be enrolled in a given cohort. Patients were not enrolled in subsequent cohorts until all patients in the previous cohort completed 21 days of therapy (i.e., 1 cycle), and the toxicity profile and pharmacokinetics results from cycle 1 were available. Dose escalation continued at 100% of the preceding dose level until a dose-limiting toxicity (DLT) was observed or the maximum dose level of 800 mg QD was achieved in the absence of DLTs. The maximum tolerated dose (MTD) was defined as the highest daily dose of pazopanib at which no more than 1 of 6 patients experienced a DLT.

In addition to the standard definitions of DLTs (any grade 3 or 4 clinically significant nonhematologic toxicity except alopecia) used in other studies of pazopanib monotherapy, additional adverse events (AE) relevant to the population under study were defined as DLTs. These included liver toxicity for which clinical and radiologic criteria supported either progressive disease or viral reactivation as the cause of increased hepatic dysfunction, and an
increase in the Child–Pugh score by 2 or more in association with liver toxicity considered to be related to pazopanib (see Supplementary Methods for a complete list).

**Cohort-expansion phase**

Once the MTD was determined, up to 10 additional patients could be enrolled at the MTD to further evaluate the safety and tolerability of pazopanib and acquire additional and pharmacokinetics data.

**Study objectives.** The primary objectives of this study were the safety, tolerability, and MTD of pazopanib in patients with HCCs. Secondary objectives included characterization of pharmacokinetics, evaluation of changes in tumor vasculature based on DCE-MRI, serial serum α-fetoprotein (AFP) measurements, and evaluation of contrast-enhanced CT scans or MRI for response per RECIST guidelines (15).

**Safety assessments and disease evaluation**

Clinical assessments were conducted at least every 3 weeks and more frequently during the first 3 cycles for all patients on treatment. AEs were reported in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (16). Viral hepatitis replication parameters were assessed at the start of each cycle. Radiologic assessments, either CT or MRI scans, were conducted at baseline and at 6-week intervals thereafter.

**Pharmacokinetics.** To characterize the pharmacokinetics of pazopanib after single and multiple doses, serial blood samples were collected over 6 hours on day 15 during the dose-escalation phase, over 72 hours after pazopanib administration on day 1, and over 24 hours on day 15 during the cohort-expansion phase. Concentrations of plasma pazopanib and pazopanib metabolites (GSK1268992, GSK1268997, and GSK1071306) were measured by tandem high-performance liquid chromatography mass spectrometry.

Pharmacokinetic parameters included area under the concentration–time curve (AUC) from 0 to 6 hours (AUC0–6), maximum plasma concentration (Cmax), time to maximum observed concentration (tmax), and 24-hour plasma concentration (C24) of pazopanib on study day 15. Pharmacokinetic analyses of concentration–time data for plasma pazopanib and pazopanib metabolite were conducted using the noncompartmental Model 200 (for extravascular administration) of WinNonlin Professional Edition version 5.2 (Pharsight Corporation).

**DCE-MRI.** Changes in tumor vascular parameters in response to pazopanib were characterized by DCE-MRI. Specifically, DCE-MRI was used to determine the contrast agent transfer coefficient (Ktrans) and the initial area under the tissue gadolinium concentration–time curve (IAUGC) at baseline and on day 22 after pazopanib treatment. Two DCE-MRIs, at least 24 hours apart, were conducted during screening, within 7 days of day 1 of cycle 1 to evaluate measurement variability. A third DCE-MRI was conducted on day 1 of cycle 2 (study day 22). The pazopanib dose and exposure parameters at day 22 were compared with baseline (defined by the mean of the 2 baseline measurements) using Ktrans and IAUGC.

The IAUGC was derived from the area under the tissue gadolinium concentration–time curve over 60 seconds following bolus arrival (IAUGC0–60). Tumors were manually outlined, and all DCE-MRI parameters were calculated within the enhancing portion of the tumor.

