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ORIGINAL REPORT

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

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Clinical Trials repository link available on JCO.org.

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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-naive 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-naive 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-naive and cytokine-pretreated patients with advanced and/or metastatic RCC.

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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,[8,9] bevacizumab (plus IFN-α),[10,11] temsirolimus,[12] and everolimus[13] for treatment of RCC.

Pazopanib is an oral angiogenesis inhibitor targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-Kit.[14-16] 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

pazopanib monotherapy in treatment-naive and cytokine-pretreated patients with advanced and/or metastatic RCC.

PATIENTS AND METHODS

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 Tumors[17]; age $\geq$ 18 years; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$ 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 $\geq$ 140 mmHg or diastolic blood pressure of $\geq$ 90 mmHg, despite antihypertensive therapy); QTc interval $\geq$ 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, cardiac angioplasty or stenting, 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 *v* 1), prior nephrectomy (yes *v* no), and prior systemic treatment for advanced RCC (treatment naive *v* 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 (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

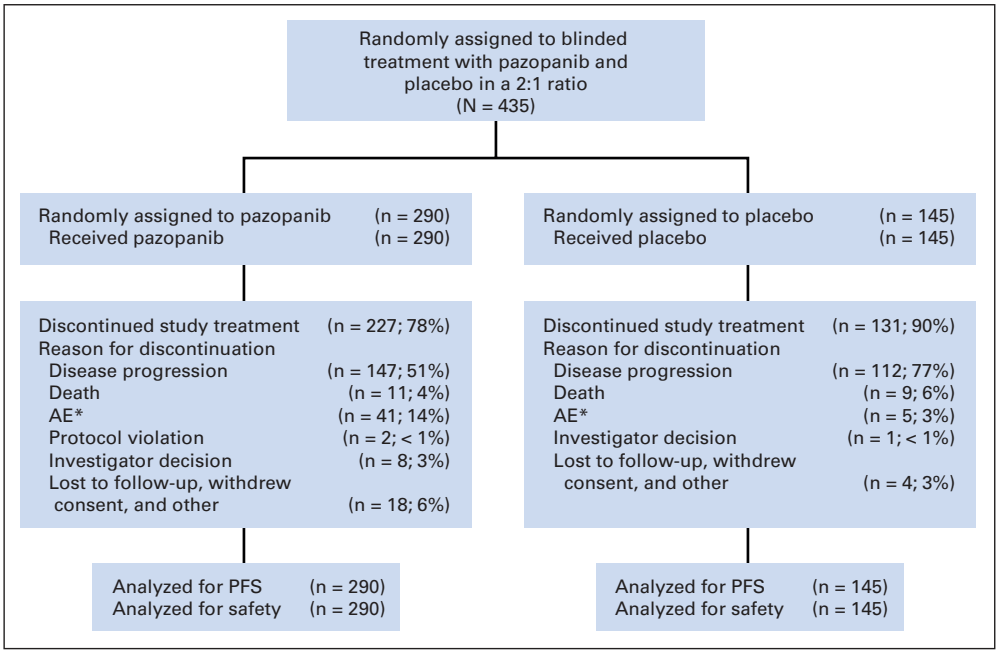

Fig 1. CONSORT diagram. AE, adverse event; PFS, progression-free survival. (*) This does not include three patients who, in addition to AEs, had concurrent other reasons at the time they discontinued participation in the study.

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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 (EORTC QLQ-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 end point) and 90% power to detect a 50% improvement (HR, 0.67) in OS (secondary end point). 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 subpopulation (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 subpopulation 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 subpopulation.

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 $\geq$ 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 1. Patient Demographics and Disease Characteristics

