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Prospective Observational Study of Pazopanib in Patients with Advanced Renal Cell Carcinoma (PRINCIPAL Study)

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Renal cell carcinoma • Pazopanib • Real-world • Observational • Tyrosine kinase inhibitor

Abstract

Background. Real-world data are essential to accurately assessing efficacy and toxicity of approved agents in everyday practice. PRINCIPAL, a prospective, observational study, was designed to confirm the real-world safety and efficacy of pazopanib in patients with advanced renal cell carcinoma (RCC).

Subjects, Materials, and Methods. Patients with clear cell advanced/metastatic RCC and a clinical decision to initiate pazopanib treatment within 30 days of enrollment were eligible. Primary objectives included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), relative dose intensity (RDI) and its effect on treatment outcomes, change in health-related quality of life (HRQoL), and safety. We also compared characteristics and outcomes of clinical-trial-eligible (CTE) patients, defined using COMPARZ trial eligibility criteria, with those of non-clinical-trial-eligible (NCTE) patients. Secondary study objectives were to evaluate clinical efficacy, safety, and RDI in patient subgroups.

Results. Six hundred fifty-seven patients were enrolled and received ≥1 dose of pazopanib. Median PFS and OS were 10.3 months (95% confidence interval [CI], 9.2–12.0) and 29.9 months (95% CI, 24.7 to not reached), respectively, and the ORR was 30.3%. HRQoL showed no or little deterioration over time. Treatment-related serious adverse events (AEs) and AEs of special interest occurred in 64 (9.7%), and 399 (60.7%) patients, respectively. More patients were classified NCTE than CTE (85.2% vs. 14.8%). Efficacy of pazopanib was similar between the two groups.

Conclusion. PRINCIPAL confirms the efficacy and safety of pazopanib in patients with advanced/metastatic RCC in a real-world clinical setting. ***The Oncologist*** 2019;24:491–497

Implications for Practice: PRINCIPAL is the largest (n = 657) prospective, observational study of pazopanib in patients with advanced/metastatic renal cell carcinoma, to the authors' knowledge. Consistent with clinical trial results that often contain specific patient types, the PRINCIPAL study demonstrated that the effectiveness and safety of pazopanib is similarly safe and effective in patients with advanced kidney cancer in a real-world clinical setting. The PRINCIPAL study showed that patients with advanced kidney cancer who are treated with first-line pazopanib generally do not show disease progression for approximately 10 months and generally survive for nearly 30 months.

Introduction

The pazopanib approval for the treatment of patients with advanced RCC was granted following the randomized phase III VEG105192 trial, in which pazopanib significantly improved progression-free survival (PFS) versus placebo (median, 9.2 vs. 4.2 months; $p < .0001$) [1]. The subsequent randomized, phase IIIb, noninferiority COMPARZ trial demonstrated

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comparable efficacy of first-line pazopanib and sunitinib in patients with advanced RCC, with health-related quality-of-life (HRQoL) analyses favoring pazopanib over sunitinib [2]. Since these clinical trials, real-world pazopanib studies in RCC are accumulating and providing information about patients under-represented or excluded from clinical trials (e.g., patients with poor performance status [PS] or nonmeasurable lesions) [3]. The PRINCIPAL study evaluated the efficacy and safety of pazopanib in a multinational, real-world clinical setting.

Subjects, Materials, and Methods

Study Design and Patients

PRINCIPAL was a global, prospective, observational study of patients with advanced/metastatic RCC treated with frontline pazopanib. All patients provided informed consent, and the study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice, patient privacy requirements, and ethical principles outlined in the Declaration of Helsinki 2008.

The study was designed to enroll ~500–700 patients over approximately 30 months. Sample size was chosen based on the expected precision for the outcomes of interest (<5% for PFS, overall survival [OS], and objective response rate [ORR]), and the feasibility of enrolling the desired patient population over the enrollment period. Consecutive patients meeting eligibility were enrolled and followed for 30 months or until premature discontinuation due to death, consent withdrawal, loss to follow-up, or study termination. Patients who permanently discontinued study treatment were followed for progression, survival, HRQoL, and efficacy of subsequent therapies for up to 30 months. Patients completed the study if 30 months of follow-up was conducted, or if the patient died during study treatment or the follow-up period.