A standardized DCE-MRI protocol was implemented at 3 clinical trial sites, and all the images were centrally analyzed by a group blinded to study treatment (Imaging Science and Biomedical Engineering, University of Manchester, Manchester, UK). Additional details of the DCE-MRI methods and analysis protocol are provided in Supplementary Methods.

**Statistical analysis**

Survival analysis was computed by the Kaplan–Meier method. Progression-free survival (PFS) was calculated from the date of commencement of study drugs to the date of documented progression or death and was conducted on intent-to-treat basis. All statistical analysis was conducted using SAS version 8.2 (SAS Institute Inc.).

**Results**

**Patients**

Median patient age was 61 years, and 24 patients (86%) were male (Table 1). Twenty-two patients (79%) met the cytostatologic criteria defined by European Association for the Study of the Liver for HCC, and 6 patients (21%) met the European Association for the Study of the Liver noninvasive criteria (restricted to cirrhotic patients) for HCC. Twenty-eight patients received pazopanib once daily. Median days (minimum–maximum) on study were 133.5 (42–798), 55 (8–295), 127 (4–289), and 169 (9–274) for pazopanib 200 mg (n = 4), 400 mg (n = 11), 600 mg (n = 8), and 800 mg (n = 5) QD doses, respectively.

**Dose-escalation phase and DLT**

Overall, 21 patients were enrolled in the dose-escalation phase and 3 patients experienced DLTs. At the pazopanib 800 mg QD dose level, 2 patients experienced DLTs (grade 3 AST/ALT elevations and grade 3 malaise) and the MTD was exceeded. Six patients were subsequently enrolled at pazopanib 600 mg in the dose-escalation phase of the study, according to the protocol. This dose met the protocol-defined MTD, in that 1 of the 6 patients enrolled at this dose level experienced a DLT (i.e., unable to receive >75% of dose during cycle 1 because of grade 2 neutropenia, grade 2 AST elevation, and grade 2 hyperbilirubinemia). Thus, the MTD was defined as 600 mg according to the protocol.

**Cohort-expansion phase**

Although not specified as part of the original study design, due to insufficient DCE-MRI data available that met prespecified technical requirements from the original 5...
patients enrolled at the 400 mg dose level during the dose-escalation phase, an additional 6 patients were enrolled at this dose, rather than the MTD of 600 mg during the cohort-expansion phase. After completion of cycle 1 and acquisition of DCE-MRI data, and in the absence of DLTs, these patients were permitted to escalate to the MTD of 600 mg QD. However, 2 additional patients were enrolled to receive pazopanib at the MTD of 600 mg starting from cycle 1 in the cohort-expansion phase. Nevertheless, one of these patients experienced a grade 4 gastrointestinal hemorrhage during the first 21 days of dosing, related, in part, to occult metastases invading the gastrointestinal tract, and withdrew from the study. The second patient enrolled in the cohort-expansion phase at 600 mg starting from cycle 1 was not evaluable for treatment-related toxicities because of rapid disease progression and withdrawal from the study after receiving 2 doses of pazopanib. No additional patients were enrolled in the cohort-expansion phase at the 600 mg dose level because of slow accrual and in light of additional patients having been exposed to 600 mg QD as a result of intrapatient dose modification (i.e., 10 patients received 600 mg for the majority of their on-study duration).

Safety

The most commonly reported AEs (Table 2) were diarrhea (17 patients; 61%), hypertension (10 patients; 36%), AST elevation (9 patients; 32%), and ALT elevation (6 patients; 21%). The most commonly reported AEs at the MTD were diarrhea (4 patients; 50%), skin hypopigmentation (4 patients; 50%), and AST elevation (5 patients; 38%). Most toxicities were grade 1 or 2 and resolved after discontinuation of pazopanib. Hypertension was the most common AE with a maximum toxicity of grade 3 or higher across all treatment groups.

