Pazopanib in Locally Advanced or Metastatic Renal Cell Carcinoma: Results of a Randomized Phase III Trial


ABSTRACT

Purpose
Pazopanib is an oral angiogenesis inhibitor targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-Kit. This randomized, double-blind, placebo-controlled phase III study evaluated efficacy and safety of pazopanib monotherapy in treatment-naïve and cytokine-pretreated patients with advanced renal cell carcinoma (RCC).

Patients and Methods
Adult patients with measurable, locally advanced, and/or metastatic RCC were randomly assigned 2:1 to receive oral pazopanib or placebo. The primary end point was progression-free survival (PFS). Secondary end points included overall survival, tumor response rate (Response Evaluation Criteria in Solid Tumors), and safety. Radiographic assessments of tumors were independently reviewed.

Results
Of 435 patients enrolled, 233 were treatment naive (54%) and 202 were cytokine pretreated (46%). PFS was significantly prolonged with pazopanib compared with placebo in the overall study population (median, PFS 9.2 v 4.2 months; hazard ratio [HR], 0.46; 95% CI, 0.34 to 0.62; P < .0001), the treatment-naïve subpopulation (median PFS 11.1 v 2.8 months; HR, 0.40; 95% CI, 0.27 to 0.60; P < .0001), and the cytokine-pretreated subpopulation (median PFS, 7.4 v 4.2 months; HR, 0.54; 95% CI, 0.35 to 0.84; P < .001). The objective response rate was 30% with pazopanib compared with 3% with placebo (P < .001). The median duration of response was longer than 1 year. The most common adverse events were diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting. There was no evidence of clinically important differences in quality of life for pazopanib versus placebo.

Conclusion
Pazopanib demonstrated significant improvement in PFS and tumor response compared with placebo in treatment-naïve and cytokine-pretreated patients with advanced and/or metastatic RCC.

INTRODUCTION

In the United States, there were 39,226 new cases of renal cell carcinoma (RCC) and 10,662 deaths estimated in 2008.1 In the European Union, RCC accounts for approximately 3% of all cancers in males and 2% in females.2 Approximately 90% of kidney cancers are RCCs, and 70% to 80% of these are of clear-cell histology.3,4 Renal cell carcinoma is inherently resistant to cytotoxic therapy, radiation, or hormone therapy.4,6 Before the recent advent of angiogenesis inhibitors, cytokine-based therapy including interferon-α (IFN-α) and/or interleukin-2 (IL-2) were the mainstay of treatment for advanced RCC, despite limited clinical activity and significant toxicity.5,6 Advances in the understanding of RCC tumor biology, including the role of vascular endothelial growth factor and mammalian target of rapamycin pathways, led to the successful clinical development of several agents including sorafenib,7 sunitinib,8 bevacizumab (plus IFN-α),9,10 temsirolimus,11 and everolimus12 for treatment of RCC.

Pazopanib is an oral angiogenesis inhibitor targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-Kit.13-16 Pazopanib is under clinical development for the treatment of multiple tumor types and has demonstrated monotherapy activity in patients with RCC in phase I/II trials.14-16 This randomized, double-blind, placebo-controlled phase III study evaluated the efficacy and safety of...
Patients

This study initially enrolled patients with advanced and/or metastatic RCC who had progressed on one prior cytokine-based systemic therapy. The protocol was subsequently amended to include treatment-naive patients (after enrollment of seven patients) because of emerging evidence of activity of angiogenesis inhibitors and decreased use of cytokines in the first-line setting. Patients without prior systemic therapy could be enrolled provided they were living in countries where there were barriers to the access of established therapies such as sunitinib, sorafenib, IFN-α, or IL-2 or where cytokines were not recognized as standard treatment for RCC.

