A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: Final overall survival results and safety update [☆,☆☆,☆☆☆]

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Abstract **Background:** In this randomised phase III study (VEG105192; NCT00334282), pazopanib previously demonstrated statistically and clinically meaningful improvement of progression-free survival versus placebo in patients with advanced/metastatic renal cell carcinoma (mRCC). Final overall survival (OS) and updated safety results are now reported.
Methods: Treatment-naive or cytokine-pretreated mRCC patients ($n = 435$) stratified and randomised (2:1) to pazopanib 800 mg daily or placebo, were treated until disease progression, death or unacceptable toxicity. Upon progression, placebo patients could receive pazopanib

through an open-label study. Final OS in the intent-to-treat population was analysed using a stratified log-rank test. Rank-preserving structural failure time (RPSFT) and inverse probability of censoring weighted (IPCW) analyses were performed post-hoc to adjust for crossover. *Findings:* The difference in final OS between pazopanib- and placebo-treated patients was not statistically significant (22.9 versus 20.5 months, respectively; hazard ratio [HR] = 0.91; 95% confidence interval [CI], 0.71–1.16; one-sided P = .224). Early and frequent crossover from placebo to pazopanib and prolonged duration of crossover treatment confounded the OS analysis. In IPCW analyses, pazopanib decreased mortality (HR = 0.504; 95% CI, 0.315–0.762; two-sided P = .002). Similar, albeit non-significant, results were obtained in RPSFT analyses (HR = 0.43; 95% CI, 0.215–1.388; two-sided P = .172). Since the last cutoff, cumulative exposure to pazopanib increased by 30%. The pazopanib safety profile showed no new safety signals or changes in the type, frequency and severity of adverse events. *Interpretation:* Although no significant difference in OS was observed in this study, extensive crossover from placebo to pazopanib confounded final OS analysis. Post-hoc analyses adjusting for crossover suggest OS benefit with pazopanib treatment for mRCC patients.

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1. Introduction

Renal cell carcinoma (RCC) accounts for 80%–85% of kidney cancers.[1] Approximately 80% of RCC patients present with clear-cell or predominantly clear-cell histology.[2,3] In the United States (US), new kidney cancer cases and deaths in 2010 were estimated as 58,240 and 13,040, respectively.[4] In Europe, new kidney cancer cases and deaths in 2008 were estimated as 88,400 and 39,300, respectively.[5]

The development of novel therapies targeting tumour angiogenesis and mammalian target of rapamycin (mTOR) pathways has significantly improved clinical outcomes in patients with advanced RCC. Since 2005, six targeted agents, sunitinib, sorafenib, pazopanib, temsirolimus, everolimus and bevacizumab with interferon alfa-2a, have received regulatory approval in the US, Europe and other countries worldwide. These agents have been included in US and European treatment guidelines as front-line and/or second-line therapies for advanced RCC.[6,7]

Pazopanib (Votrient™, GlaxoSmithKline) is an oral angiogenesis inhibitor targeting vascular endothelial growth factor receptors (VEGFR)-1/-2/-3, platelet-derived growth factor receptors (PDGFR)-α/-β and stem cell factor receptor c-Kit.[8] The regulatory approval of pazopanib[9,10] was supported primarily by clinical evidence from the pivotal, randomised and double-blind, phase III study VEG105192 (clinicaltrials.gov NCT00334282) in treatment-naive or cytokine-pretreated patients with advanced and/or metastatic RCC.[11] The study demonstrated that pazopanib treatment significantly improved progression-free survival (PFS) versus placebo in the overall study population (median, 9.2 versus 4.2 months; hazard ratio [HR] = 0.46; P < .0001) and in the treatment-naive (median, 11.1 versus 2.8 months; HR = 0.40; P < .0001) and cytokine-pretreated subgroups (median, 7.4 versus 4.2 months; HR = 0.54; P < .001). These

previously reported results are based on data obtained by May 23, 2008, for the final PFS analysis.[11] This report provides the preplanned final analysis of overall survival (OS) and updated safety results.