The most common treatment-emergent hematologic laboratory abnormalities were lymphopenia (10 patients; 53%), leukopenia (13 patients; 46%), and neutropenia (8 patients; 42%). The most common treatment-emergent clinical chemistry abnormalities were AST elevation (20 patients; 71%), hyperbilirubinemia (19 patients; 68%), ALT elevation (15 patients; 54%), lipase elevation (13 patients; 50%), and hyperglycemia (14 patients; 50%). Maximum changes in hepatobiliary parameters from baseline are shown in Table 3.

Overall, 6 patients were withdrawn from the study because of AEs that included AST/ALT elevation, AST/bilirubin elevation, malaise, gastrointestinal hemorrhage, hepatic function abnormality, and myocardial ischemia (1 patient each). Nine patients experienced AEs that required dose interruption of pazopanib. The most common AEs leading to dose interruptions were AST/ALT elevations. Moreover, 6 patients had pazopanib dose reductions. The most common AEs leading to dose reductions were AST/ALT elevations and diarrhea.

Clinical activity

Twenty-six patients were evaluable for treatment response (2 patients were withdrawn during cycle 1
because of treatment-related toxicity and were not eval-
uable for response). Among evaluable patients, 2 patients
(8%) had confirmed partial responses, 17 patients (65%)
had stable disease, and 7 patients (27%) had progressive
disease. The partial responses (1 patient each at the 400
and 800 mg dose levels) were maintained for at least 12
weeks. Overall, 19 patients (73%) had either partial
response or stable disease while receiving pazopanib
treatment.

The median estimation of PFS for the entire study pop-
ulation was 17.7 weeks (95% CI: 11.9–23.9 weeks; Fig. 1A).
The best percentage change from baseline in the sum of the
longest diameters of target lesions according to pazopanib
dose received on the largest number of days (i.e., modal
dose rather than the originally assigned dose) is displayed
in Figure 1B to provide a more accurate picture of the
association between dose and antitumor activity. Of the
patients with a modal dose of 600 mg QD, 1 patient had a

### Table 2. Summary of AEs (any grade) occurring in 10% or more of all patients across all treatment groups and AEs ≥grade 3

<table>
<thead>
<tr>
<th>AE (preferred terms)</th>
<th>Patients, n (%)</th>
<th>200 (n = 4)</th>
<th>400 (n = 11)</th>
<th>600 (n = 8)</th>
<th>800 (n = 5)</th>
<th>Total (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17 (61)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (50)</td>
<td>9 (82)</td>
<td>4 (50)</td>
<td>2 (40)</td>
<td>17 (61)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (50)</td>
<td>2 (18)</td>
<td>1 (13)</td>
<td>0</td>
<td>5 (18)</td>
<td></td>
</tr>
<tr>
<td>AST increased</td>
<td>0</td>
<td>1 (9)</td>
<td>4 (50)</td>
<td>0</td>
<td>5 (18)</td>
<td></td>
</tr>
<tr>
<td>ALT increased</td>
<td>4 (50)</td>
<td>2 (25)</td>
<td>1 (20)</td>
<td>6 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>2 (50)</td>
<td>2 (18)</td>
<td>1 (13)</td>
<td>0</td>
<td>5 (18)</td>
<td></td>
</tr>
<tr>
<td>Skin hypopigmentation</td>
<td>0</td>
<td>1 (9)</td>
<td>4 (50)</td>
<td>0</td>
<td>5 (18)</td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>0</td>
<td>2 (18)</td>
<td>2 (25)</td>
<td>1 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>1 (25)</td>
<td>0</td>
<td>1 (13)</td>
<td>2 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>1 (25)</td>
<td>3 (27)</td>
<td>0</td>
<td>4 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (25)</td>
<td>1 (9)</td>
<td>1 (13)</td>
<td>4 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair depigmentation</td>
<td>0</td>
<td>1 (9)</td>
<td>0</td>
<td>3 (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>0</td>
<td>1 (9)</td>
<td>2 (25)</td>
<td>4 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td>1 (25)</td>
<td>2 (18)</td>
<td>1 (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>1 (25)</td>
<td>0</td>
<td>2 (25)</td>
<td>3 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>1 (9)</td>
<td>2 (25)</td>
<td>3 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (25)</td>
<td>1 (9)</td>
<td>1 (13)</td>
<td>3 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0</td>
<td>2 (18)</td>
<td>1 (13)</td>
<td>3 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>0</td>
<td>0</td>
<td>2 (25)</td>
<td>3 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (50)</td>
<td>0</td>
<td>1 (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 (50)</td>
<td>0</td>
<td>1 (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 (25)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (50)</td>
<td>2 (18)</td>
<td>1 (13)</td>
<td>7 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST increased</td>
<td>0</td>
<td>1 (9)</td>
<td>1 (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT increased</td>
<td>0</td>
<td>1 (9)</td>
<td>1 (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>2 (18)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0</td>
<td>0</td>
<td>1 (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0</td>
<td>0</td>
<td>1 (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1 (25)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase increased</td>
<td>0</td>
<td>1 (9)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td>0</td>
<td>0</td>
<td>1 (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (4)</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>0</td>
<td>0</td>
<td>1 (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>0</td>
<td>0</td>
<td>1 (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transaminases increased</td>
<td>0</td>
<td>0</td>
<td>1 (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hepatic function abnormal</td>
<td>0</td>
<td>0</td>
<td>1 (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient had rapid disease progression in the liver.
confirmed partial response, 6 patients had stable disease, and 1 patient had progressive disease.

