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Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomised phase III trial

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ABSTRACT

Background: In a double-blind, randomised phase III trial of advanced renal cell carcinoma patients, pazopanib 800 mg QD ($n = 290$) versus placebo ($n = 145$) significantly prolonged progression-free survival (hazard ratio (HR) = 0.46, 95% confidence interval [CI] 0.34–0.62, p-value < 0.0001), without important differences in health-related quality of life (HRQoL). This *post-hoc* analysis evaluated time to HRQoL deterioration and whether tumour response/stabilisation was associated with HRQoL improvement.

Methods: HRQoL was assessed using EORTC QLQ-C30 and EQ-5D. Effect of pazopanib on time to ⩾20% decline from baseline in summary scores was estimated for all patients and by prior treatment. Analyses were conducted for different HRQoL deterioration thresholds. HRQoL changes were stratified by benefit and compared: complete response (CR) or partial response (PR) versus progressive disease (PD); CR/PR versus stable disease (SD), and SD versus PD.

Results: There was a trend for pazopanib patients to be less likely than placebo patients to experience ⩾20% HRQoL deterioration in EORTC-QLQ-C-30 global health status/QOL scale (HR = 0.77; 95% CI 0.57–1.03, not significant). Results by prior treatment and different HRQoL deterioration thresholds were similar. Patients with CR/PR and SD experienced significantly less HRQoL deterioration than those with PD ($p < 0.001$, $p = 0.0024$, respectively); mean differences between patients with CR/PR and PD exceeded the pre-determined minimally important difference (MID). Differences between patients with SD and PD did not exceed pre-determined MID. Results were generally consistent across treatment and EQ-5D summary scores.

Conclusion: Results support the favourable benefit-risk profile of pazopanib and suggest patients experiencing tumour response/stabilisation also may have better HRQoL compared to those without this response.

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1. Introduction

1.1. Background

Renal cell carcinoma (RCC) is the most common cancer of the kidney, with 30% of patients presenting with metastatic disease at initial diagnosis.[1,2] Treatments such as interleukin (IL)-2 or interferon (IFN)-α, which were until recently considered the standard of care, are associated with adverse events and symptoms that affect overall health-related quality of life (HRQoL). Several targeted therapies have recently been developed as new treatment options for RCC (e.g. monoclonal antibodies, multitargeted receptor tyrosine kinase inhibitors and mammalian target of rapamycin inhibitors), although these agents lead to frequent adverse events. However, as shown by several studies, these novel treatments generally result in better HRQoL or no differences in HRQoL compared to the current standard of care or placebo.[3]

Pazopanib is an oral small-molecule angiogenesis inhibitor that targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and c-kit. A randomised, double-blind, multi-center phase III trial ("study VEG105192") comparing pazopanib with placebo found that patients treated with pazopanib ($n = 290$) demonstrated significantly prolonged progression-free survival (PFS) compared to placebo ($n = 145$), in the sample of all patients (9.2 versus 4.2 months; hazard ratio [HR] = 0.46, 95% confidence interval [CI]: 0.34–0.62, p-value < 0.0001), in treatment-naïve patients (11.1 versus 2.8 months; HR = 0.40, 95% CI: 0.27–0.60, p-value < 0.0001), and in cytokine-pretreated patients (7.4 versus 4.2 months; HR = 0.54, 95% CI: 0.35–0.84, p-value < 0.001). Patients treated with pazopanib also experienced higher response rates compared to placebo patients in the sample of all patients 30% (95% CI: 25.1–35.6) versus 3% (95% CI: 0.5–6.4), in treatment-naïve patients 32% (95% CI: 24.3–38.9) versus 4% (95% CI: 0.0–8.1), and in cytokine-pretreated patients 29% (95% CI: 21.2–36.5) versus 3% (95% CI: 0.0–7.1).[4] Pre-planned analyses of HRQoL change from baseline at different assessment timepoints using a mixed-model repeated-measures model consistently showed no statistical difference between pazopanib and placebo arms at each assessment time point in global health status/HRQoL. Additionally, the between- and within-group differences were smaller than minimally important differences (MIDs). Therefore, compared with placebo, pazopanib increased PFS significantly and did not meaningfully reduce HRQoL despite adverse events.

To further evaluate the HRQoL associated with pazopanib treatment, the present study performed in-depth *post-hoc* analyses of HRQoL changes in patients treated with pazopanib versus placebo using the data from study VEG105192. This analysis extends the Sternberg et al.[4] findings of the original analysis which compared the magnitude of average changes in HRQoL between the treatment arms at each specific HRQoL assessment time point. The current analysis examines HRQoL data over the entire course of the trial rather than in fixed time points. For the present study, two separate exploratory analyses were performed. First, a time to HRQoL deterioration analysis was performed to compare patients treated with pazopanib versus placebo. This methodology was used previously to determine that the median time to health status deterioration was significantly greater for renal cancer patients on sorafenib versus placebo.[5] Another study utilised this methodology to compare time to deterioration among metastatic colorectal cancer patients who were randomised to treatment with chemotherapy with bevacizumab or placebo and found that bevacizumab prolonged overall survival and PFS without impairing the quality of life.[6] Second, the association of changes in HRQoL with response was analysed by stratifying HRQoL changes by response and comparing between groups with complete response (CR) or partial response (PR) versus stable disease (SD), CR/PR versus progressive disease (PD), and SD versus PD. Additional analyses were conducted since the dropout rate due to progression differed by treatment group and it was assumed that patients who progressed had deteriorated HRQoL. For these reasons, the original analysis presents a more conservative assessment of the effect of pazopanib on time to deterioration.

2. Data source, assessments and patients

2.1. Data source

Patient data for this study were obtained from the randomised, double-blind, placebo-controlled, multicenter phase III clinical trial that evaluated the efficacy and safety of pazopanib versus placebo in patients with locally advanced and metastatic RCC (mRCC). Details of the trial were previously described elsewhere.[4] The trial consisted of a screening/baseline period, a randomised double-blind treatment period, and a post-treatment follow-up period. Prior to randomisation, 435 eligible subjects were stratified based on Eastern Cooperative Oncology Group performance status (ECOG PS) (0 or 1), whether they had prior nephrectomy, and whether they had received prior systemic treatment for RCC (treatment-naïve or cytokine-pretreated). Subsequently, subjects were centrally randomised in a 2:1 ratio to receive either 800 mg pazopanib daily or a matching placebo. Patients on the placebo arm were eligible to receive pazopanib upon progression.