2. Methods

2.1. Patients

Patients with advanced and/or metastatic RCC and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST)[12] who were treatment-naive or had received one prior cytokine-based systemic therapy were eligible. Detailed eligibility criteria and study conduct were previously described.[11]

2.2. Study design: randomisation and masking

Patients stratified by ECOG PS (0 versus 1), prior nephrectomy status (yes versus no) and prior systemic treatment for advanced RCC (treatment-naive versus cytokine-pretreated) were randomised (2:1) to pazopanib 800 mg/day or matching placebo and treated until disease progression, death, unacceptable toxicity or consent withdrawal. Upon progression, patients could be unblinded and receive any available subsequent anticancer therapy at the discretion of the investigator and patient. Patients who progressed from the placebo arm had the option of receiving pazopanib via a parallel open-label extension study (VEG107769; clinicaltrials.gov NCT00387764). Eligibility criteria for this study were similar to those of the parent study except that patients with ECOG PS 2 were also eligible.

2.3. Study end-points and assessments

The primary end-point was PFS; the principal secondary end-point was OS. Other secondary end-points included objective response rate, duration of response

and safety. Imaging assessments of disease status were performed at scheduled time points as previously described.[11] Follow-up for survival was performed every 3 months after disease progression until observation of the required number of deaths for final OS analysis.

Clinical assessments for safety, including physical examinations, vital signs, laboratory evaluations, electrocardiograms and documentation of adverse events (AEs), were evaluated at baseline and during study treatment as previously reported.[11] Adverse events were graded according to Common Terminology Criteria for Adverse Events v3.[13]

2.4. Statistical methods

Overall survival was defined as the time from randomisation until death from any cause. Patients who did not die were censored at the date of last contact. With one planned interim analysis and a final analysis after 287 deaths, there was 90% power to detect a 50% improvement in OS with pazopanib treatment versus placebo, with one-sided $\alpha = 0.025$. This power calculation did not account for the impact of crossover. The study was not powered for subgroup analyses.

In the planned analysis, treatment comparison was made between the two arms following the intent-to-treat (ITT) principle using a log-rank test (one-sided) stratified by ECOG PS and prior systemic treatment status for advanced RCC. Hazard ratios were calculated using a stratified Pike estimator.

2.4.1. Post-hoc analyses to adjust for crossover

To correct the treatment-effect estimate from the ITT analysis for bias introduced by the crossover of patients from placebo to open-label pazopanib, post-hoc analyses using inverse probability of censor weighting (IPCW)[14–16] and rank-preserving structural failure time (RPSFT)[17,18] were conducted. The 95% confidence intervals (CIs) and two-sided *P* values for both methodologies were calculated using bootstrapping.

The IPCW method uses a weighted Cox model to overcome estimation bias associated with non-adherence to randomised assignment (e.g. crossover). This implementation censors patients at the start of any new systemic anticancer therapy. Although censoring at selective change of treatment is generally biased, IPCW modelling corrects for this bias by using weighting. The results are unbiased, assuming that no confounding variables are missing in the weight estimation. The weights allow follow-up of patients who remain on their randomised treatment to account not only for themselves, but also for comparable patients with similar baseline and time-dependent characteristics who received post-study treatment. Time-dependent characteristics adjusted in this analysis were progressive disease status, time since progression,

ECOG PS, history and the presence of grade 3/4 AEs, number of available treatments with regulatory approval and the number of reimbursable treatments in the patient's country.

The RPSFT model is based on the assumption that treatment prolongs (or shortens) survival by a multiplicative factor of the total treatment duration. Using this model, the placebo survival curve can be reconstructed as if no placebo patients switched to pazopanib, permitting the estimation of an adjusted HR. The RPSFT analysis conducted adjusts for prognostic factors and crossover to pazopanib, but not other, non-pazopanib therapies.