Serial AFP changes
Of the 16 patients who had elevation in baseline AFP (i.e., >20 μg/L); 10 patients (63%) showed a 20% or greater decline in AFP than in baseline during the study whereas 2 patients had no postbaseline AFP measurements (Supplementary Table S1). Among the 10 patients who had elevated AFP at baseline and achieved a partial response or stable disease as their best response, 8 patients had a 20% or greater decline in AFP than in baseline and 2 patients had an increase in AFP than in baseline. In addition, among the 6 patients who had elevated AFP and achieved PFS of 17.7 weeks or longer, 5 patients had a 20% or greater decline in AFP than in baseline and only 1 patient had an increase in AFP compared with baseline.

Pharmacokinetics
After repeated oral administration of pazopanib 200, 400, 600, or 800 mg QD in the dose-escalation phase, median \( t_{\text{max}} \) values ranged from 2 to 3 hours (Supplementary Table S2). The highest AUC \( 0-6 \), \( C_{\text{max}} \), and \( C_{24} \) values were observed in the pazopanib 800 mg QD cohort. However, systemic exposure (AUC \( 0-6 \)) to pazopanib did not increase in a dose-proportional manner when the pazopanib dose was increased and ranged from 151 μg h/mL at pazopanib 200 mg QD to 214 μg h/mL at pazopanib 800 mg QD. Similarly, the mean \( C_{\text{max}} \) values for pazopanib did not vary widely across the range of pazopanib doses used in this study (29.8 g/mL at pazopanib 200 mg QD; 31.6 g/mL at pazopanib 400 mg QD; 28.8 g/mL at pazopanib 600 mg QD; and 39.5 g/mL at pazopanib 800 mg QD). The trough plasma \( C_{24} \) level was more than 15 μg/mL for all doses tested and was highest at the pazopanib 800 mg QD dose level (28.1 μg/mL).

After 14 days of once daily administration, metabolites in the pazopanib 800 mg cohort were greater than or equal to the mean values observed in the 200, 400, and 600 mg dose cohorts. Similar to pazopanib, systemic exposure to pazopanib metabolites did not increase in a dose proportional fashion when the dose of pazopanib was increased from 200 to 800 mg QD.