Additional eligibility criteria included a diagnosis of clear-cell or predominantly clear-cell histology; measurable disease per Response Evaluation Criteria in Solid Tumors17; age dominantly clear-cell histology; measurable disease per Response Evaluation Criteria in Solid Tumors17; age 18 years; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1; and adequate renal, hepatic, and hematologic function. Patients were excluded if they had CNS metastasis; leptomeningeal lesions; poorly controlled hypertension (systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg, despite antihypertensive therapy); QTc interval ≥ 470 milliseconds; or a history of the following cardiac and vascular conditions within 6 months of screening: class III/IV congestive heart failure per New York Heart Association classification, cardiogenic shock, myocardial infarction, unstable angina, or cerebrovascular accident. The study was approved by local institutional review boards and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before study-related procedures were performed.

Study Design

Study VEG105192 (clinicaltrials.gov identifier NCT00334282) was a placebo-controlled, randomized, double-blind, global, multicenter, phase III study. Randomization was stratified on the basis of ECOG PS (0 vs 1), prior nephrectomy (yes vs no), and prior systemic treatment for advanced RCC (treatment naive vs cytokine pretreated). Patients were centrally randomly assigned in a 2:1 ratio to receive either 800 mg pazopanib once daily or matching placebo. Study medications were administered orally 1 hour before or 2 hours after meals. Dose modification guidelines for adverse events (AEs) were prespecified.

Patients received continuous treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any reason. Subsequent anticancer therapy for patients with progressive disease was at the discretion of the patients and their physicians. Patients who progressed were unblinded, and if found to be on placebo, had the option of receiving pazopanib via an open-label study (VEG107769), provided they met predefined eligibility criteria. Seventy-four (48%) of 145 placebo-arm patients enrolled in VEG107769. An independent data-monitoring committee was established to monitor safety and review interim overall survival data.

End Points and Assessments

The primary end point was progression-free survival (PFS), defined as the time interval between the date of random assignment and the date of progression or death. The principal secondary end point was overall survival (OS), defined as the time interval between the date of random assignment and date of death. Other secondary end points included confirmed objective response rate (complete response [CR] plus partial response [PR]), duration of response, and safety. Health-related quality of life (HRQoL) was also assessed.

Disease assessments using computed tomography or magnetic resonance imaging were performed at baseline, every 6 weeks until week 24, and every 8 weeks thereafter until progression. Bone scans were performed at least every 24 weeks in all patients and on confirmation of objective response. Objective responses were confirmed at the next scheduled disease-assessment visit. Patients who discontinued study treatment before disease progression were to continue disease assessments until progression or initiation of an alternate anticancer treatment. All imaging scans were evaluated by an independent imaging-review committee (IRC) blinded to study treatment. Tumor response evaluations by the investigators and the IRC were based on Response Evaluation Criteria in Solid Tumors.17 Follow-up for OS was performed every 3 months after disease progression until death or study withdrawal.

Clinical assessments for safety, including physical examinations, vital signs (with blood pressure monitoring), clinical laboratory evaluations, ECG, ECOG PS, and AEs, were evaluated at baseline, day 8, every 3 weeks until week 24, and every 4 weeks thereafter until study treatment discontinuation. Thyroid function tests were performed every 12 weeks and if thyroid-stimulating hormone levels were abnormal, evaluations of free triiodothyronine/thyroxine levels were prespecified.

PATIENTS AND METHODS

<table>
<thead>
<tr>
<th>Reason for discontinuation</th>
<th>Discontinued study treatment</th>
<th>Analyzed for PFS</th>
<th>Analyzed for safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression</td>
<td>(n = 147; 51%)</td>
<td>(n = 290)</td>
<td>(n = 290)</td>
</tr>
<tr>
<td>Death</td>
<td>(n = 11; 4%)</td>
<td></td>
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<tr>
<td>AE*</td>
<td>(n = 41; 14%)</td>
<td></td>
<td></td>
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<tr>
<td>Protocol violation</td>
<td>(n = 2; &lt; 1%)</td>
<td></td>
<td></td>
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<tr>
<td>Investigator decision</td>
<td>(n = 8; 3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up, withdrew consent, and other</td>
<td>(n = 18; 6%)</td>
<td>(n = 290)</td>
<td>(n = 290)</td>
</tr>
<tr>
<td>Randomly assigned to pazopanib</td>
<td>(n = 290)</td>
<td>(n = 290)</td>
<td></td>
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<tr>
<td>Received pazopanib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomly assigned to placebo</td>
<td>(n = 145)</td>
<td>(n = 145)</td>
<td></td>
</tr>
<tr>
<td>Received placebo</td>
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</table>

Fig 1. CONSORT diagram. AE, adverse event; PFS, progression-free survival. (*) This does not include three patients who, in addition to AEs, had concurrent other reasons at the time they discontinued participation in the study.
were obtained. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0.18

Patient-reported HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTCQLQ-C30 version 3) and the EuroQol (EQ-5D) questionnaires at baseline and at weeks 6, 12, 18, 24, and 48.