3. Results

The pivotal study VEG105192 enrolled 435 patients with advanced/metastatic RCC (233 treatment-naive, 202 cytokine-pretreated) from April 2006 to April 2007; 79 placebo patients received pazopanib in the extension study (VEG107769).[11] Demographic and disease characteristics of patients in VEG105192 were well balanced between treatment arms and similar to those in VEG107769 (Table 1).[11]

Clinical cutoff for the final OS analysis was reached on March 15, 2010, when 290 deaths had been recorded. In the pazopanib arm, 190 patients (66%) died: 169 from RCC; 11 from serious AEs (SAEs) while on blinded pazopanib treatment; one from an SAE after enrolling into the extension study as an exemption; and nine from other diseases or reasons. In the placebo arm, 100 patients (69%) died: 93 from RCC; three from SAEs while receiving placebo; two from other diseases; and two from SAEs during the extension study.

3.1. Efficacy

3.1.1. Final OS results and summary of subsequent anticancer therapies

The final ITT analysis of OS did not show a statistically significant survival benefit from pazopanib treatment; median OS for pazopanib and placebo was 22.9 versus 20.5 months, respectively (HR = 0.91; 95% CI, 0.71–1.16; one-sided stratified log-rank *P* = .224; Fig. 1). This analysis was, however, confounded by the early, high rate of crossover of placebo patients to pazopanib and their prolonged duration of treatment with pazopanib or other anticancer therapies after progression.

As shown in Table 2, 66% of patients in the placebo arm received at least one post-study systemic anticancer treatment compared with 30% in the pazopanib arm; 63% of patients in the placebo arm received a VEGFR or mTOR inhibitor compared with only 22% in the pazopanib arm. The imbalance in post-study treatment between the two arms resulted primarily from the availability of pazopanib to patients who progressed on

Table 1
Patient demographics and baseline disease characteristics.

Parameter	VEG105192		VEG107769
	Pazopanib (N = 290)	Placebo (N = 145)	Pazopanib (N = 80)[*]
Median age, years (range)	59 (28–85)	60 (25–81)	65 (25–80)
Sex, n (%)			
Male	198 (68)	109 (75)	61 (76)
Race, n (%)			
White	252 (8)	122 (84)	68 (85)
Asian	36 (12)	23 (16)	12 (15)
Black/other	2 (<1)	0	0
Histology, n (%)[**]			
Clear cell	264 (91)	129 (89)	74 (93)
Predominantly clear cell	25 (9)	16 (11)	6 (8)
Most common sites of metastasis, n (%)[†]			
Lung	214 (74)	106 (73)	64 (80)
Lymph nodes	157 (54)	86 (59)	46 (58)
Bone	81 (28)	38 (26)	21 (26)
Liver	75 (26)	32 (22)	13 (16)
Kidney	66 (23)	36 (25)	16 (20)
Number of organs involved, n (%)[†]			
1	53 (18)	20 (14)	8 (10)
2	78 (27)	50 (34)	30 (38)
⩾3	159 (55)	75 (52)	42 (53)
ECOG performance status, n (%)			
0	123 (42)	60 (41)	27 (34)
1	167 (58)	85 (59)	43 (54)
2	0	0	10 (13)
MSKCC risk category, n (%)[‡]			
Favourable risk	113 (39)	57 (39)	31 (39)
Intermediate risk	159 (55)	77 (53)	38 (48)
Poor risk/Unknown[§]	9/9 (3/3)	5/6 (3/4)	1/10 (1/13)
Prior nephrectomy, n (%)	258 (89)	127 (88)	74 (93)
Prior cytokine treatment, n (%)			
Treatment-naive	155 (135)	78 (67)	41 (39)
Cytokine-pretreated[¶]	53 (47)	54 (46)	51 (49)

Adapted from Sternberg CN, et al. J Clin Oncol 2010; 28(6): 1061–8.[11]

ECOG = Eastern Cooperative Oncology Group; MSKCC = Memorial Sloan-Kettering Cancer Center.

[*] One patient in the pazopanib arm of VEG105192 was permitted to enroll into VEG107769 after progression at the request of the investigator who observed tumour necrosis even though the tumour was enlarged.

[**] Histology at initial diagnosis was missing for one patient in the pazopanib arm of VEG105192.

[†] As defined by the investigator.

[‡] One hundred and 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.

[¶] One patient was not cytokine-pretreated but received chemotherapy.

placebo. Overall, 54% of placebo patients received pazopanib via the open-label extension study. Some patients initiated pazopanib treatment as early as 6 weeks after having been randomised to the placebo arm.