Parameter	Pazopanib (n = 290) No.	%	Placebo (n = 145) No.	%
Median age, years	59		60	
Range	28-85		25-81	
Sex				
Male	198	68	109	75
Race				
White	252	87	122	84
Asian	36	12	23	16
Black	1	< 1	0	
Other	1	< 1	0	
Histology*				
Clear cell	264	91	129	89
Predominantly clear cell	25	9	16	11
Median time since initial diagnosis, months	15.7		13.8	
Range	0-184.0		1.0-152	
Most common sites of metastasis†				
Lung	214	74	106	73
Lymph nodes	157	54	86	59
Bone	81	28	38	26
Liver	75	26	32	22
Kidney	66	23	36	25
No. of organs involved†				
1	53	18	20	14
2	78	27	50	34
$\geq$ 3	159	55	75	52
ECOG performance status				
0	123	42	60	41
1	167	58	85	59
MSKCC risk category‡				
Favorable	113	39	57	39
Intermediate	159	55	77	53
Poor	9	3	5	3
Unknown§	9	3	6	4
Prior nephrectomy	258	89	127	88
Prior systemic treatment				
Treatment naïve	155	53	78	54
Cytokine pretreated	135	47	67	46

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

*Histology at initial diagnosis was missing for one patient in the pazopanib arm.

†As defined by the investigator.

‡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.

§Patients with an unknown MSKCC risk category were missing results for one or more of the five risk criteria.

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 *v* 4.2 months; HR, 0.46; 95% CI, 0.34 to 0.62; $P < .0001$), the treatment-naive 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; $P < .001$; 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 *v* 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.

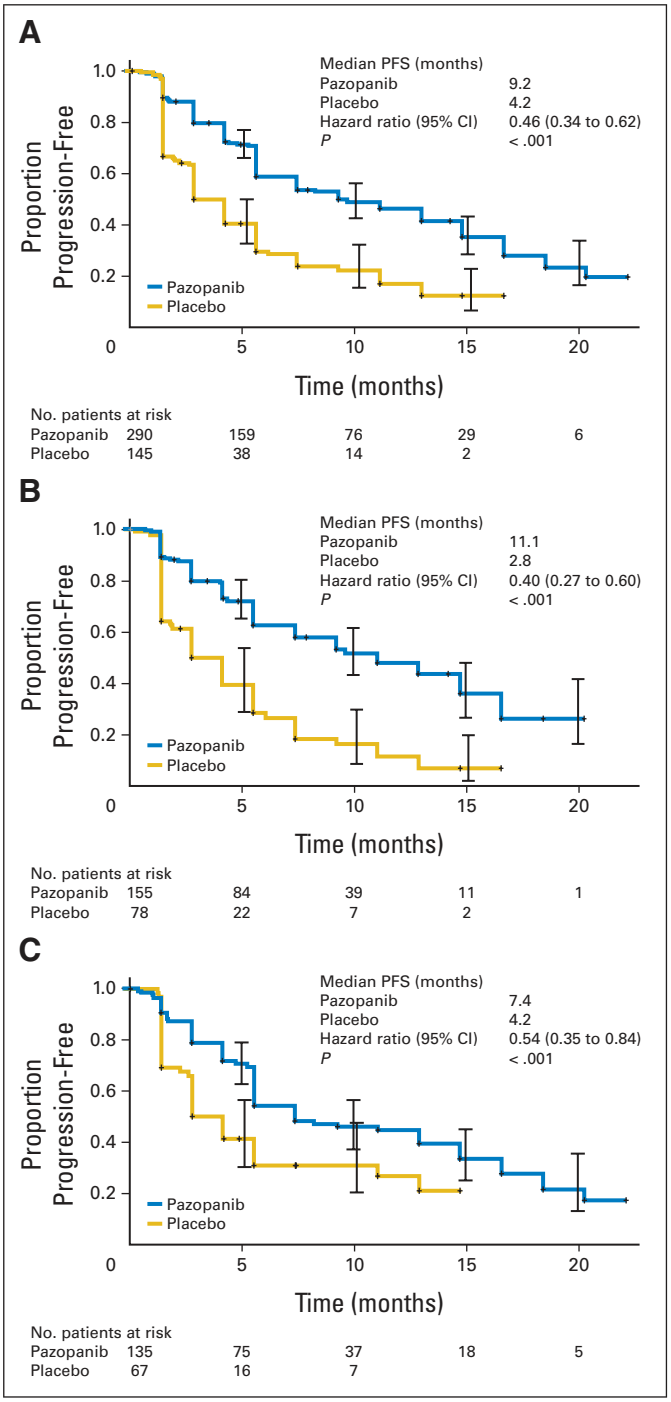

Fig 2. Kaplan-Meier survival curve of progression-free survival (PFS) by independent review in (A) overall study population, (B) treatment-naive population, and (C) cytokine-pretreated population. The difference in median PFS between cytokine-naive and cytokine-pretreated placebo patients is an artifact of the visit-based analysis.