**Statistical Methods and Analysis**

Target enrollment and event requirements were defined to provide at least 90% power to detect an 80% improvement (hazard ratio [HR], 0.56) in PFS (primary endpoint) and 90% power to detect a 50% improvement (HR, 0.67) in OS (secondary endpoint). After the amendment to include treatment-naive patients, PFS event requirements were amended to additionally provide approximately 80% power to detect an 80% improvement (HR, 0.56) or 90% power to detect a 100% improvement (HR, 0.5) in PFS in each subgroup (ie, treatment naive and cytokine pretreated).

There were no planned (or unplanned) interim analyses for PFS. An interim analysis of OS was to be performed at the time of the final PFS analysis. Thus, the sample size calculation for OS included one planned interim analysis (after 70% of the required deaths) using flexible O’Brien-Fleming type error spending functions for superiority and futility. All sample size calculations were performed assuming a one-sided 2.5% α and a 2:1 randomization.

Based on the above requirements, final PFS analysis was planned to be performed after at least 90 PFS events (by IRC) in each subgroup and at least 160 deaths; final analysis of OS was planned to be performed after 287 deaths. The resulting planned enrollment of the study was a total of 400 patients with 150 to 250 patients in each subgroup.

Efficacy end points were analyzed in all patients randomized to a treatment arm according to the intention-to-treat principle. Safety analyses were performed on the basis of the actual treatment received in patients who were randomized and received ≥ one dose of investigational product.

Kaplan-Meier methods were used to analyze PFS and OS. Comparisons between arms were made using a log-rank test (one sided) stratified by ECOG PS and prior therapy. Hazard ratios were calculated using a stratified Pike estimator utilizing the same factors. The primary analysis of PFS was based on IRC assessments. Progression and censoring dates for the primary analysis were assigned to the visit time point for scheduled visits. Progressions found at unscheduled visits were assigned to the next scheduled visit time point to adjust for any unplanned deviations from the protocol-defined visit schedule, as agreed to with the United States Food and Drug Administration during the study-design process. Nine predefined sensitivity analyses of PFS were performed to confirm the robustness of the primary result using various assumptions, including alternate definitions of progression and censoring dates, data sources (IRC v investigator), and analysis methods. Comparison of PFS between treatment arms was done using the log-rank test in predefined subgroup analyses based on prior treatment, age, sex, Memorial Sloan-Kettering Cancer Center (MSKCC) risk group,19 and ECOG PS. Approximate 95% CIs for response rate (RR) differences were calculated. Duration of response and time to response were summarized descriptively using medians and quartiles.

A mixed-model repeated-measures analysis of change from baseline was performed for QoL measures that were collected by blinded patient self-reports using the EORTC QLQ-C30 and EQ-5D questionnaires.20,21 The key end points for these analyses were summary scores from these questionnaires that included the EORTC QLQ-Global Health Status/QoL Score, EQ-5D Index, and EQ-5D visual analog scale (VAS). The minimal important differences (MID) for these questionnaires were previously established as 5 to 10 for EORTC QLQ-C30,22 0.08 for EQ-5D Index, and 7 for EQ-5D VAS.23

### RESULTS

**Patients**

Of 435 patients with advanced and/or metastatic RCC (233 treatment naive; 202 cytokine pretreated) were enrolled between April 2006 and April 2007 from 80 centers in Europe, Asia, South America, North Africa, Australia, and New Zealand; 290 patients were randomly assigned to pazopanib and 145 were randomly assigned to placebo.