Patients aged ≥18 years at enrollment with a diagnosis of advanced or metastatic RCC of clear cell or predominant clear cell histology and a clinical decision to initiate treatment with pazopanib within 30 days of enrollment were eligible for the study. No prior exposure to multikinase inhibitor or anti-vascular endothelial growth factor (VEGF) inhibitor for advanced or metastatic disease was allowed.

Patients were assessed to determine whether they met key eligibility criteria from the COMPARZ [2] study (clinical trial eligible [CTE]): RCC diagnosis with clear-cell component histology (predominantly clear cell); no prior systemic therapy (interferon-α, interleukin-2) for advanced or metastatic RCC; locally advanced (disease not amenable to curative surgery or radiation therapy) or metastatic RCC (equivalent to stage IV RCC according to American Joint Committee on Cancer staging); measurable disease per RECIST v1.1; Karnofsky Performance Score (KPS) ≥70; age ≥18 years; total serum calcium concentration < 12.0 mg/dL; adequate organ function at baseline (absolute neutrophil count ≥1.5 × 10^9/L, hemoglobin ≥9 g/dL, platelets ≥100 × 10^9/L, total bilirubin ≤1.5× upper limit of normal [ULN], aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤2.5× ULN); no prior use of an investigational or licensed drug that targets VEGF or VEGF receptor (VEGFR); no history or clinical evidence of central nervous system metastases; and no coronary artery disease or cerebral artery disease at baseline. Patients in the PRINCIPAL study who did not meet COMPARZ eligibility criteria or had missing data for any of the CTE criteria were considered the non-clinical-trial-eligible (NCTE) population.

Assessments

There were no protocol-mandated visits or procedures. Patient demographics, medical history, and disease characteristics were obtained at the baseline visit, and follow-up information was collected approximately every 3 months (±4 weeks). Tumor responses were assessed according to local processes and physician's clinical judgement.

Primary efficacy measures were PFS, OS, and ORR defined as complete response (CR) or partial response (PR). Other primary objectives were to determine relative dose intensity (RDI) and its effect on treatment outcomes; change in HRQoL relative to baseline; and frequency of serious adverse events (SAEs) and adverse events of special interest (AESIs). AESIs were defined as any adverse event (AE) resulting in a dose modification or discontinuation, or any reports of new onset/worsened hypertension, cardiac or thyroid dysfunction, or evidence of liver toxicity. The final primary objective was to compare the population demographics, disease characteristics, and RCC treatment history of patients in the CTE population with those of patients in the NCTE population. Secondary study objectives were to evaluate efficacy, safety, and RDI in patient subgroups.

Patients who received ≥1 dose of pazopanib were evaluable for efficacy (PFS and OS) and safety analyses (All-Treated [AT] population). The Measurable Disease (MD) population comprised patients with measurable disease at baseline and was used for the analysis of ORR.

Statistical Analysis

Continuous variables were reported as medians and ranges, and categorical variables were reported as number and percentage of the total population. Evaluations were based on point estimates and 95% confidence intervals (CIs), and efficacy and safety analyses were stratified by baseline patient characteristics such as Eastern Cooperative Oncology Group (ECOG) PS and histologic subtype, as appropriate. No formal hypothesis or statistical significance testing was planned. A multivariate logistic regression analysis was performed to investigate the impact of baseline demographics and disease characteristics on pazopanib exposure (RDI <85% vs. ≥85%). RDI was calculated as the ratio of average daily dose of pazopanib to the recommended daily dose of pazopanib (expressed as a percentage). The mean RDI in the COMPARZ study was 84%; thus, the cutoff of 85% was used for the PRINCIPAL analysis. To explore the impact of baseline demographics, disease characteristics, and RDI on efficacy outcomes, a logistic regression model (for overall response) and Cox proportional hazards regression models (for PFS and OS) were used.