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

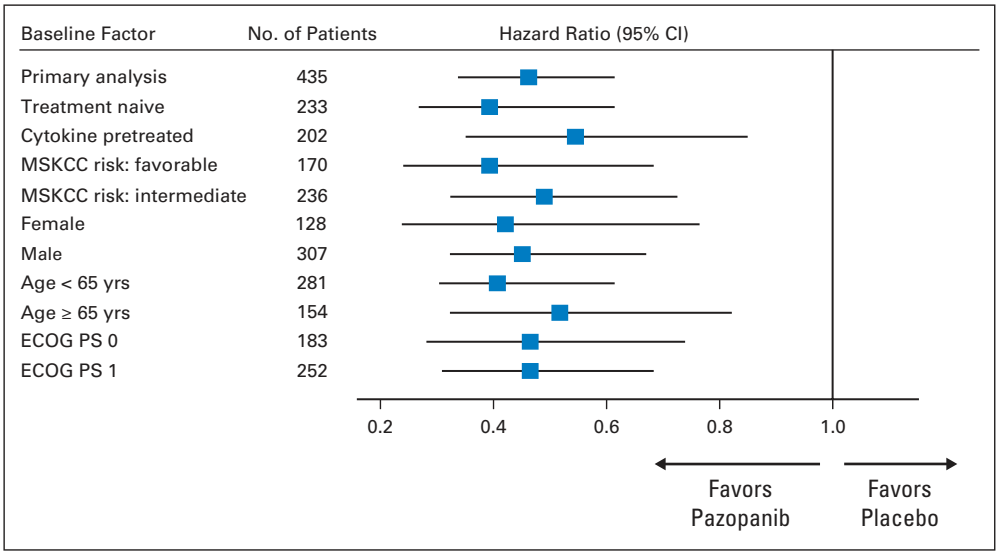

Fig 3. Predefined subgroup analysis of progression-free survival per independent review. MSKCC, Memorial Sloan-Kettering Cancer Center; ECOG PS, Eastern Cooperative Oncology Group performance status.

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.

Table 2. Summary of Tumor Response by Independent Review

Parameter	Pazopanib (n = 290) No.	Pazopanib (n = 290) %	Placebo (n = 145) No.	Placebo (n = 145) %
Overall study population				
Best response				
Complete response	1	< 1	0	
Partial response	87	30	5	3
Stable disease	110	38	59	41
Progressive disease	51	18	58	40
Unknown*	41	14	23	16
Response rate (CR + PR)	88†	30	5	3
95% CI	25.1 to 35.6		0.5 to 6.4	
Median duration of response, weeks	58.7		—	
95% CI	52.1 to 68.1		—	
Median time to response, weeks	11.9		—	
95% CI	9.4 to 12.3		—	
Treatment-naive subgroup	155		78	
Response rate (CR + PR)	49	32	3	4
95% CI	24.3 to 38.9		0.0 to 8.1	
Cytokine-pretreated subgroup	135		67	
Response rate (CR + PR)	39	29	2	3
95% CI	21.2 to 36.5		0.0 to 7.1	

Abbreviations: CR, complete response; PR, partial response.
*A patient was classified as unknown if he or she never had progressive disease and did not have stable disease for at least 12 weeks (the minimum requirement to be classified as stable disease). This includes patients with no follow-up and some patients censored by independent review.
†$P < .001$, based on Fisher's exact test comparison of treatment arms.