At the cutoff date (May 23, 2008), 78% of patients in the pazopanib arm and 90% of patients in the placebo arm had discontinued study treatment. Disease progression was the most common reason for death and discontinuation (Fig 1). Demographic and disease characteristics were well balanced between treatment arms (Table 1). All patients had clear cell or predominantly clear-cell histology.

<table>
<thead>
<tr>
<th>Table 1. Patient Demographics and Disease Characteristics</th>
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<tbody>
<tr>
<td><strong>Parameter</strong></td>
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<tr>
<td><strong>Median age, years</strong></td>
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<tr>
<td><strong>Range</strong></td>
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<tr>
<td><strong>Sex</strong></td>
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<td><strong>Male</strong></td>
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<td><strong>Female</strong></td>
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<tr>
<td><strong>Race</strong></td>
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<td><strong>White</strong></td>
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<tr>
<td><strong>Asian</strong></td>
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<tr>
<td><strong>Other</strong></td>
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<tr>
<td><strong>Histology</strong></td>
</tr>
<tr>
<td><strong>Clear cell</strong></td>
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<tr>
<td><strong>Favorable</strong></td>
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<tr>
<td><strong>Predominantly clear cell</strong></td>
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<tr>
<td><strong>Prostate</strong></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td><strong>Histology at initial diagnosis, months</strong></td>
</tr>
<tr>
<td><strong>Range</strong></td>
</tr>
<tr>
<td><strong>Most common sites of metastasis</strong></td>
</tr>
<tr>
<td><strong>Lung</strong></td>
</tr>
<tr>
<td><strong>Lymph nodes</strong></td>
</tr>
<tr>
<td><strong>Bone</strong></td>
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<tr>
<td><strong>Liver</strong></td>
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<tr>
<td><strong>Kidney</strong></td>
</tr>
<tr>
<td><strong>No. of organs involved</strong></td>
</tr>
<tr>
<td><strong>1</strong></td>
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<tr>
<td><strong>2</strong></td>
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<tr>
<td><strong>≥ 3</strong></td>
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<td><strong>ECOG performance status</strong></td>
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<tr>
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<tr>
<td><strong>1</strong></td>
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<tr>
<td><strong>2</strong></td>
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<tr>
<td><strong>3</strong></td>
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<tr>
<td><strong>Unknown</strong></td>
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<tr>
<td><strong>MSKCC risk category</strong></td>
</tr>
<tr>
<td><strong>Favorable</strong></td>
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<td><strong>Intermediate</strong></td>
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<td><strong>Poor</strong></td>
</tr>
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</tr>
<tr>
<td><strong>Prior nephrectomy</strong></td>
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<tr>
<td><strong>Prior systemic treatment</strong></td>
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<tr>
<td><strong>Treatment naive</strong></td>
</tr>
<tr>
<td><strong>Cytokine pretreated</strong></td>
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</tbody>
</table>

**Abbreviations:** ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center.

1. Histology at initial diagnosis was missing for one patient in the pazopanib arm.
2. As defined by the investigator.
3. One hundred eight of the MSKCC risk group assignments required the use of total calcium measurements because of missing baseline albumin levels to calculate corrected calcium.
4. Patients with an unknown MSKCC risk category were missing results for death and discontinuation.

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Efficacy: PFS

At the final PFS analysis, 148 patients progressed on pazopanib and 98 patients progressed on placebo, based on independent review. In the treatment-naive and cytokine-pretreated subpopulations, 130 and 116 PFS events were recorded, respectively. Pazopanib significantly prolonged PFS compared with placebo in the overall study population (median PFS, 9.2 vs 4.2 months; HR, 0.46; 95% CI, 0.34 to 0.62; \( P < .0001 \)), the treatment-naive subpopulation (median PFS, 11.1 vs 2.8 months; HR, 0.40; 95% CI, 0.27 to 0.60; \( P < .0001 \)), and the cytokine-pretreated subpopulation (median PFS, 7.4 vs 4.2 months; HR, 0.54; 95% CI, 0.35 to 0.84; \( P < .001 \); Fig 2).