All subjects were followed until death, withdrawal of consent, or until trial completion, whichever came first. Efficacy evaluations consisted of disease response assessments and survival assessments; quality of life assessments were also conducted. Imaging-based disease assessments were performed at baseline, every 6 weeks up to week 24 and every 8 weeks thereafter. HRQoL data were collected at weeks 6, 12, 18, 24 and 48 and at investigational product discontinuation. Since HRQoL data collection only occurred during treatment, no data were collected after the visit assessing investigational product discontinuation. Post-progression HRQoL data were not collected per protocol because treatment did not continue post-progression.

The present study uses the data on clinical efficacy and HRQoL measurements from the trial.

2.2. Assessments of HRQoL

HRQoL was assessed using European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Ques-

tionnaire Core 30 (QLQ-C30) version 3 and EQ-5D. The EORTC QLQ-C30 is a generic, self-report, 30-item HRQoL cancer-specific instrument. It is grouped into five functional scales, three multi-item symptom scales, six individual questions concerning common symptoms (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), and two questions assessing overall HRQoL. Patients assessed how true each of the five statements had been for them on a four-point scale: 1 (not at all), 2 (a little), 3 (quite a bit), and 4 (very much). The rest of the questions assessed their health over the same four-point scale during the past week. The two global questions assessed the overall health and quality of life over a 7-point scale. The scoring of the EORTC QLQ-C30 was based on published methods that transformed all scales and single-item measures to scores between 0 and 100.

The EQ-5D is a standardised measure of health outcomes, providing a simple descriptive profile and a single index score for health. In this study, the preference-based algorithm derived from the general population in the United Kingdom by Dolan was used.[7] It contains a health status measure consisting of five items, each evaluated on a three-point scale. The health status measures include mobility, self-care, usual activities, pain, discomfort and anxiety/depression. The second part of the EQ-5D is a visual analog scale (VAS) where respondents rate how they feel about their current health, anchored at 0 and 100 (worst and best health states imaginable, respectively).

These results were interpreted using previously established MIDs for each HRQoL instrument (EORTC QLQ-C30: MID = 5–10,[8] EQ-5D utility index: MID = 0.08, and EQ-5D VAS: MID = 7[9]).

2.3. Patients

The study population included 435 adults (⩾18 years of age). Patients were eligible if they had a diagnosis of advanced RCC (Stage IV) of clear cell or predominantly clear cell histology, were treatment-naïve or cytokine pretreated, had measurable disease at baseline, had adequate organ function and had an ECOG PS of 0 or 1.

3. Methods

3.1. Analysis of time to HRQoL deterioration

3.1.1. Statistical analyses

Changes in HRQoL were defined based on the proportion of patients in each treatment arm (pazopanib or placebo) with the first recorded deterioration from the baseline score as defined by a given percentage (10%, 20%, and 30%)[10] instead of a MID. The process to select thresholds for deterioration of HRQoL from baseline followed the method described in FDA guidance for industry.[11] To determine the given percentage, we first examined the distribution of HRQoL deterioration from baseline and compared the distributions between patients treated with pazopanib versus placebo. The proportion of patients experiencing HRQoL deterioration from baseline was plotted for 0–100% HRQoL deterioration from baseline, for both pazopanib and placebo patients. These cumulative distribution curves were used to determine the thresholds for analysis by identifying the points of overlap between the placebo and pazopanib curves. Upon examining these curves, deterioration of 20% was chosen for the primary analyses and 10% and 30% were chosen for sensitivity analyses. As mentioned, results were interpreted in light of previously-published MIDs and earlier preliminary analyses with MID values rather than percent change values produced similar results.

Patients who did not experience HRQoL deterioration from baseline score by at least 20% were censored at the time of their last assessment. Time to the first deterioration was estimated using a Cox proportional hazard model with the treatment arm as the covariate of interest. Models were estimated with and without controls for baseline HRQoL scores. Analyses were performed on the sample of all patients and on samples of patients stratified by line of therapy (treatment-naïve versus cytokine-pretreated).

The global health status/QOL scale from the EORTC QLQ-C30 version 3 was used to perform the core analysis of HRQoL deterioration. Additional analyses considered deterioration using EQ-5D utility index and EQ-5D VAS as measures of HRQoL.

3.2. Analysis of response and HRQoL

3.2.1. Study design

Tumour response was evaluated centrally by an independent imaging review committee in a blinded fashion, based on the response evaluation criteria in solid tumours (RECIST) as CR, PR, SD or PD. The period between the first date of best response and progression was considered a period of best response. HRQoL assessments measured during the period of best response for each patient were included in the analyses, and changes in HRQoL from baseline were calculated. Comparisons of changes in HRQoL were performed for subjects whose best response was PD, CR/PR and SD.

3.2.2. Statistical analyses

All available HRQoL assessments during the periods of best response for each patient were used. A random-effects model was estimated to account for the intra-subject correlation of changes in HRQoL. Analyses were performed on the sample of all patients and on samples of patients stratified by treatment arm (pazopanib versus placebo). Univariate and multivariate versions of the model were developed to determine the association between changes in HRQoL with benefit defined by tumour response. The multivariate model was adjusted for baseline HRQoL score.

The core analysis was based on HRQoL assessments using the global health status/QOL scale from the EORTC QLQ-C30, which is a cancer-specific HRQoL instrument. In addition, similar HRQoL analyses were conducted using the EQ-5D utility index and EQ-5D VAS scores.