DCE-MRI findings
Seventeen of 28 patients treated with pazopanib 200 mg (\( n = 4 \)), 400 mg (\( n = 5 \)), 600 mg (\( n = 5 \)), or 800 mg (\( n = 3 \)) successfully completed both baseline and day 22 DCE-MRI acquisitions. Baseline scanning was repeated to estimate measurement variability. The mean percentage (SD) differences between 2 baseline scans for IAUGC\(_{60}\) and \( k_{\text{trans}} \) were 17.8% (17.3%) and 24.8% (23.1%), respectively. Median percentage changes from baseline in IAUGC\(_{60}\) and \( k_{\text{trans}} \) were −36.3, −23.0, −44.6, and −73.8 for the pazopanib 200 mg, 400 mg, 600 mg, and 800 mg QD doses, respectively (Table 4). The percentage changes from baseline in IAUGC and
$k_{\text{trans}}$ were variable across observed pazopanib $C_{24}$ and $C_{\text{max}}$ values; however, the largest decrease from baseline in $k_{\text{trans}}$ occurred in patients with $C_{24}$ values above 20 $\mu$g/mL (Fig. 2A). Decreases of 40% or greater from baseline in IAUGC were observed only in patients with $C_{24}$ of approximately 20 $\mu$g/mL or higher. One patient receiving pazopanib 800 mg QD had a best response of partial response, achieved $C_{24}$ of approximately 30 $\mu$g/mL and had large decreases from baseline in IAUGC (~60%) and $k_{\text{trans}}$ (~74%; Fig. 2B). All 3 patients who had a best response of progressive disease and underwent paired DCE-MRI acquisitions achieved $C_{24}$ values below 30 $\mu$g/mL and less than 40% decreases from baseline in IAUGC or $k_{\text{trans}}$. A similar trend was observed for $C_{\text{max}}$.

Discussion

For patients with advanced HCC in Child–Pugh class A, the MTD for pazopanib was 600 mg QD on the basis of DLT frequency during the first 21 days of pazopanib in the dose-escalation phase. During the cohort-expansion phase of the study (pazopanib 600 mg QD), one patient died and another experienced grade 4 gastrointestinal bleeding. Both the death and the gastrointestinal bleeding were likely related to rapid disease progression and occult metastases invading the gastrointestinal tract, respectively. Overall, 10 patients received pazopanib 600 mg for the majority of their time on treatment and appeared to tolerate this dose (with the exception of the 2 patients described above). Although a potential contribution of study drug to the serious AEs observed in the 2 patients receiving 600 mg during the cohort-expansion phase cannot be excluded, based on available data, pazopanib 600 mg QD was determined to be both the protocol-defined MTD and the recommended dose for further development in patients with advanced HCCs.

Notably, in view of the potential hepatotoxicity reported in the phase I pazopanib study (6), the current study specified that an increase of 2 or more in the Child–Pugh score was one of the criteria defining DLT if the liver toxicity was considered to be related to pazopanib. In fact, the frequency of transaminase and bilirubin elevations was higher in the current study than other pazopanib studies (6). This observed increase in the incidence of liver toxicities may be related to exacerbation of hepatic AEs in a population with underlying disease (HCC) that compromised liver
showed that patients with higher. Results from a previous pazopanib study (6) inhibition observed in clinical trials of anti-VEGF therapy 39%), which is a predominant AE associated with VEGF markedly higher rate of developing hypertension (77% vs. comparison are limited by sample size, differences in Nevertheless, it is important to note that such cross-study frequency in this study than that reported for sorafenib. Preliminary clinical activity was observed with pazopanib in this study of patients with HCCs. The overall response rate was 8% and the median PFS was 17.7 weeks. Overall, 73% of patients had a best response of either a partial response or stable disease while on pazopanib treatment, and among patients with elevations in baseline AFP, those with a 20% or greater decline in AFP seemed to benefit more from pazopanib treatment than patients without this decline. Notably, at the time this study was conducted, RECIST guidelines remain the standard for assessing tumor response (15). As yet, there is no consensus in the HCC community about whether modified RECIST would be a better method to assess response in patients with HCC receiving targeted therapy alone. Nevertheless, there may be an even higher rate of radio-logic response if the results of the study are evaluated account tumor necrosis.