All nine sensitivity analyses of PFS confirmed the primary PFS result, with HR range of 0.42 to 0.49. In most cases, larger estimates of treatment effect by pazopanib (ie, lower HRs) were observed with the sensitivity analyses compared with the primary analysis, including PFS based on investigators’ assessment (HR, 0.44; 95% CI, 0.34 to 0.57; \( P < .0001 \)). The prespecified subgroup analyses showed that PFS was improved for patients treated with pazopanib compared with placebo regardless of MSKCC risk category, sex, age, or ECOG PS (HR range, 0.40 to 0.52; \( P < .001 \) by log-rank test for all; Fig 3).

Tumor Response

The RR (by independent review) for pazopanib-treated patients in the overall study population was 30% (95% CI, 25.1 to 35.6), with a median duration of response of 58.7 weeks. A similar RR was seen in pazopanib-treated patients in the treatment-naive (32%) and cytokine-pretreated (29%) populations (Table 2). The investigator-assessed RR in the overall population (36%; 95% CI, 30.0 to 41.0; median duration of response of 62.4 weeks) is consistent with RR based on independent review.

Interim OS

The interim analysis of OS in the overall study population was based on 176 death events, which was 61% of the required 287 death events for the final OS analysis. The interim OS result did not cross the prespecified O’Brien-Fleming boundaries for either superiority or futility. Final OS results will be reported when data are mature.

Safety

The median duration of exposure to treatment was approximately double in the pazopanib arm compared with placebo (7.4 vs 3.8 months). At the time of data cutoff, 32% of patients on pazopanib and 15% of patients on placebo had received treatment for more than 12 months.

Most AEs were grade 1/2 (Table 3). Diarrhea (52%), hypertension (40%), hair color changes (38%), nausea (26%), anorexia (22%), and vomiting (21%) were the most common AEs reported in the pazopanib arm. Proportions of patients experiencing an AE with maximum grade of 3 or 4 were 33% and 7%, respectively, in the pazopanib arm compared with 14% and 6%, respectively, in the placebo arm. The most common grade 3/4 AEs in the pazopanib arm were hypertension (4%) and diarrhea (4%). The AE profile was similar in treatment-naive and cytokine-pretreated patients, although discontinuation rates because of AEs were higher in cytokine-pretreated (19%) compared with treatment-naive (12%) patients.

Arterial thrombotic events occurred in 3% of pazopanib-treated patients (myocardial infarction/ischemia [2%], cerebrovascular accident [<1%], and transient ischemic attack [<1%]) compared with none in the placebo arm. The incidence of hemorrhagic events (all grades) in the pazopanib arm was 13% compared with 5% in the placebo arm.

Most laboratory abnormalities were grade 1/2 (Table 3). The most common clinical laboratory abnormalities observed in the pazopanib arm were ALT elevation and AST elevation. Elevations in
ALT ≥ 3× the upper limit of normal occurred in 52 pazopanib-treated patients (18%): ALT elevation recovered to ≤ grade 1 after dose modification, interruption, or discontinuation in 45 patients (87%); seven patients (13%) did not have adequate follow-up data to assess recovery.

Death resulting from AEs was reported in 4% of patients in the pazopanib arm and 3% of patients in the placebo arm. Four patients (1%) in the pazopanib arm had fatal AEs that were assessed by the investigator as attributable to study treatment: ischemic stroke, abnormal hepatic function and rectal hemorrhage, peritonitis/bowel perforation, and abnormal hepatic function (one patient each). The patient who died of peritonitis/bowel perforation had RCC metastasis present at the site of perforation. The later patient who died of abnormal hepatic function was found on autopsy to have extensive infiltration of the liver with metastatic disease.

**HRQoL**

Completion rates for QoL questionnaires were high across most of the assessment timepoints for each instrument (> 90%). The longitudinal means for the three QoL end points showed a trend for maintenance of QoL across time between treatment and placebo groups, with differences that were not clinically important according to established MID for the questionnaires. The mixed-model repeated-measures analyses showed no statistical differences between pazopanib and placebo at any of the assessment time points for the three key QoL end points (Table 4). There was a difference in the rate of withdrawal of patients from the placebo arm because of disease progression, which became apparent after week 6 and was especially evident at later assessment timepoints.