4. Results

4.1. Patient baseline characteristics

Baseline characteristics of the study population are presented in Table 1. The average age did not differ by treatment arm

Table 1 – Patient characteristics by treatment groups (N = 434).[a]

	Placebo (N = 145)	Pazopanib (N = 289)
Demographic characteristics		
Age		
Age (years; mean ± std)	59.6 ± 11.0	59.0 ± 10.0
Gender, N (%)		
Male	109 (75.2)	197 (68.2)
Race, N (%)		
White/caucasian	110 (75.9)	235 (81.3)
Baseline clinical characteristics		
First-line treatment, N (%)		
Treatment-naïve	78 (53.8)	155 (53.6)
Cytokine-pretreated	67 (46.2)	134 (46.4)
ECOG score, N (%)[b]		
0	60 (41.4)	123 (42.6)
1	85 (58.6)	166 (57.4)
Completion rates of HRQoL questionnaires		
EORTC QLQ-C30 questionnaire, N (%)[c]		
Baseline	142 (97.9)	288 (99.7)
Week 6	117 (92.9)	248 (96.1)
Week 12	83 (94.3)	222 (95.3)
Week 18	62 (88.6)	191 (93.2)
Week 24	51 (92.7)	164 (96.5)
Week 48	25 (96.2)	99 (93.4)
EQ-5D questionnaire, N (%)[c]		
Baseline	143 (98.6)	287 (99.3)
Week 6	119 (94.4)	248 (96.1)
Week 12	83 (94.3)	219 (94.0)
Week 18	62 (88.6)	191 (93.2)
Week 24	51 (92.7)	164 (96.5)
Week 48	24 (92.3)	98 (92.5)

Abbreviations: HRQoL, health-related quality of life.

[a] Out of 435 patients in the trial, 434 had non-missing information on HRQoL assessments.

[b] ECOG performance status: 0 = normal activity, asymptomatic; 1 = symptomatic, but fully ambulatory.

[c] Number of patients who completed the corresponding questionnaire at each visit.

(placebo: 59.6 years old versus pazopanib: 59 years old, p-value = 0.48). There were more males in the placebo group than in the pazopanib group, but the difference was not statistically significant (75% versus 68%, p-value = 0.13). HRQoL questionnaire response rates were high, ranging from 88.6% to 99.7% during the trial, and did not vary significantly between the treatment arms. Table 2 presents summary statistics on EORTC QLQ-C30 global health status/QOL scale, EQ-5D utility index, and their change from baseline by study week and treatment arm. For instance, among patients on placebo (baseline, n = 141), EORTC QLQ-C30 scores had declined by 0.5 (SD of change score = 17.55) among those patients retained at week 12 (n = 81).

4.2. *Analysis of time to HRQoL deterioration*

Among the population of study VEG105192 (n = 435), patients with non-missing HRQoL values at baseline and with at least one post-baseline HRQoL assessment were selected. HRQoL scores were available for 267 patients out of 289 in the pazopanib arm, and for 131 out of 145 in the placebo arm. As a result, the estimation sample comprised 398 patients.

Fig. 1a–c presents the Kaplan–Meier curves by treatment arm for all patients, treatment-naïve patients, and cytokine-pretreated patients, respectively. Fig. 2a shows that for the EORTC QLQ-C30 global health status/QOL scale, cumulative distribution functions of HRQoL deterioration since baseline for pazopanib patients and placebo patients intersect at 8%, 20%, 33%, and coincide after 55%. These points of intersection indicate that the same proportion of pazopanib and placebo patients experienced HRQoL deterioration of 8%, 20%, 33% and 55%. Thus, the data suggest using 10%, 20% and 30% as cutoff points for the time to deterioration analyses. Fig. 2b and c presents cumulative distribution functions for the EQ-5D utility index and EQ-5D VAS score.

Results for the core analysis are presented in the top panel of Table 3. Patients receiving pazopanib tended to have a lower risk of at least 20% HRQoL deterioration than the placebo group, but the difference was not statistically significant (all patients: univariate HR = 0.75, 95% CI: 0.55–1.01; multivariate HR = 0.77, 95% CI: 0.57–1.03). These results were consistent across treatment-naïve and cytokine-pretreated groups (treatment-naïve: univariate HR = 0.73, 95% CI: 0.49–1.10; multivariate HR = 0.75, 95% CI: 0.50–1.13; cytokine-pretreated: univariate HR = 0.75, 95% CI: 0.48–1.18; multivariate HR = 0.75, 95% CI: 0.48–1.18).

Results for the additional analyses are presented in the lower panel of Table 3 and in Tables 4 and 5. Patients receiving pazopanib tended to have lower risk for 10% and 30% HRQoL deterioration as measured by all three questionnaires. Significantly lower risks of at least 20% HRQoL deterioration (univariate HR = 0.70, 95% CI: 0.50–0.97, multivariate HR = 0.70, 95% CI: 0.51–0.98) and of at least 30% HRQoL deterioration (univariate HR = 0.66, 95% CI: 0.45–0.99; multivariate HR = 0.67, 95% CI: 0.45–0.99) were found in the sample of all patients when HRQoL was measured using the EQ-5D VAS.

The HRQoL in patients who discontinued HRQoL assessments due to treatment discontinuation because of progressive disease may be not be representative of subjects who continued HRQoL assessments without PD. These subjects with progressive disease may be more likely to experience HRQoL deterioration and, therefore, may represent informative censoring. Therefore, sensitivity analyses of HRQoL deterioration using a composite end-point were performed, where progressive disease and HRQoL deterioration were considered as an event. These additional analyses demonstrated that pazopanib had a lower risk of HRQoL deterioration compared with placebo patients.

4.3. *Analysis of response and HRQoL*

Among the population of study VEG105192 (n = 435), patients with non-missing information on tumour evaluations and HRQoL assessments at baseline and during the period of best response were selected. This information was available for 105 out of 145 patients in the placebo arm and for 223 patients out of 289 in the pazopanib arm. As a result, the estimation sample consisted of 328 patients.

Table 2 – Summary of change from baseline in EORTC QLQ-C30 global health status/QOL scale, EQ-5D utility index, and EQ-5D VAS.