Results

Patients

Of the 657 patients in the AT population, 501 (76.3%) completed the study, 62 (9.4%) were lost to follow up, and 55 (8.4%) withdrew consent (supplemental online Table 1). The median age was 66 years (range, 22–90), and approximately two thirds of patients were male (supplemental online Table 2). The percentage of all patients with favorable/intermediate/poor risk was 3.8%/55.3%/13.9%, respectively, per Memorial Sloan Kettering Cancer Center (MSKCC) criteria and 5.0%/52.2%/23.3% per International Metastatic Renal Cell Database Consortium (IMDC) criteria. MSKCC and IMDC risk data were missing for 27.1% and 19.5% of patients, respectively. Follow-up assessment data were available for 74% of patients at 3 months, 43% at 12 months, 27% at 24 months, and 20% at ≥30 months (supplemental online Table 3).

Efficacy

In the AT population, median PFS was 10.3 months (95% CI, 9.2–12.0) and median OS was 29.9 months (24.7 to not reached [NR]; supplemental online Fig. 1).

Event-free probability estimates for PFS at 6, 12, and 24 months were 0.673 (95% CI, 0.631–0.711), 0.453 (95% CI, 0.409–0.496), and 0.269 (95% CI, 0.229–0.310), respectively. Event-free probability estimates for OS at 6, 12, and 24 months were 0.846 (95% CI, 0.815–0.872), 0.722 (95% CI, 0.684–0.756), and 0.552 (95% CI, 0.509–0.592), respectively. The ORR was 30.3%, and the median duration of response and median time to response were 11 months (95% CI, 8.6–14.6) and 3 months (95% CI, 2.9–3.1), respectively (MD population). Subgroup efficacy analyses (PFS, OS, and ORR) suggested inferior outcomes in patients with ECOG PS ≥2, poor MSKCC or IMDC risk grouping, no prior nephrectomy, and cytokine pretreatment (Table 1).

Cox regression analyses supported significantly shorter PFS and OS in patients with ECOG PS ≥2 (vs. <2; $p < .001$ and $p < .001$, respectively) and poor MSKCC risk (vs. favorable risk; $p = .003$ and $p = .001$), and significantly longer PFS and OS in patients who received prior nephrectomy (vs. no prior nephrectomy; $p = .034$ and $p < .001$; supplemental online Table 4). Intermediate MSKCC risk grouping (vs. favorable risk; $p = .039$) was associated with significantly shorter OS, but this difference was not statistically significant for PFS. Similarly, the odds of overall response (CR/PR) were significantly lower in patients with poor MSKCC risk (vs. favorable risk; $p = .020$); furthermore, treatment-naive patients had significantly higher odds of overall response (vs. cytokine pretreated; $p = .042$).

Safety

At least one AE was reported by 486 (74%) patients overall, and the most commonly reported AEs were hypertension (22.8%), diarrhea (12.8%), increased ALT (11.1%), increased AST (7.0%), hypothyroidism (6.1%), increased blood thyroid-stimulating hormone (6.4%), and nausea (5.6%). Treatment-related SAEs were reported by 64 (9.7%) patients. Overall, 1,079 nonserious AESIs occurred in 399 (60.7%) patients, including new-onset or worsened hypertension ($n = 160$), evidence of liver toxicity ($n = 137$), thyroid dysfunction ($n = 90$), cardiac dysfunction ($n = 16$), and any other event resulting in pazopanib dose modification or discontinuation ($n = 233$; Table 2).

Pazopanib Exposure

Most patients (84.0%) started on the standard daily pazopanib dose of 800 mg and were treated with a median average total daily dose of 800 mg over the study period (Table 3). Patients who received lower than the 800 mg daily dose of pazopanib had longer durations of pazopanib exposure. The median duration of exposure (without dose interruption) was 6.9 months, 11.1 months, 9.6 months, and 12.7 months for pazopanib doses of 800 mg, 600 mg, 400 mg, and 200 mg, respectively (supplemental online Table 5).

The percentage of patients with an RDI <85% was 41.4% overall. The multivariate logistic regression analysis identified poor MSKCC risk classification (vs. favorable risk; $p = .046$) as a baseline patient characteristic associated with significantly greater odds of receiving ≥85% (vs. <85%) RDI. The percentage of patients with favorable/intermediate/poor MSKCC risk who received an RDI <85% was 52%/43.8%/26.4%, respectively. Conversely, baseline characteristics associated with significantly reduced odds of receiving an RDI ≥85% included treatment-naive status (vs. cytokine pretreatment; $p = .038$) and coronary artery disease (vs. no coronary artery disease; $p = .001$; supplemental online Table 6).