In addition, patients who subsequently received open-label pazopanib via the extension study had a prolonged treatment duration versus those who received blinded pazopanib treatment in the pivotal study (median treatment duration 9.7 versus 7.4 months; 43% versus 32% treated for ⩾12 months). Baseline prognostic characteristics of both groups were similar at the

beginning of pazopanib treatment, except for worse baseline ECOG PS in patients in the extension study versus those in the pivotal study (ECOG PS 0/1/2: 34%/54%/13% versus 42%/58%/0%).

Reasons for some patients not receiving subsequent anticancer therapy included death soon after discontinuing study treatment, ineligibility for additional treatment due to poor prognosis or lack of access to other effective treatments. Similar proportions of patients in both arms died within 28 days of discontinuing study treatment (11% pazopanib versus 9% placebo) or were
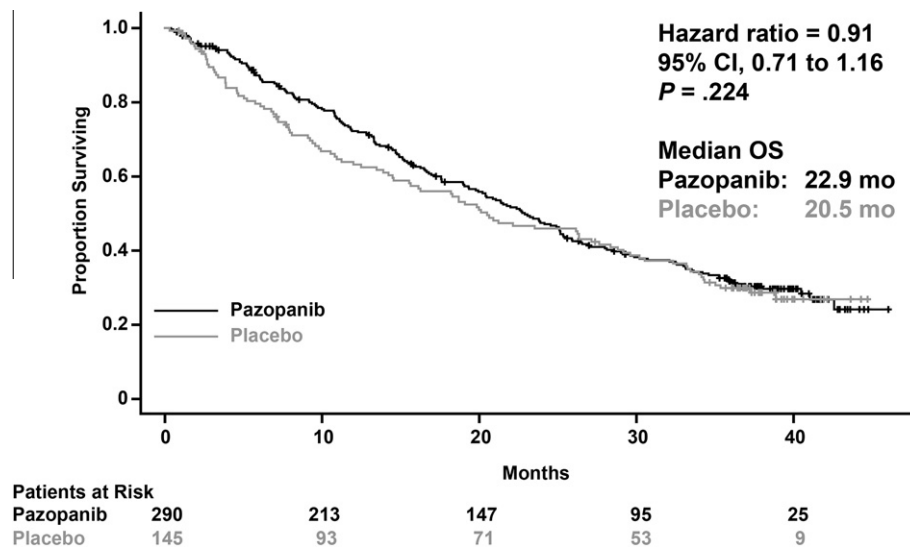
Fig. 1. Kaplan–Meier estimate of overall survival (OS) in patients randomly assigned to pazopanib or placebo. CI = confidence interval.

Table 2
Summary of post-progression systemic anticancer therapies.

	Patients, n (%)	
	Pazopanib ($N = 290$)	Placebo ($N = 145$)
Any systemic therapy	88 (30)	95 (66)
Any VEGFR or mTOR inhibitor	64 (22)	91 (63)
Pazopanib	1 (<1)	79 (54)
Sunitinib	36 (12)	11 (8)
Sorafenib	33 (11)	7 (5)
Temsirolimus	4 (1)	4 (3)
Everolimus	5 (2)	2 (1)
Bevacizumab	3 (1)	0
Any cytokine	25 (9)	8 (6)
Other	8 (3)	2 (1)
Number of subsequent anticancer therapies		
1	64 (22)	78 (54)
2	19 (7)	16 (11)
⩾3	5 (2)	1 (<1)
Days to start of subsequent anticancer therapies, median (range)	323 (45–1075)	202 (43–861)

mTOR = mammalian target of rapamycin; VEGFR = vascular endothelial growth factor receptor.

likely ineligible for additional therapy (11% in both arms had ECOG PS ⩾ 3 or died within 1–3 months of discontinuing study drug). However, a greater proportion of patients with better prognosis (life expectancy >3 months and ECOG PS 0–2 at discontinuation) in the pazopanib arm versus the placebo arm did not receive additional treatment (34% versus 12%, respectively), most likely because effective therapeutic options were not available.