		Baseline	Week 6	Week 12	Week 18	Week 24	Week 48
EORTC QLQ-C30							
Placebo	Global health status/QOL						
	Mean ± sd	65.8 ± 20.2	65.2 ± 21.96	67.5 ± 19.76	68.4 ± 20.42	67.3 ± 20.68	69.4 ± 19.91
	N	141	114	82	61	49	24
	Change from baseline						
	Mean ± sd	–	–2.6 ± 19.18	–0.5 ± 17.55	–0.3 ± 18.13	–0.5 ± 18.67	0.3 ± 15.63
	N	–	110	81	61	49	24
Pazopanib	Global health status/QOL scale						
	Mean ± sd	64.6 ± 20.31	62.6 ± 19.9	63.3 ± 20.76	64.6 ± 19.75	67.1 ± 18.49	69.2 ± 16.93
	N	286	245	221	193	166	97
	Change from baseline						
	Mean ± sd	–	–3.2 ± 19.66	–3.6 ± 20.16	–2.5 ± 21.70	0.1 ± 19.81	–0.3 ± 18.36
	N	–	243	219	191	164	96
EQ-5D index							
Placebo	Utility index						
	Mean ± sd	0.73 ± 0.24	0.72 ± 0.30	0.75 ± 0.23	0.76 ± 0.22	0.76 ± 0.23	0.80 ± 0.24
	N	143	127	87	62	51	24
	Change from baseline						
	Mean ± sd	–	–0.03 ± 0.27	0.01 ± 0.20	–0.01 ± 0.15	–0.001 ± 0.24	–0.01 ± 0.20
	N	–	125	86	62	51	24
Pazopanib	Utility index						
	Mean ± sd	0.72 ± 0.25	0.71 ± 0.22	0.70 ± 0.25	0.71 ± 0.26	0.71 ± 0.24	0.79 ± 0.20
	N	287	255	221	197	168	98
	Change from baseline						
	Mean ± sd	–	–0.01 ± 0.22	–0.04 ± 0.21	–0.02 ± 0.23	–0.03 ± 0.24	0.03 ± 0.20
	N	–	253	219	196	166	98
EQ-5D VAS							
Placebo	VAS score						
	Mean ± sd	65.9 ± 23.84	64.7 ± 24.37	68.6 ± 22.75	68.4 ± 20.24	70.4 ± 19.5	73.1 ± 17.29
	N	141	115	82	61	49	23
	Change from baseline						
	Mean ± sd	–	–3.6 ± 23.04	0.2 ± 25.35	0.1 ± 19.35	5.4 ± 21.27	8.8 ± 23.96
	N	–	111	80	60	49	23
Pazopanib	VAS score						
	Mean ± sd	64.6 ± 23.69	65.5 ± 21.84	67.8 ± 20.89	67.6 ± 20.18	70.8 ± 17.32	72.0 ± 17.78
	N	283	244	216	191	164	95
	Change from baseline						
	Mean ± sd	–	–0.9 ± 21.07	0.4 ± 22.55	0.1 ± 23.20	2.6 ± 22.16	2.4 ± 24.21
	N	–	239	212	189	161	95

The results for these analyses are presented in Table 6. Patients whose best response was PD experienced greater deterioration of HRQoL than patients with CR/PR or SD as the best response. Patients whose best response was SD experienced greater deterioration of HRQoL than patients with CR/PR. In the sample of all patients assessed by the EORTC QLQ-C30 questionnaire, the multivariate differences in HRQoL change between patients with CR/PR and SD, between patients with CR/PR and PD, and between patients with SD and PD were 5.2, 11.8 and 6.5, respectively. All three multivariate differences were statistically significant (95% CI: 1.2–9.3, 95% CI: 7.1–16.5, and 95% CI: 2.3–10.7, respectively). Among patients treated with placebo, patients with SD experienced significantly less HRQoL deterioration than patients with PD (multivariate difference 10.3; 95% CI: 4.2–16.3). Among patients treated with pazopanib, patients with CR/PR experienced significantly less HRQoL deterioration compared to patients with SD and patients with PD (multivariate difference 7.6; 95% CI: 3.1–12.1 and 12.2; 95% CI: 6.3–18.2, respectively). Similarly, statistically significant differences in change scores were also observed when using the EQ-5D utility index and EQ-5D VAS as measures of HRQoL. While many differences were