Approximately half of the patients underwent dose/regimen change or interruptions (Table 3), and AEs were the primary reason for dose change or interruption (93.8%). Pazopanib was discontinued in 78.1% of patients overall, owing primarily to disease progression (44.3%) and AEs (14.5%; Table 3). The most common AE leading to treatment discontinuation was hepatotoxicity ($n = 7$; 1.1%).

Comparison of CTE and NCTE Populations

Ninety-seven (14.8%) and 560 (85.2%) patients were included in the CTE and NCTE populations, respectively. The primary reasons for ineligibility to enter a clinical trial were the absence of data on measurable disease per RECIST v1.1 ($n = 177$; 100 patients had extant measurable lesion that was not consistent with RECIST v1.1 and 77 patients had no existence of measurable lesion), presence of coronary artery disease at baseline visit ($n = 51$), prior systemic therapy for advanced/metastatic RCC ($n = 38$), and history or clinical evidence of central nervous system metastases ($n = 31$; supplemental online Table 7).

For patients in the CTE and NCTE populations, the percentage with favorable/intermediate/poor risk was 7.2%/75.3%/11.3% and 3.2%/51.8%/14.3%, respectively, per MSKCC criteria and 7.2%/70.1%/22.7% and 4.6%/49.1%/23.4%, respectively, per IMDC criteria (supplemental online Table 1). However, data for MSKCC and IMDC risk classification were missing for 172 (30.7%) and 128 (22.9%) patients in the NCTE population, respectively. Other baseline disease characteristics such as number and location of metastatic sites and prior treatments were generally comparable between the CTE and NCTE populations. For the CTE and NCTE

Table 1. Efficacy (PFS, OS, and ORR) in patient subgroups

Subgroup	PFS[a]		OS[a]		
	Events, *n/N*	Median (95% CI), months	Events, *n/N*	Median (95% CI), months	ORR[b], *n/N* (%)
Overall	386/655	10.3 (9.2–12.0)	284/657	29.9 (24.7–NR)	168/554 (30.3)
Age at enrollment					
<65 years	159/279	11.6 (9.2–14.8)	111/281	33.9 (27.9–33.9)	77/237 (32.5)
≥65 years	227/376	9.9 (8.4–11.1)	173/376	25.9 (20.2–NR)	91/317 (28.7)
Sex					
Male	269/447	11.1 (9.5–12.6)	195/449	29.9 (24.3–NR)	113/381 (29.7)
Female	117/208	9.3 (7.0–11.0)	89/208	28.2 (20.3–NR)	55/173 (31.8)
Baseline ECOG PS					
<2	310/541	11.2 (9.8–13.2)	217/542	33.9 (28.6–NR)	147/455 (32.3)
≥2	40/50	2.8 (2.2–3.2)	38/51	5.5 (2.4–10.4)	6/45 (13.3)
Missing	36/64	11.4 (5.9–13.8)	29/64	25.9 (16.4–32.9)	15/54 (27.8)
Baseline MSKCC risk					
Favorable	10/24	25.4 (12.0–NR)	4/25	NR (NR–NR)	10/21 (47.6)
Intermediate	210/361	11.2 (9.5–13.7)	147/361	33.9 (26.9–NR)	102/313 (32.6)
Poor	71/91	4.2 (2.9–6.7)	65/91	9.6 (5.9–14.6)	14/73 (19.2)
Missing	95/179	12.1 (9.8–16.1)	68/180	32.9 (24.7–NR)	42/147 (28.6)
Baseline IMDC risk					
Favorable	18/32	25.4 (12.0–30.8)	6/33	NR (NR–NR)	14/27 (51.9)
Intermediate	196/341	11.6 (9.8–14.1)	127/341	32.9 (30.5–NR)	96/295 (32.5)
Poor	109/152	5.9 (4.1–8.0)	100/153	12.3 (8.7–16.4)	25/122 (20.5)
Missing	63/130	13.3 (9.2–17.4)	51/130	28.2 (22.3–NR)	33/110 (30.0)
Prior nephrectomy					
Yes	294/509	11.5 (10.2–13.8)	197/511	32.9 (29.7–NR)	141/427 (33.0)
No	88/141	6.7 (5.4–9.2)	84/141	14.8 (11.3–20.2)	23/122 (18.9)
Unknown	4/5	9.1 (2.2–14.1)	3/5	20.5 (7.6–NR)	4/5 (80.0)
Prior treatment					
Cytokine	32/37	6.7 (3.7–12.0)	20/38	22.0 (7.8–NR)	3/32 (9.4)
Treatment-naive	354/618	10.7 (9.5–12.5)	264/619	30.5 (24.7–NR)	165/522 (31.6)
RDI					
<85%	147/271	13.8 (11.0–17.3)	98/272	33.9 (30.5–NR)	77/225 (34.2)
≥85%	239/384	8.6 (7.0–10.3)	186/385	23.7 (18.5–29.6)	91/326 (27.9)
Eligibility for participation in clinical trial					
Yes (CTE population)	60/96	9.6 (7.8–13.2)	47/97	26.3 (16.9–NR)	32/97 (33.0)
No (NCTE population)	326/559	10.7 (9.2–12.3)	237/560	32.9 (24.5–NR)	136/457 (29.8)