**DISCUSSION**

In this phase III trial, pazopanib demonstrated a significant improvement in PFS and RR compared with placebo in patients with advanced and/or metastatic RCC in the overall population and in the treatment-naive and cytokine-pretreated subpopulations. The efficacy of pazopanib observed in this study confirms results observed in a previous phase II trial in patients with advanced RCC (VEG102616; median PFS, 11.9 months; RR, 35%; median duration of response, 68 weeks). The effects of PFS and RR in the treatment-naive subpopulation observed in this phase III trial are comparable to published data for sunitinib and bevacizumab (with IFN-α). The later effects of PFS and RR in the treatment-naive subpopulation observed in this phase III trial are comparable to published data for sunitinib and bevacizumab (with IFN-α).

When this study was initiated in April 2006, limited access to the multikinase inhibitors sunitinib and sorafenib precluded the use of either as a comparator. Therefore, placebo with best supportive care was considered an appropriate comparator for cytokine-pretreated patients.
In conclusion, once-daily oral pazopanib significantly improved PFS and RR in treatment-naive and cytokine-pretreated patients with advanced and/or metastatic RCC. Furthermore, pazopanib was well tolerated in this population. These findings support the continued evaluation of the efficacy, safety, and effect on QoL of pazopanib in this patient population. A phase III trial comparing pazopanib monotherapy with sunitinib in treatment-naive patients occurred with an incidence of fewer than 10% each, with grade 3/4 events reported in less than 1% of patients. It is notable in the current analysis that patients who were treated with pazopanib did not have a clinically important difference (relative to the MID) in QoL compared with placebo in blinded patient self-reports, despite toxicities that may be expected with an active agent. These results are consistent with the observed tolerability profile for pazopanib, which is particularly important because patients with RCC are often asymptomatic when therapy is initiated and may remain on therapy for prolonged periods of time. Although some AEs observed with pazopanib are related to target inhibition, others may result from off-target activity. Potential differences in the safety profiles of multikinase inhibitors may be explained by differences in the potency and selectivity of kinases inhibited.\textsuperscript{24} Pazopanib, although an inhibitor of c-Kit, is not a potent inhibitor of fms-related tyrosine kinase 3,\textsuperscript{25} which may explain the low rate (\textless 1%) of grade 3/4 cytopenias observed with pazopanib.