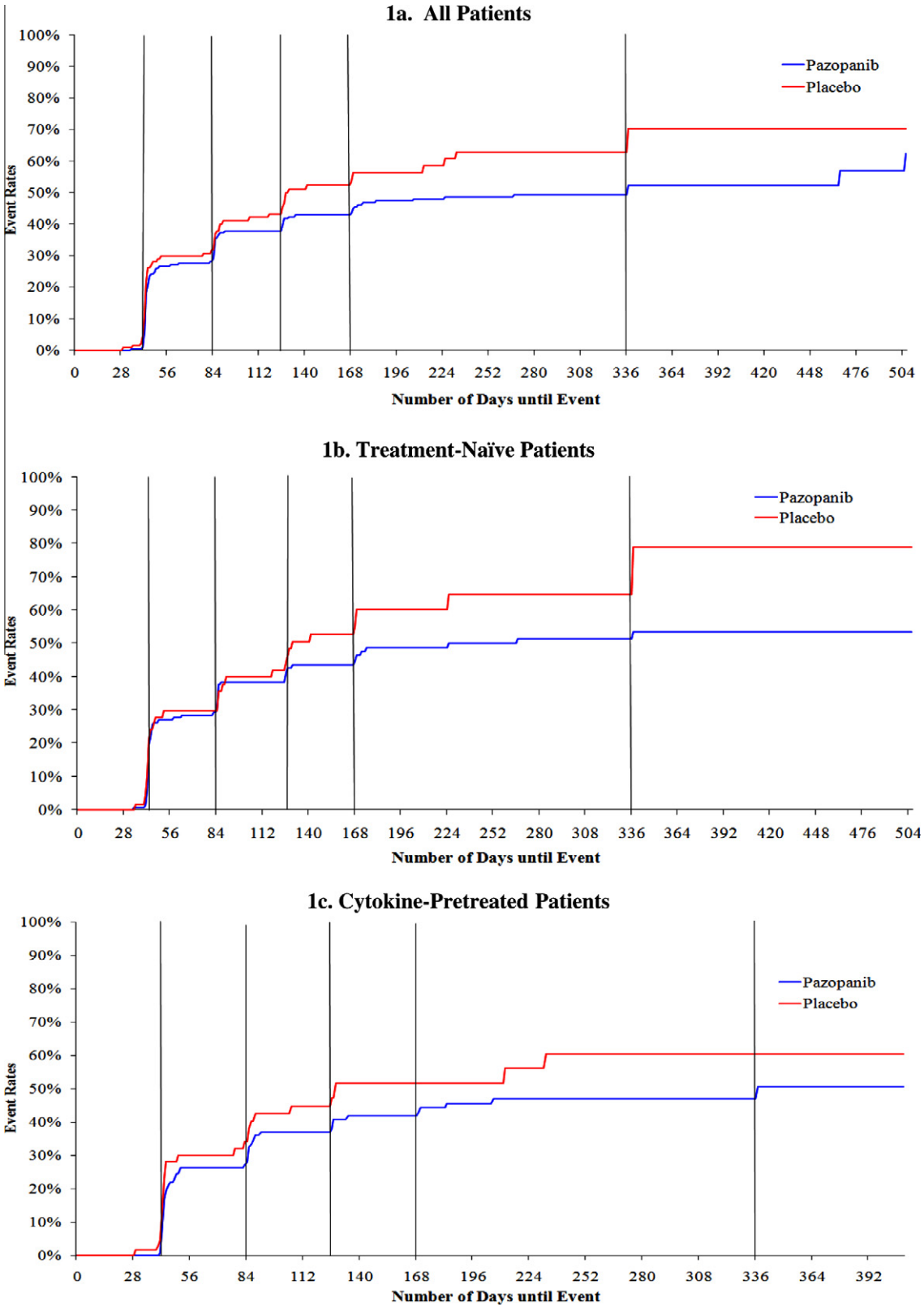

Fig. 1 – Kaplan–Meier estimates – comparison of 20% QoL deterioration rates of pazopanib and placebo patients, EORTC-QLQ30.

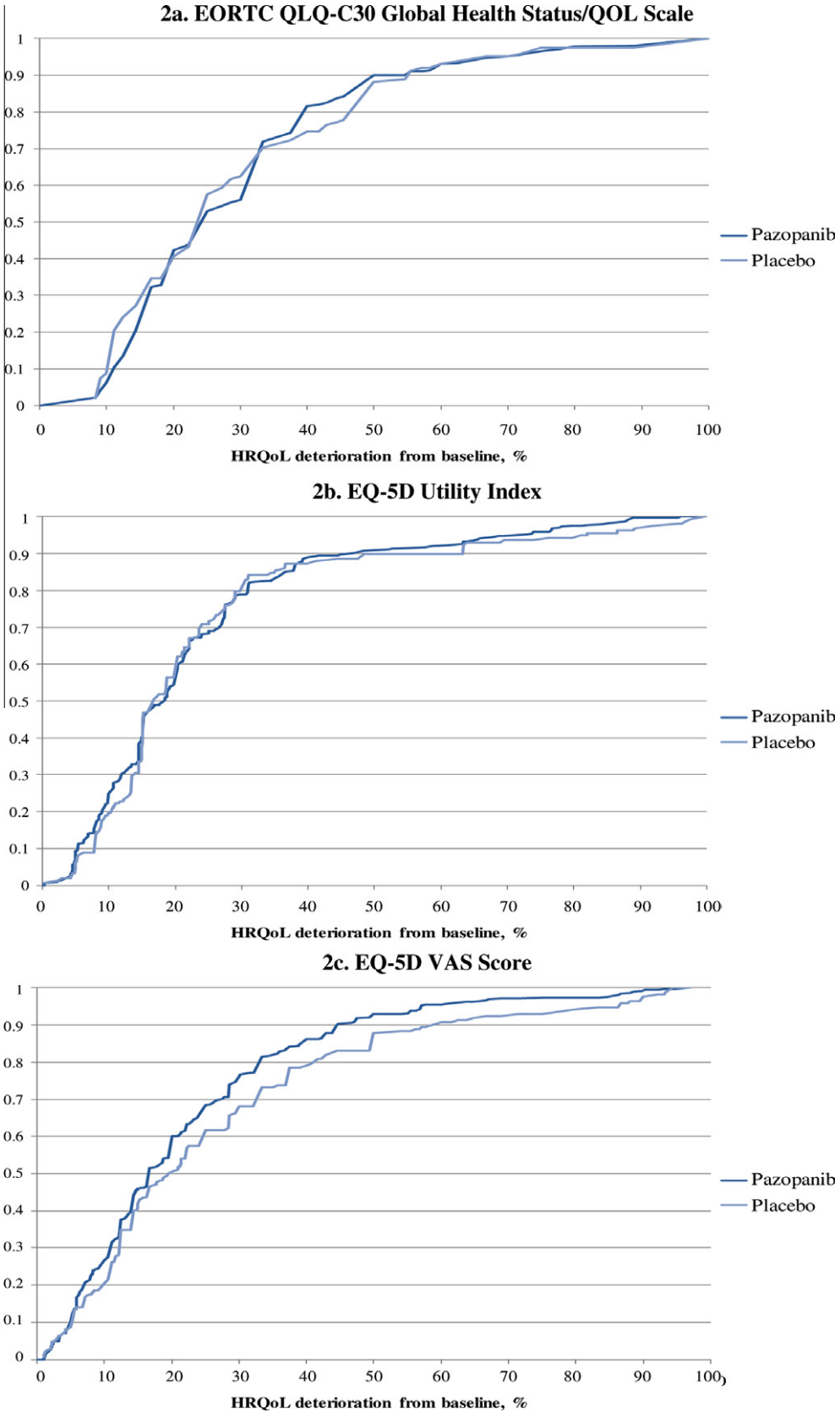

Fig. 2 – Cumulative distribution functions of HRQoL deterioration.