[a]Analysis conducted in All Treated (AT) population.
[b]Analysis conducted in Measurable Disease (MD) population.
Abbreviations: CTE, clinical trial eligible; ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic Renal Cell Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; NCTE, non-clinical trial eligible; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity.

populations, the median average daily dose was reported as 800 mg and 733 mg, respectively, and the percentage of patients with an RDI <85% was 29.9% and 43.4%, respectively (Table 3). Efficacy was similar between the CTE and NCTE populations (Table 1). The frequency of all-grade AEs was 64.9% and 75.5%, and the frequency of grade ≥ 3 AEs was 32.0% and 44.5%, in the respective CTE and NCTE populations.

Efficacy in the NCTE Population

In the subgroup of patients within the NCTE population with no existence of a measurable lesion (*n* = 77; 13.8%), median PFS was 10.7 (95% CI, 6.4–18.0); median OS was not evaluable (supplemental online Table 8). The ORR was 20.8%, and the median duration of response and median time to response were 7 months (95% CI, 4.2–11.8) and 3 months (95% CI, 2.6–4.3), respectively (MD population).

Table 2. Nonserious AESIs

AESIs	Total no. of events	Patients with AESI[a], *n* (%)
Any AESI	1,079	399 (60.7)
Evidence of liver toxicity	249	137 (20.9)
New onset or worsened hypertension	199	160 (24.4)
Thyroid dysfunction	108	90 (13.7)
Cardiac dysfunction	18	16 (2.4)
Any other event resulting in pazopanib dose modification or discontinuation	505	233 (35.5)

[a]All treated patients (*n* = 657).
Abbreviations: AESIs, adverse events of special interest.

Among treatment-naive patients (*n* = 522; 93.2%), median PFS was 10.8 (95% CI, 9.5–12.8) and median OS was 32.9 (95% CI, 24.7–NR) The ORR was 31.3%, and the median duration of response and median time to response were 9 months (95% CI, 7.1–13.8) and 3 months (95% CI, 2.9–3.1). Subgroup efficacy analyses (PFS, OS, and ORR) based on concomitant disease at baseline did not identify any associations between the presence/absence of comorbidity at baseline and efficacy outcomes within the NCTE population.

Subsequent Treatments

The most common subsequent therapeutic procedure since study start was radiotherapy (14.8%; supplemental online Table 9). Following pazopanib discontinuation, 45.1% of patients received subsequent systemic therapy for RCC, the most common being sunitinib (25.6%), everolimus (25.1%), and axitinib (21.6%; supplemental online Table 9).