3.1.2. Exploratory analyses to assess impact of crossover on OS

In the IPCW analysis, treatment with pazopanib was associated with ~50% reduction in the risk of mortality (HR = 0.50; 95% CI, 0.315–0.762; two-sided $P = .002$) versus placebo (Table 3).

The point estimate from the RPSFT analysis also suggests improved OS with pazopanib treatment (HR = 0.43; 95% CI, 0.215–1.388; two-sided $P = .172$). Although adjusted OS durations were calculated for the placebo arm within this analysis, the median OS was not reached because of the short length of the adjusted follow-up.

3.1.3. OS analyses in prior treatment subgroups

Similar to the ITT analysis of the overall study population, ITT analyses in these subgroups did not show a statistically significant improvement in OS with pazopanib (Table 3). These analyses were also confounded because of the imbalance in treatments at crossover. Post-hoc IPCW and RPSFT analyses on both subgroups showed results similar to the overall study

Table 3
Summary of statistical analysis of overall survival.

Population	Methodology	Hazard ratio (95% CI)	Overall survival, median months (95% CI)	
			Placebo[*]	Pazopanib
Overall	ITT	0.91 (0.71–1.16)	20.5 (15.6–27.6)	22.9 (19.9–25.4)
	IPCW	0.50 (0.315–0.762)		
	RPSFT	0.43 (0.215–1.388)		
Treatment-naive	ITT	1.01 (0.72–1.42)	23.5 (12.0–34.3)	22.9 (17.6–25.4)
	IPCW	0.64 (0.266–1.248)		
	RPSFT	0.31 (0.073–1.715)		
Cytokine-pretreated	ITT	0.82 (0.57–1.16)	18.7 (14.2–26.3)	22.7 (19.3–28.3)
	IPCW	0.53 (0.315–1.112)		
	RPSFT	0.53 (0.341–4.849)		

CI = confidence interval, IPCW = inverse probability of censor weighting; ITT = intent-to-treat; RPSFT = rank-preserving structural failure time.
[*] An adjusted placebo median could not be estimated in any of the RPSFT analyses.

population, suggesting a trend for improvement in survival that was not statistically significant.

3.2. Safety

3.2.1. Exposure to study treatment

Since the previous clinical cutoff in May 2008, there has been a 30% increase in cumulative exposure in the pazopanib arm (increase of 70 patient-years, from 233.5 to 303.7). This increase resulted from the 63 patients (22%) who continued pazopanib treatment after the first cutoff. At the final OS cutoff, 93 (32%), 43 (15%) and 23 (8%) patients had received pazopanib treatment for more than 12, 24 and 36 months, respectively. The median duration of exposure remained the same as previously reported (pazopanib 7.4 months versus placebo 3.8 months).

3.2.2. Adverse events

The AE profile at final analysis (Table 4) was similar to that previously reported.[11] In the pazopanib arm, diarrhoea, hypertension and hair colour change remained the most common AEs, with the incidence of grade 3/4 AEs only slightly increased (from 33% and 7% to 36% and 9%, respectively). Treatment discontinuation due to AEs increased by 1% (16% versus 15%). Liver abnormalities (3.8%), diarrhoea (2%) and arterial thrombotic events (2%) were the most common reasons for treatment discontinuation. Treatment-emergent hypertension had an early onset and was manageable with antihypertensive medication and/or study drug dose modification; only two patients discontinued study treatment.

Adverse events with an incidence of <10% that are considered a class effect associated with tyrosine kinase inhibitors are shown in Table 5.

3.2.3. Laboratory abnormalities

Alanine aminotransferase (ALT) elevations greater than 3 × upper limit of normal (ULN) occurred in 54 patients (18.6%), including 20 (7%) with ALT elevations greater than 8 × ULN. Of these 54 patients, 46 (85%) had documented recovery (defined as ALT recovered to grade ⩽ 1 or 2.5 × ULN) with or without dose interruption. Of the remaining eight patients, four did not have complete follow-up but ALT was trending down during available follow-up, two had no follow-up and two died without recovery. One of the patients who died without recovery had extensive hepatic metastases found at autopsy. The second patient who died without recovery had extensive metastatic disease and died of respiratory and cardiac failure.