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).[16] 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).[8,10,11]

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

Table 3. Common Treatment-Emergent Adverse Events* and Selected Clinical Laboratory Abnormalities† in Patients With At Least One Adverse Event

	Grade											
	Pazopanib (n = 290)						Placebo (n = 145)					
	Any*		3		4		Any *		3		4	
Parameter	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
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		0	
Nausea	74	26	2	< 1	0		13	9	0		0	
Anorexia	65	22	6	2	0		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		0	
Abdominal pain	32	11	6	2	0		2	1	0		0	
Headache	30	10	0		0		7	5	0		0	
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		0	
Hypocalcemia	91	33	4	1	4	1	35	26	2	1	1	< 1
Hyponatremia	86	31	11	4	4	1	35	24	6	4	0	
Hypomagnesemia	31	11	9	3	0		13	9	3	2	0	
Hypoglycemia	47	17	0		1	< 1	4	3	0		0	
Hematologic												
Leukopenia	103	37	0		0		9	6	0		0	
Neutropenia	94	34	3	1	1	< 1	9	6	0		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	

*Adverse events with an incidence of ≥ 10% in the pazopanib arm are displayed.
†Clinical laboratory abnormalities with an incidence of ≥ 30% in the pazopanib arm or with a 5% increase in incidence in the pazopanib arm compared with the placebo arm are displayed.

patients. In addition, using a placebo control in a randomized double-blind design enabled better characterization of the safety and efficacy profile of pazopanib. When the protocol was amended to allow enrollment of treatment-naive patients, placebo with best supportive care was retained as the control arm. (Criteria for enrolling treatment-naive patients are described in detail in the Patients and Methods section.) Moreover, cytokines as a standard of care were being challenged in some participating countries, based on their unfavorable risk-benefit profile[24,25] and emerging data for multikinase inhibitors. Exposure of patients to placebo in the study was minimized by 2:1 random assignment, and pazopanib was provided as a treatment option for patients who progressed on placebo.

Pazopanib demonstrated acceptable safety and tolerability. Diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting were the most commonly reported AEs (incidence of ≥ 20%). Most AEs related to pazopanib treatment were grade 1/2 and were clinically manageable. The most common grade 3/4 AEs were hypertension and diarrhea. The most common grade 3/4 chemistry abnormalities were ALT elevation and AST elevation. Most cases of drug-induced liver enzyme elevations were asymptomatic and occurred within the first 4 months of treatment. Certain AEs known to occur with this class of agents, including proteinuria, thrombocytopenia, hypothyroidism, hand-foot syndrome, and mucositis/stomatitis, 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 angiogenesis inhibitors may be explained by differences in the potency and selectivity of kinases inhibited.[26] Pazopanib, although an inhibitor of c-Kit, is not a potent inhibitor of fms-related tyrosine kinase 3,[26] which may explain the low rate (≤ 1%) of grade 3/4 cytopenias observed with pazopanib.

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

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Table 4. Mixed-Model Repeated-Measures Analyses for QoL Change From Baseline

Model	No. of Patients: Pazopanib	No. of Patients: Placebo*	Difference†	95% CI	P
EORTC QLQ-C30 Global Health Status/QoL by week					
6	243	110	−1.90	−5.84 to 2.04	.34
12	219	81	−2.82	−7.17 to 1.53	.20
18	191	61	−2.05	−6.95 to 2.86	.41
24	164	49	0.39	−4.47 to 5.25	.88
48	96	24	−0.67	−6.48 to 5.14	.82
EQ-5D index by week					
6	253	125	0.01	−0.04 to 0.05	.84
12	219	86	−0.04	−0.09 to 0.01	.08
18	196	62	−0.02	−0.08 to 0.04	.50
24	166	51	−0.03	−0.09 to 0.04	.44
48	98	24	0.03	−0.03 to 0.10	.33
EQ-5D VAS by week					
6	239	111	1.85	−2.41 to 6.12	.39
12	212	80	0.06	−4.79 to 4.91	.98
18	189	60	−0.08	−5.04 to 4.89	.98
24	161	49	−0.15	−4.83 to 4.53	.95
48	95	23	−1.97	−9.02 to 5.09	.58

Abbreviations: QoL, quality of life; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQuol questionnaire; VAS, visual analogue scale.

*More patients in the placebo arm discontinued study treatment because of disease progression compared with patients in the pazopanib arm.

†The minimal important differences for the questionnaires have been previously established as 5 to 10 for the EORTC-QLQ-C30, 0.08 for the EQ-5D Index, and 7 for the EQ-5D VAS. Values greater than 0 indicate a trend in favor of pazopanib, and values less than 0 indicate a trend in favor of placebo.

with advanced and/or metastatic RCC is ongoing (clinicaltrials.gov identifier NCT00720941).

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