To measure the changes in HCC tumor vessel function, we used DCE-MRI, a technique widely used to evaluate changes in the vasculature in response to antiangiogenic therapies. Parameters such as Ktrans are considered related to vascular permeability and are considered biomarker candidates because they can detect functional changes in tumor vasculature after treatment with anti-VEGF agents (24–27). To our

<table>
<thead>
<tr>
<th>Table 4. Pharmacokinetic/pharmacodynamic relationships with respect to pazopanib dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pazopanib dose, mg</strong></td>
</tr>
<tr>
<td>200 (n = 4)</td>
</tr>
<tr>
<td>C24a, μg/mL</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Minimum-maximum</td>
</tr>
<tr>
<td>Ktrans, % change</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Minimum-maximum</td>
</tr>
<tr>
<td>IAUGC60, % change</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Minimum-maximum</td>
</tr>
<tr>
<td>Number of days on study, a, d</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Minimum-maximum</td>
</tr>
</tbody>
</table>

aC24 was defined as the predose plasma drug concentration on day 15. b n = 10. c n = 6. d n = 4. e n = 5. f n = 4. aNumber of days on study counts the number of days from first dose to last dose of study drug.
knowledge, this is one of the few published studies to evaluate functional changes in HCC tumor vasculature in response to a range of doses of an antiangiogenic agent. Notably, in the current study, the extent of decrease in both \(K_{\text{trans}}\) and IAUGC was greater in patients with clinical benefit, suggesting that control of vessel leakage may be a determinant of HCC tumor response to pazopanib. However, the predictive value of imaging biomarkers remains to be standardized and validated in larger studies.

In conclusion, we established a tolerable dose of pazopanib and provided initial evidence of antitumor activity in selected patients with advanced HCCs. Pazopanib reduces tumor vessel leakage, as estimated by DCE-MRI, indicating a direct effect on HCC vasculature that might be associated with clinical benefit. With the manageable safety profile of pazopanib showed in this study of selected patients with HCCs, further evaluation of pazopanib in phase II trials is warranted.

**Disclosure of Potential Conflicts of Interest**

T. Yau has participated in advisory boards for Bayer and Pfizer, for which he was compensated, but he reports no honoraria, research funding, or other remuneration. P.J. Chen has received honoraria from Novartis and Bristol-Myers Squibb for advisory/consultancy relationships, and has received research funding from GlaxoSmithKline and Abbott. C.M. Curtis, P.S. Murphy, A.B. Suttle, J. Gauvin, J.P. Hodge, and M.M. Dar are employed by GlaxoSmithKline and own company stock. P. Chan and R.T. Poon report no potential conflict of interest.

**Acknowledgments**

Imaging was supported by Frank Stornanti, Perceptive Informatics, Billerica, and Dr. Brandon Whitcher, GlaxoSmithKline Clinical Imaging Centre, London. Image analysis was conducted by Dr. Caleb Roberts and Professor Geoff Parker, Imaging Science and Biomedical Engineering, University of Manchester. We thank Bret Wing, PhD, ProEd Communications, Inc., for his medical editorial assistance with the manuscript.

**Grant Support**

This study was sponsored by GlaxoSmithKline Research and Development and GlaxoSmithKline provided funding for medical editorial assistance and financial support for this study; medical editorial assistance was provided by GlaxoSmithKline Pharmaceuticals, Philadelphia, PA.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received March 24, 2011; revised July 30, 2011; accepted August 1, 2011; published OnlineFirst August 10, 2011.
References


Phase I Dose-Finding Study of Pazopanib in Hepatocellular Carcinoma: Evaluation of Early Efficacy, Pharmacokinetics, and Pharmacodynamics

Thomas Yau, Pei-Jer Chen, Pierre Chan, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-11-0793

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2011/08/10/1078-0432.CCR-11-0793.DC1

Cited articles
This article cites 26 articles, 15 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/17/21/6914.full.html#ref-list-1

Citing articles
This article has been cited by 3 HighWire-hosted articles. Access the articles at:
/content/17/21/6914.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.