4. Discussion

In this phase III study, pazopanib demonstrated a statistically significant and clinically meaningful improvement in PFS compared with placebo in treatment-naive and cytokine-pretreated patients with advanced RCC.[11] However, pazopanib did not show a statistically significant effect on OS in the final ITT analysis. This lack of correlation between OS and PFS is likely due to the extensive crossover of placebo-treated patients to pazopanib via the parallel open-label extension, as well as other subsequent anticancer treatments that patients from both arms received after progression. Similar confounding issues on final OS analysis were also reported for other phase III advanced RCC trials with anti-VEGFR and mTOR inhibitors.[19–23]

The availability of pazopanib for placebo patients created an imbalance in access to post-progression therapy between treatment arms. When this study was initiated in April 2006, there was limited access to alternative targeted agents in the countries where the study was conducted. Whereas placebo-treated patients had access to pazopanib treatment after progression, patients from both arms had limited access to other active systemic anticancer therapies as shown in Table 2. Compared to historical survival data in advanced RCC when cytokines were the mainstay treatment (median

Table 4
Treatment-emergent adverse events and laboratory abnormalities regardless of causality in ⩾ 10% of patients.

Adverse events*	Patients, n (%)					
	Pazopanib (N = 290)			Placebo (N = 145)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Diarrhoea	152 (52)	11 (4)	2 (<1)	13 (9)	1 (<1)	0
Hypertension	116 (40)	13 (4)	0	15 (10)	1 (<1)	0
Hair colour changes	109 (38)	1 (<1)	0	4 (3)	0	0
Nausea	74 (26)	2 (<1)	0	13 (9)	0	0
Anorexia	70 (24)	6 (2)	0	17 (12)	1 (<1)	0
Vomiting	62 (21)	7 (2)	1 (<1)	13 (9)	3 (2)	0
Fatigue	57 (20)	7 (2)	0	14 (10)	2 (1)	2 (1)
Asthaenia	42 (14)	8 (3)	0	13 (9)	0	0
Haemorrhage	41 (14)	3 (1)	0	9 (6)	1 (<1)	0
Abdominal pain	32 (11)	7 (2)	0	2 (1)	0	0
Headache	31 (11)	0	0	7 (5)	0	0
Proteinuria	30 (10)	6 (2)	1 (<1)	0	0	0
Weight decreased	30 (10)	2 (<1)	0	5 (3)	1 (<1)	0
Laboratory Abnormalities†						
Clinical chemistry‡						
ALT increase	153 (53)	31 (11)	5 (2)	33 (23)	2 (1)	0
AST increase	153 (53)	21 (7)	2 (<1)	28 (19)	1 (<1)	0
Hyperglycaemia	120 (43)	2 (<1)	0	48 (33)	2 (1)	0
Hyperbilirubinaemia	103 (37)	7 (3)	2 (<1)	16 (11)	2 (1)	1 (<1)
Hypophosphatemia	100 (36)	15 (5)	0	18 (13)	2 (1)	0
Hypocalcaemia	96 (35)	4 (1)	4 (1)	35 (26)	2 (1)	1 (<1)
Hyponatremia	92 (33)	12 (4)	4 (1)	35 (24)	6 (4)	0
Hypoglycaemia	50 (18)	0	1 (<1)	4 (3)	0	0
Hypokalaemia	28 (10)	3 (1)	2 (<1)	3 (2)	0	0
Haematologic						
Leukopaenia	106 (38)	1 (<1)	0	10 (7)	0	0
Neutropenia	100 (36)	4 (1)	1 (<1)	9 (6)	0	0
Thrombocytopenia	95 (34)	4 (1)	1 (<1)	7 (5)	0	1 (<1)
Lymphopaenia	96 (34)	13 (5)	1 (<1)	35 (24)	2 (1)	0
Anaemia	73 (26)	6 (2)	3 (1)	45 (31)	2 (1)	1 (<1)

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

* In the pazopanib arm, 13 patients (4%) were reported with grade 5 adverse events. Among the 13 cases, 4 (1%) were assessed by investigator as related to study treatment: gastrointestinal haemorrhage, gastrointestinal perforation, cerebral vascular accident and hepatic replacement by tumour; 2 with tumour bleeding were assessed with final cause of death as due to disease under study. In the placebo arm, 4 patients (3%) were reported with grade 5 adverse events. Among these 4 cases, none was assessed by investigator as related to study treatment and 1 (asthaenia) was assessed with the final cause of death as due to the disease under study.