Table 3 – Hazard ratios for time to 20% HRQoL deterioration.

	Number of patients who experienced HRQoL deterioration of at least 20%			Time to HRQoL deterioration of at least 20% from baseline			
	Placebo *N* (%)	Pazopanib *N* (%)	*p*-Value[a]	Univariate HR[b] (95% CI)	*p*-Value	Multivariate HR[b,c] (95% CI)	*p*-Value
Core analysis							
EORTC QLQ-C30 global health status/QOL scale							
All patients	66 (50.4)	124 (46.4)	0.4597	0.75 (0.55–1.01)	0.0583	0.77 (0.57–1.03)	0.0817
Cytokine-pretreated	30 (47.6)	57 (46.3)	0.8687	0.75 (0.48–1.18)	0.2189	0.75 (0.48–1.18)	0.2141
Treatment-naïve	36 (52.9)	67 (46.5)	0.3832	0.73 (0.49–1.10)	0.1345	0.75 (0.50–1.13)	0.1698
Additional analyses							
EQ-5D utility index							
All patients	49 (36.3)	124 (46.3)	0.0563	1.01 (0.72–1.41)	0.9513	1.02 (0.73–1.42)	0.9279
Cytokine-pretreated	21 (32.3)	53 (43.1)	0.1501	0.94 (0.56–1.57)	0.8107	0.91 (0.55–1.53)	0.7238
Treatment-naïve	28 (40.0)	71 (49.0)	0.2165	1.07 (0.69–1.66)	0.7679	1.08 (0.70–1.68)	0.7274
EQ-5D VAS							
All patients	57 (43.2)	104 (39.4)	0.4694	0.70 (0.50–0.97)	0.0305*	0.70 (0.51–0.98)	0.0350*
Cytokine-pretreated	25 (39.1)	40 (33.3)	0.4387	0.64 (0.39–1.06)	0.0852	0.66 (0.39–1.09)	0.1037
Treatment-naïve	32 (47.1)	64 (44.4)	0.7211	0.73 (0.48–1.12)	0.1460	0.72 (0.47–1.11)	0.1399

Abbreviations: HRQoL, health-related quality of life; HR, hazard ratio; VAS, visual analog scale.

[a] *p*-Values were computed using Chi-Square tests for discrete variables.

[b] HR = $\text{hazard}_{\text{pazopanib}}/\text{hazard}_{\text{placebo}}$.

[c] Multivariate hazard ratios were estimated controlling for baseline score.

* Statistically significant at the 95% level.

Table 4 – Hazard ratios for time to 10% HRQoL deterioration.

	Number of patients who experienced HRQoL deterioration of at least 10%			Time to HRQoL deterioration of at least 10% from baseline			
	Placebo N (%)	Pazopanib N (%)	p-Value[a]	Univariate HR[b] (95% CI)	p-Value	Multivariate HR[b,c] (95%CI)	p-Value
EORTC QLQ-C30 global health status/QOL scale							
All patients	77 (58.8)	161 (60.3)	0.7712	0.87 (0.66–1.15)	0.3259	0.92 (0.70–1.21)	0.5416
Cytokine-pretreated	33 (52.4)	73 (59.3)	0.3636	0.96 (0.63–1.45)	0.8415	0.99 (0.65–1.49)	0.9517
Treatment-naïve	44 (64.7)	88 (61.1)	0.6143	0.80 (0.56–1.15)	0.2283	0.85 (0.59–1.23)	0.3886
EQ-5D utility index							
All patients	73 (54.1)	161 (60.1)	0.2492	0.93 (0.70–1.23)	0.5976	0.94 (0.71–1.24)	0.6647
Cytokine-pretreated	32 (49.2)	71 (57.7)	0.2658	0.95 (0.62–1.44)	0.8029	0.92 (0.61–1.41)	0.7069
Treatment-naïve	41 (58.6)	90 (62.1)	0.6223	0.91 (0.63–1.32)	0.6072	0.94 (0.65–1.37)	0.747
EQ-5D VAS							
All patients	76 (57.6)	152 (57.6)	1.0000	0.80 (0.60–1.05)	0.1062	0.81 (0.61–1.07)	0.1334
Cytokine-pretreated	39 (60.9)	68 (56.7)	0.5759	0.75 (0.51–1.12)	0.1619	0.75 (0.51–1.12)	0.1619
Treatment-naïve	37 (54.4)	84 (58.3)	0.5903	0.88 (0.59–1.29)	0.5074	0.87 (0.59–1.28)	0.4842

Abbreviations: HRQoL, health-related quality of life; HR, hazard ratio; VAS, visual analog scale.

[a] p-Values were computed using Chi-Square tests for discrete variables.

[b] HR = $\text{hazard}_{\text{pazopanib}}/\text{hazard}_{\text{placebo}}$.

[c] Multivariate hazard ratios were estimated controlling for baseline score.

statistically significant, in all cases, the confidence intervals did not exclude values smaller than the MID.

5. Discussion

The present exploratory study was carried out in order to further evaluate and compare HRQoL in advanced renal cell carcinoma patients treated with pazopanib or placebo. Taken together, the analyses suggest that there was a trend for pazopanib treatment to be associated with less HRQoL deterioration and a longer time to deterioration than the placebo group. In some analyses, we observed less risk for HRQoL deterioration for pazopanib that was also statistically significant. The results tended to be consistent for different measures of HRQoL and thresholds of HRQoL deterioration. Since most RCC patients present with no clinical symptoms in the first-line setting HRQoL similar to baseline is an encouraging outcome in this patient population.

In terms of the association of changes in HRQoL with response, patients whose best response was CR/PR or SD experienced significantly less HRQoL deterioration compared to patients whose best response was PD. For the EORTC QLQ-C30 (global health status/QOL scale), the mean differences between patients with CR/PR and patients with PD exceeded previously established MIDs and were within MID between patients with SD and PD. For the EQ-5D utility index and EQ-5D VAS score, the differences between groups exceeded the MID. In all cases, confidence intervals did not exclude values smaller than MID.