Discussion

This large, prospective, observational study confirmed the efficacy and favorable safety profile of pazopanib in patients with advanced/metastatic RCC. The median PFS (10.3 months) and median OS (29.9 months) in this real-

Table 3. Pazopanib exposure

Parameter	CTE (*n* = 97)	NCTE (*n* = 560)	All patients (*n* = 657)
Starting daily dose, *n* (%)			
200 mg	0	3 (0.5)	3 (0.5)
400 mg	5 (5.2)	58 (10.4)	63 (9.6)
600 mg	5 (5.2)	34 (6.1)	39 (5.9)
800 mg	87 (89.7)	465 (83.0)	552 (84.0)
Once-daily frequency of total starting daily dose, *n* (%)	97 (100.0)	551 (98.4)	648 (98.6)
Average total daily dose, mg, median (range)	800 (250–800)	733 (200–1,067)	800 (200–1,067)
RDI %, median (range)	100 (31–100)	91.7 (25–133)	100 (25–133)
RDI <85%, *n* (%)	29 (29.9)	243 (43.4)	272 (41.4)
Patients with any dose/regimen changes or interruption, *n* (%)	43 (44.3)	298 (53.2)	341 (51.9)
Number of dose/regimen change(s) or interruptions, *n* (%)			
0	54 (55.7)	262 (46.8)	316 (48.1)
1	17 (17.5)	131 (23.4)	148 (22.5)
2	8 (8.2)	81 (14.5)	89 (13.5)
≥3	18 (18.6)	86 (15.4)	104 (15.8)
Primary reason for dose change/interruption, *n* (%)			
AE	81 (83.5)	535 (95.5)	616 (93.8)
Toxicity resolved	8 (8.2)	46 (8.2)	54 (8.2)
Other	24 (24.7)	225 (40.2)	249 (37.9)
Patients with dose/regimen discontinuation, *n* (%)	68 (70.1)	445 (79.5)	513 (78.1)
Primary reason for dose discontinuation, *n* (%)			
Death	6 (6.2)	43 (7.7)	49 (7.5)
Disease progression	41 (42.3)	250 (44.6)	291 (44.3)
Patient decision	3 (3.1)	23 (4.1)	26 (4.0)
Lost to follow-up	2 (2.1)	12 (2.1)	14 (2.1)
AE	8 (8.2)	87 (15.5)	95 (14.5)
Presurgical procedure	0	5 (0.9)	5 (0.8)
Other[a]	9 (9.3)	35 (6.3)	44 (6.7)

[a]This may include patients who discontinued due to reaching the end of the 30-month follow-up period.
Abbreviations: AE, adverse event; CTE, clinical trial eligible; NCTE, non-clinical trial eligible; RDI, relative dose intensity.

world study were comparable to clinical trial data of pazopanib in advanced/metastatic RCC [1, 2, 4, 5]. Median OS within each MSKCC or IMDC risk group was longer than expected based on previous clinical trial and real-world data of pazopanib [5, 6]. One potential explanation for the prolonged survival within each risk group could be the benefit gained from subsequent treatment with newer agents (e.g., axitinib, nivolumab, and cabozantinib) [7, 8]. However, fewer than 10% of patients received subsequent treatment with agents other than the VEGF- or mammalian target of rapamycin-targeted therapies that have all been available since 2012 or earlier, suggesting that improved prolonged survival is not due to agents like nivolumab and cabozantinib.

Patients in this real-world study were separated into two groups based on eligibility criteria from the COMPARZ trial. Although there appeared to be no stark differences in PFS or OS between the CTE and NCTE populations, outcomes were numerically better in the NCTE population. This is contrary to previous real-world analyses of patients with advanced RCC who generally have a less favorable MSKCC risk profile and worse PS compared with clinical trial participants [3], as well as significantly poorer survival outcomes (PFS and OS) with first-line systemic or VEGF-targeted therapies [9] in trial-ineligible patients.

Time from diagnosis of locally advanced/metastatic RCC to treatment was <12 months in the overall patient population; in the NCTE population, it was double that in the CTE population. Time to treatment was similar between the NCTE population and overall population because of the larger sample size of NCTE versus CTE relative to the overall population. Importantly, patients in the CTE population, by definition, were not cytokine pretreated, which may have contributed to the imbalance in time to treatment between the CTE and NCTE populations. In the NCTE population, cytokine-pretreated patients had poor outcomes (PFS, OS, and ORR) compared with treatment-naive patients; however, as these patients made up a small proportion of the NCTE population (5.2%), it is difficult to make any meaningful conclusions about the effect of prior treatment on efficacy outcomes.