† Percentages are based on the number of patients with post-baseline data.

‡ Selected clinical chemistry parameters.

Table 5
Adverse events of clinical interest associated with anti-VEGFR tyrosine kinase inhibitors.

Adverse events	Patients, n (%)			
	Pazopanib (N = 290)		Placebo (N = 145)	
	Any grade	Grade ⩾ 3	Any grade	Grade ⩾ 3
Mucositis/stomatitis	26 (9)	1 (<1)	1 (<1)	0
Hypothyroidism	19 (7)	1 (<1)	0	0
Hand-foot syndrome	17 (6)	2 (<1)	1 (<1)	0
Arterial thromboembolic event	13 (4)	9 (3)	0	0
Myocardial dysfunction	2 (<1)	2 (<1)	1 (<1)	1 (<1)

VEGFR = vascular endothelial growth factor receptor.

survival ~11–13 months),[24–27] in this trial the median OS in the placebo arm (20.5 months) was approximately doubled, which suggests that crossover to pazopanib may have substantially improved survival, although other subsequent treatments may have also contributed.

Given the extensive use of pazopanib by patients in the placebo arm, exploratory analyses using RPSFT and IPCW methodologies were conducted to correct for the effect of post-progression therapy on OS. These methods have been previously applied to adjust for selective crossover in oncology trials.[21,28–30] The use of more than one method was considered because no single methodology is theoretically superior, and concordance between analyses using different methods was sought. The analyses to adjust for crossover suggest an OS benefit with pazopanib treatment, but there are limitations that should be noted.

The IPCW modelling corrects for bias associated with censoring at selective change of treatment, given that the assumption of exchangeability is met. This assumption can be violated in small studies.[31] If the data are highly stratified by the predictors, there may be inadequate numbers of patients who did not receive additional therapy within each set of predictors to accurately measure what would have happened to patients with those same predictors who did receive another therapy. Post-progression data collection was also limited, so the modelling was less likely to accurately predict a treatment change long after progression. Most patients switch to a new treatment fairly soon after progression, but nevertheless, this is a limitation that could violate the exchangeability assumption.

In the RPSFT model, the assumed proportional relationship between treatment duration and change in survival is not validated. It is unclear to what degree deviations from these assumptions could bias the results. Additionally, RPSFT analysis is useful for estimating an adjusted HR, but it is not expected to change the conclusion regarding statistical significance reached by the ITT analysis. Moreover, in RPSFT analysis, when the estimated scale factor represents a large positive treatment effect on survival, as in the case of pazopanib, a step in the algorithm can result in the exclusion of a large portion of a study's control-arm follow-up (e.g. placebo arm in this study). Consequently, the final adjusted HR result will be based on the early follow-up of the control arm, which could bias results if the treatment effect was different in the early versus late study follow-up period.

Data on the treatment-naive patient subgroup have been included because of the high level of clinical interest in these results given the declining use of first-line cytokine therapy; however, these results must be interpreted with caution. In addition to confounding due to crossover, these analyses are limited by the small number of patients and/or deaths to precisely estimate either the HR or medians.

In addition to the confounding issue with crossover, evaluation of the true survival benefit as a single agent or single regimen has also been confounded by active subsequent anticancer therapies depending upon the extent of their utility. For example, in the recently reported phase III study of pazopanib versus sunitinib (VEG108844),[32] median OS in the pazopanib arm was 28.4 months (95% CI, 26.2–35.6), which is substantially longer than the median OS of 22.9 months (19.9–25.4) observed in the pazopanib arm from the current study. While such cross-study comparisons have limitations, the difference in the extent of subsequent anticancer therapies is noteworthy: 56% of pazopanib-treated patients in the VEG108844 trial received at least one subsequent anticancer treatment versus 30% in this trial, and 49% received any anti-VEGF or mTOR inhibitors versus 22% in this trial (unpublished data from VEG108844).