The preliminary HRQoL results reported by Sternberg et al. were focused on the pre-planned analysis for HRQoL in the registration trial. Commonly, *post-hoc* analyses of HRQoL may provide an extension to the statistical methods used in analyses of HRQoL in clinical trials in order to evaluate additional end-points, results in sub-populations, etc. which may be beyond the trial-based analyses. In this study, the HRQoL analysis was extended in *post-hoc* analysis by conducting a time to event analysis (i.e. time to deterioration) and a responder analysis.

There are three important differences in the methodologies used in this *post-hoc* versus the pre-planned analyses. First, the present analysis compared the magnitude and timing of HRQoL deterioration between patients receiving pazopanib and patients receiving placebo. In this case, observations with HRQoL improvements or no change in HRQoL were censored. In contrast, the analyses reported by Sternberg et al. compared the magnitude of average changes in HRQoL between the treatment arms at each specific HRQoL assessment time point. In this case, observations with HRQoL improvements and no changes in HRQoL were considered. If one treatment group had a homogenous, moderate response and the other treatment group had a bimodal distribution in terms of response (e.g. some patients improved a lot and others deteriorated a lot) then no difference in HRQoL between treatment arms may have been detected when looking at the difference in average change in response. Therefore, the current *post hoc* approach is not directly comparable with the pre-planned analyses.

Second, the present analysis population was defined in a somewhat different manner than in the original analysis. To

Table 5 – Hazard ratios for time to 30% HRQoL deterioration.

	Number of patients who experienced HRQoL deterioration of at least 30%			Time to HRQoL deterioration of at least 30% from baseline			
	Placebo *N* (%)	Pazopanib *N* (%)	*p*-Value[a]	Univariate HR[b] (95% CI)	*p*-Value	Multivariate HR[b,c] (95%CI)	*p*-Value
EORTC QLQ-C30 global health status/QOL scale							
All patients	46 (35.1)	92 (34.5)	0.8969	0.80 (0.56–1.15)	0.2266	0.82 (0.57–1.17)	0.2715
Cytokine-pretreated	19 (30.2)	41 (33.3)	0.6611	0.85 (0.49–1.48)	0.5750	0.85 (0.49–1.47)	0.5650
Treatment-naïve	27 (39.7)	51 (35.4)	0.5455	0.77 (0.48–1.22)	0.2617	0.77 (0.48–1.24)	0.2805
EQ-5D utility index							
All patients	32 (23.7)	84 (31.3)	0.1099	1.04 (0.69–1.56)	0.8705	1.01 (0.67–1.53)	0.9525
Cytokine-pretreated	16 (24.6)	38 (30.9)	0.3655	0.86 (0.48–1.56)	0.6237	0.88 (0.49–1.59)	0.6675
Treatment-naïve	16 (22.9)	46 (31.7)	0.1787	1.19 (0.67–2.10)	0.56	1.08 (0.61–1.92)	0.7941
EQ-5D VAS							
All patients	39 (29.5)	71 (26.9)	0.5787	0.66 (0.45–0.99)	0.0427*	0.67 (0.45–0.99)	0.0458*
Cytokine-pretreated	17 (26.6)	26 (21.7)	0.4548	0.54 (0.29–1.02)	0.0563	0.55 (0.29–1.03)	0.0599
Treatment-naïve	22 (32.4)	45 (31.3)	0.8719	0.75 (0.45–1.26)	0.2795	0.75 (0.45–1.26)	0.2771

Abbreviations: HRQoL, health-related quality of life; HR, hazard ratio; VAS, visual analog scale

[a] *p*-Values were computed using Chi-Square tests for discrete variables.

[b] HR = $\text{hazard}_{\text{pazopanib}}/\text{hazard}_{\text{placebo}}$.

[c] Multivariate hazard ratios were estimated controlling for baseline score.

* Statistically significant at the 95% level.

be included in the present analysis, patients were required to have a non-missing baseline HRQoL assessment and at least one post-baseline HRQoL assessment, which allowed for the majority of patients to be included in the analyses. On the other hand, in Sternberg et al. patients were included in the analyses only if they had a non-missing baseline HRQoL assessment as well as a non-missing HRQoL assessment at each specific time point analysed (i.e. week 6, 12, 18, 24, and 48).

Third, missing data due to progression affected each of the analyses differently. If patients who progressed were more likely to experience worse HRQoL, the mean HRQoL changes used in the pre-planned analyses would be biased upwards when measured at time points after patients who progressed had dropped out. Since the dropout rates due to progression were higher for placebo patients, missing HRQoL evaluations would favour placebo compared to pazopanib at later time points in the study. In the *post hoc* analyses, a Cox model was used, in which patients who dropped out due to progression were censored. When sensitivity analyses were conducted in this study, and it was assumed that patients who progressed had deteriorated HRQoL, the reduction of risk of deterioration for pazopanib patients versus placebo patients was even larger. This is due to the fact that placebo patients were more likely to progress.

This study contributes to previous literature related to analyses of changes in HRQoL in patients with mRCC treated with novel targeted therapies. The present study uses different instruments for the assessment of HRQoL than previous studies focusing on other therapies. Such studies have used, for example, the treatment satisfaction questionnaire for medication (TSQM), the functional assessment of cancer therapy – general (FACT-G) or the FACT – biologic response modifier (FACT-BRM), as well as instruments specific to kidney cancer, such as the FACT – kidney cancer symptom index (FKSI), especially FKSI-15 and FKSI-DRS, and the recently developed RCC symptom index.