Although NCTE patients appeared to have a slightly poorer risk profile compared with CTE patients, data for risk group classifications were unavailable for a large percentage of patients in the NCTE population (30.7% for MSKCC and 22.9% for IMDC), limiting the comparisons and interpretation that can be made between trial-eligible and trial-ineligible patients in PRINCIPAL versus other trials. Moreover, although Cox regression analyses were not performed for the NCTE population, baseline comorbidity did not appear to be associated with worse survival outcomes (PFS and OS) outcomes for this group of patients, suggesting that, from a safety and efficacy perspective, patients with comorbidities who are normally excluded from clinical trials can be treated with pazopanib and achieve comparable outcomes as clinical-trial-eligible patients.

Notably, a major reason for NCTE in the current study was absence of data on measurable disease per RECIST v1.1 (almost one third of patients; 100 patients had extant measurable lesion that was not consistent with RECIST v1.1, and 77 patients had no existence of measurable lesion), whereas other real-world studies did not include measurable disease as a criterion for the trial eligible population [9, 10]. These methodological differences may have contributed to the discrepancy in results between studies.

Baseline patient characteristics associated with a significant PFS and OS benefit included ECOG PS <2 (vs. ≥2), favorable MSKCC risk (vs. poor MSKCC risk), and prior nephrectomy (vs. no prior nephrectomy). PS (KPS or ECOG) and prior nephrectomy are well-established prognostic factors in RCC and have been used to stratify patients during treatment randomization in trials such as COMPARZ [2]. The MSKCC prognostic risk grouping, which comprises five pretreatment clinical factors to split patients into three risk groups (favorable, intermediate, or poor), was first validated to predict survival with first-line interferon-α in advanced RCC [11]. Since that time, MSKCC risk grouping has also been validated for use with first-line VEGFR-tyrosine kinase inhibitor therapy [12]. Poor MSKCC risk (vs. favorable risk) grouping was also associated with a significantly greater chance of receiving an RDI ≥85% of pazopanib, suggesting that although favorable-risk patients were more likely to receive a reduced dose, efficacy was not compromised, and in fact appeared improved. It may be that patients who required dose reduction were those who experienced a pharmacodynamic effect of therapy, whereas those capable of staying on full dose did not. In support of this, a recent retrospective analysis of patients with metastatic RCC who experienced cumulative toxicity with sunitinib or pazopanib had significantly longer OS and PFS compared with patients experiencing one or no AEs [13]. It is also plausible that patients with a favorable PFS, and therefore longer pazopanib exposure, may have been at higher risk of dose reduction. This hypothesis is supported by data from a recent retrospective analysis of patients with pazopanib-treated soft-tissue sarcoma, which showed that patients with RDI <80% had a longer PFS than those with RDI >80% [14]. However, as the RDI analysis described herein focused on the effect of baseline characteristics on pazopanib dose intensity, it is not possible to speculate further on the effect of pazopanib exposure on RDI.

Pazopanib treatment was generally well tolerated. A relatively low frequency of hypertension (22.8%), diarrhea (12.8%), ALT elevations (11.1%), and AST elevations (7.0%) were observed compared with past clinical trial data [3, 15] This, in association with the HRQoL results (supplemental online Fig. 2), confirm good tolerance of pazopanib in an unselected, multinational population.

Limitations of this study include its observational nature and associated potential under-reporting of AEs, and no requirement to collect AEs other than AESIs and SAEs. Another limitation is the relatively low proportion of patients with follow-up tumor assessment data at ≥30 months (20%) as well as time to response, which may have been influenced by the recommended visit schedule of every 3 months.

Conclusion

The PRINCIPAL study is the largest prospective, observational study of pazopanib in patients with advanced/metastatic RCC to our knowledge, and the study results are consistent with

prior clinical data of pazopanib and confirm the efficacy and favorable safety profile of pazopanib treatment for this patient population in the real-world clinical setting.

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Disclosures

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