Extensive subsequent treatments may have also positively impacted OS for other anti-angiogenic agents. For example, the sunitinib versus interferon trial published by Motzer et al.[22] reported a median OS of 26.4 versus 21.8 months in the sunitinib and interferon arms, respectively; 56% of patients in the sunitinib arm received any post-study treatment, mostly anti-VEGF or mTOR inhibitors. In the pazopanib versus sunitinib trial VEG108844,[32] median OS in the sunitinib arm was 29.3 months (95% CI, 25.3–32.5); 55% of patients received subsequent anticancer treatment and 48% received any anti-VEGF or mTOR inhibitors.

In summary, assessment of OS benefit for pazopanib, as well as other approved anti-angiogenesis inhibitors in advanced RCC, has been confounded by both crossover and subsequent anticancer therapies. The aforementioned evidence supports the notion of potential survival benefit by using multiple lines of active agents in advanced RCC.

The safety update represents a total increase of 30.1% and 8.8% in cumulative patient-years for pazopanib- and placebo-treated patients, respectively. With this increase in total exposure, there have been no important changes to the type, frequency or severity of AEs, and no differences in grade 3/4 AEs since the previous clinical cutoff. Most AEs were mild to moderate in severity. Rare, but severe, AEs previously described for VEGFR inhibitors, including cardiac/cerebral ischaemia, haemorrhage and bowel perforation, were observed with pazopanib treatment. No new safety signals were detected, and overall, the safety profile was consistent with that previously reported with the clinical cutoff for PFS analysis.[11]

5. Conclusions

Although pazopanib treatment significantly improved PFS in patients with advanced/metastatic RCC compared with placebo, no statistically significant difference was observed in the final ITT analysis of OS. Final OS analysis of this study (VEG105192) was confounded by the extensive crossover of placebo patients to pazopanib. Post-hoc analyses adjusting for crossover

suggest an OS benefit with pazopanib treatment. Updated safety results showed a similar profile as reported previously, with no new safety signals identified.

Authorship contributions

CNS, CHB and SDR contributed to study conception/design, collection/assembly of data and analysis/interpretation of data. REH contributed to study conception/design, collection/assembly of data, analysis/interpretation of data and provision of materials/patients. IDD contributed to collection/assembly of data, analysis/interpretation of data and provision of materials/patients. JW, CS and LM contributed to collection/assembly of data and analysis/interpretation of data. PS contributed to study conception/design. JJZ and OAG contributed to analysis/interpretation of data and provision of material/patients. EL contributed to collection/assembly of data. MC contributed to study conception/design. All authors participated in writing/revising the manuscript and had final approval for publication.

Role of the funding source

GlaxoSmithKline funded this study, and GlaxoSmithKline employees McCann, Rubin and Chen were involved in study design, data management/analysis and writing. Dr. Sternberg had full access to the data and final responsibility for the decision to submit for publication.

Conflict of interest statement

CNS: Honoraria from Bayer, Novartis, Pfizer and GlaxoSmithKline. REH: Consultant/advisor to GlaxoSmithKline; honoraria from GlaxoSmithKline. IDD: Consultant/advisor to GlaxoSmithKline, Pfizer, Novartis and Bayer; all honoraria paid to institution. JW: Consultant/advisor to GlaxoSmithKline; honoraria from GlaxoSmithKline. JM: Honoraria related to medical education activities. CHB: Consultant/advisor to GlaxoSmithKline; honoraria and research funding from GlaxoSmithKline. JJZ: Consultant/advisor to GlaxoSmithKline; honoraria from GlaxoSmithKline. CS: Consultant/advisor to Pfizer, Bayer and AVEO; honoraria from Pfizer and Bayer. LM, SDR and MC: GlaxoSmithKline employees and stockholders. PS, OAD and EL: No potential conflict of interest.

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