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|c|c|c|c|c|c|c|}
\hline
\textbf{Parameter} & \multicolumn{4}{c|}{\textbf{Pazopanib (n = 290)}} & \multicolumn{4}{c|}{\textbf{Placebo (n = 145)}} \\
\hline
 & \textbf{Any}\textsuperscript{a} & \textbf{3} & \textbf{4} & \textbf{Any}\textsuperscript{a} & \textbf{3} & \textbf{4} & \textbf{3} & \textbf{4} \\
\hline
\textbf{Adverse event} & & & & & & & & & & & & \\
Diarrhea & 150 & 52 & 9 & 3 & 2 & <1 & 13 & 9 & 1 & <1 & 0 & \\
Hypertension & 115 & 40 & 13 & 4 & 0 & 15 & 10 & 1 & <1 & 0 & \\
Hair color changes & 109 & 38 & 1 & <1 & 0 & 4 & 3 & 0 & & & & \\
Nausea & 74 & 26 & 2 & <1 & 0 & 13 & 9 & 0 & & & & \\
Anorexia & 65 & 22 & 6 & 2 & 1 & <1 & 14 & 10 & 1 & <1 & 0 & \\
Vomiting & 61 & 21 & 6 & 2 & 1 & <1 & 11 & 8 & 3 & 2 & 0 & \\
Fatigue & 55 & 19 & 7 & 2 & 0 & 11 & 8 & 2 & 1 & 2 & 1 & \\
Asthenia & 41 & 14 & 8 & 3 & 0 & 12 & 8 & 0 & & & & \\
Abdominal pain & 32 & 11 & 6 & 2 & 0 & 2 & 1 & 0 & & & & \\
Headache & 30 & 10 & 0 & & & 7 & 5 & 0 & & & & \\
\hline
\textbf{Clinical chemistry} & & & & & & & & & & & & \\
ALT increase & 152 & 53 & 30 & 10 & 5 & 2 & 32 & 22 & 2 & 1 & 0 & \\
AST increase & 152 & 53 & 21 & 7 & 2 & <1 & 27 & 19 & 1 & <1 & 0 & \\
Hyperglycemia & 115 & 41 & 2 & <1 & 0 & 47 & 33 & 2 & 1 & 0 & \\
Total bilirubin increase & 102 & 36 & 7 & 3 & 2 & <1 & 15 & 10 & 2 & 1 & 1 & <1 & \\
Hypophosphatemia & 95 & 34 & 11 & 4 & 0 & 16 & 11 & 0 & & & & \\
Hypocalcemia & 91 & 33 & 4 & 1 & 4 & 1 & 35 & 26 & 2 & 1 & 1 & <1 & \\
Hypomagnesemia & 86 & 31 & 11 & 4 & 4 & 1 & 35 & 24 & 6 & 4 & 0 & \\
Hypoglycemia & 31 & 11 & 9 & 3 & 0 & 13 & 9 & 3 & 2 & 0 & \\
Headache & 47 & 17 & 0 & 1 & <1 & 4 & 3 & 0 & & & & \\
\hline
\textbf{Hematologic} & & & & & & & & & & & & \\
Leukopenia & 103 & 37 & 0 & & & 9 & 6 & 0 & & & & \\
Neutropenia & 94 & 34 & 3 & 1 & 1 & <1 & 9 & 6 & 0 & & & & \\
Thrombocytopenia & 89 & 32 & 2 & <1 & 1 & <1 & 7 & 5 & 0 & & & 1 & <1 & \\
Lymphocytopenia & 86 & 31 & 11 & 4 & 1 & <1 & 34 & 24 & 2 & 1 & 0 & \\
\hline
\end{tabular}
\caption{Common Treatment-Emergent Adverse Events\textsuperscript{a} and Selected Clinical Laboratory Abnormalities\textsuperscript{a} in Patients With At Least One Adverse Event}
\textsuperscript{a}Adverse events with an incidence of \textless 10% in the pazopanib arm are displayed. \textsuperscript{a}Clinical laboratory abnormalities with an incidence of \textless 10% in the pazopanib arm or with a 5% increase in incidence in the pazopanib arm compared with the placebo arm are displayed.
\end{table}
with advanced and/or metastatic RCC is ongoing (clinicaltrials.gov identifier NCT00720941).

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** Mei Chen, GlaxoSmithKline (C); Lauren McCann, GlaxoSmithKline (C); Lini Pandite, GlaxoSmithKline (C)

**Consultant or Advisory Role:** Ian D. Davis, GlaxoSmithKline (C), Pfizer (C), Wyeth (C), Novartis (C), Bayer Pharmaceuticals (C), Celzary Szczylki, Pfizer (C), Bayer Pharmaceuticals (C), John Wagstaff, GlaxoSmithKline (C); Carlos H. Barrios, GlaxoSmithKline (C); Pamela Salman, Merck (C)

**Ownership:** Mei Chen, GlaxoSmithKline; Lauren McCann, GlaxoSmithKline; Lini Pandite, GlaxoSmithKline; Debasish F. Roychowdhury; Robert E. Hawkins, GlaxoSmithKline

**Honoraria:** Cora N. Sternberg, GlaxoSmithKline; Cezary Szczylki, Bayer Pharmaceuticals, Roche, Pfizer; Carlos H. Barrios, GlaxoSmithKline; Robert E. Hawkins, GlaxoSmithKline

**Research Funding:** Cora N. Sternberg, GlaxoSmithKline; Ian D. Davis, GlaxoSmithKline; Cezary Szczylki, Bayer Pharmaceuticals; Carlos H. Barrios, GlaxoSmithKline

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**Sale of Product:** Cora N. Sternberg, GlaxoSmithKline; Mei Chen, GlaxoSmithKline; Lini Pandite, GlaxoSmithKline; Debasish F. Roychowdhury

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**Other Remuneration:** None

**REFERENCES**