Evaluation of HRQoL is an important component to the evaluation of novel therapeutics. In general, targeted treatments have been found to result in better post-treatment HRQoL in patients with mRCC compared to the previous standard of care (IFN-α) or placebo.[3] For example, a multi-center randomised phase III clinical trial comparing sunitinib with IFN-α in treatment-naïve patients with mRCC found that patients receiving sunitinib reported significantly better HRQoL compared to those receiving IFN-α, as measured by four alternative health measures: FACT-G, FKSI-15, EQ-5D (index) and EQ-VAS.[1,12] Sorafenib was found to improve individual items of the FACT-G and FKSI-15 instruments related to respiratory function and HRQoL in a phase III randomised placebo-controlled study of patients who failed on cytokine therapy.[5] In another study, sorafenib treatment was found superior to IFN-α for treatment-naïve patients in terms of HRQoL as measured by the FKSI-15 and TSQM and time to HRQoL deterioration.[13] Temsirolimus, a novel treatment used in patients with poor prognosis, was found to produce better results than IFN-α alone in terms of quality-adjusted survival (time without symptoms and toxicity weighted by values for HRQoL measured by the EQ-5D) in a phase III, randomised, 3-arm study of temsirolimus, IFN-α, and their combination.[14] Everolimus, recently approved by the FDA as treatment for RCC after

Table 6 – Average quality of life score changes from baseline, by response.[a]

	Patients with CR/PR		Patients with SD		Patients with PD		Multivariate difference[c] (95% CI)					
	N[b]	Score change (mean ± std)	N[b]	Score change (mean ± std)	N[b]	Score change (mean ± std)	CR/PR versus SD	*p*-Value	CR/PR versus PD	*p*-Value	SD versus PD	*p*-Value
EORTC QLQ-C30 global health status/QOL scale												
All patients	87	0.9 ± 17.5	157	–3.5 ± 18.0	84	–10.2 ± 18.4	5.2 (1.2–9.3)	0.0112*	11.8 (7.1–16.5)	<.0001**	6.5 (2.3–10.7)	0.0024**
Placebo patients	5	–1.1 ± 20.8	55	–0.1 ± 14.3	45	–10.5 ± 18.4	1.5 (–12.7–15.7)	0.8314	11.8 (–2.6–26.2)	0.1080	10.3 (4.2–16.3)	0.0011**
Pazopanib patients	82	1.1 ± 17.5	102	–5.4 ± 19.5	39	–9.8 ± 18.6	7.6 (3.1–12.1)	0.0011**	12.2 (6.3–18.2)	<.0001**	4.7 (–1.1–10.5)	0.1138
EQ-5D utility index												
All patients	88	–0.01 ± 0.15	157	–0.03 ± 0.23	86	–0.16 ± 0.29	0.02 (–0.04–0.07)	0.5319	0.15 (0.09–0.21)	<.0001**	0.13 (0.08–0.19)	<.0001**
Placebo patients	5	0.03 ± 0.11	55	0.01 ± 0.17	47	–0.15 ± 0.32	0.03 (–0.19–0.24)	0.8037	0.21 (–0.01–0.43)	0.0587	0.18 (0.09–0.28)	0.0001**
Pazopanib patients	83	–0.01 ± 0.15	102	–0.05 ± 0.25	39	–0.14 ± 0.26	0.04 (–0.02–0.09)	0.2074	0.14 (0.06–0.21)	0.0004**	0.10 (0.03–0.17)	0.0069**
EQ-5D VAS score												
All patients	86	1.9 ± 22.9	153	2.9 ± 22.1	85	–8.7 ± 19.6	2.9 (–1.6–7.4)	0.2087	10.8 (5.7–16.0)	<.0001**	7.9 (3.3–12.6)	0.0008**
Placebo patients	5	6.3 ± 20.7	54	3.6 ± 23.8	46	–9.6 ± 18.4	5.4 (–11.7–22.5)	0.5322	16.8 (–0.5–34.0)	0.0567	11.4 (4.1–18.6)	0.0025**
Pazopanib patients	81	1.6 ± 23.1	99	2.5 ± 21.3	39	–7.7 ± 21.1	4.0 (–1.0–9.0)	0.1156	9.7 (3.3–16.2)	0.0032**	5.8 (–0.5–12.0)	0.0732

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; VAS, visual analog scale.

[a] Only questionnaires during the relevant follow-up period were used for every patient in each group.

[b] *N* represents the number of patients. Some patients may have multiple questionnaires included.

[c] Multivariate difference was estimated modelling all score changes using random effects models, controlling for baseline score.

* Statistically significant at the 95% level.

** Statistically significant at 99% level.

failure of sunitinib or sorafenib or both, was found not to have a detrimental effect on HRQoL measured by the EORTC QLQ-C30 and the FKSI-DRS in a phase III, randomised, double-blind, placebo-controlled trial.[15]

The present study differs from the above-mentioned literature in several ways. First, the instruments used to assess HRQoL in the present study are not specifically tailored to measure HRQoL in patients with RCC; while the EORTC QLQ-C30 is a cancer-specific measure, the EQ-5D is a generic health measure. As a generic measure of health, EQ-5D allows for the direct comparison of treatments in terms of HRQoL across different conditions, and facilitates the calculation of quality-adjusted life years for the purposes of cost-utility analyses. The findings of the present study may have been different if RCC-specific HRQoL instruments, such as those used in the clinical trials of other targeted treatments for RCC, had been used, however, these instruments were not developed and fully validated at the time of the initiation of this trial. Second, the clinical trials of several targeted treatments investigated agents in slightly different treatment settings than the current trial. For example, sunitinib was investigated as a first-line treatment (i.e. in patients with no prior cytokine therapies), sorafenib was investigated as a second-line treatment (e.g. Bukowski et al., 2007[5] considered cytokine-pretreated patients), and everolimus was investigated in patients previously treated with sunitinib, sorafenib or both.[15] In contrast, study VEG105192 included both treatment-naïve and cytokine pretreated patients who had not been previously treated with any other angiogenesis inhibitor. Thus, the patient populations varied across studies.

The main limitation of the present study is related to the issue that HRQoL assessments per the assessment schedule in the study protocol were not performed after treatment discontinuation, including treatment discontinuation due to progression. This may cause potential biases in the results. These analyses did not correct for missing data due to differential withdrawal; correcting for the missing data may have an impact on the findings. Because disease progression was more frequent and generally occurred earlier in the placebo group compared to the pazopanib group, patients in the placebo group generally had fewer HRQoL assessments available. Patients who withdrew from the study due to progression may have been more likely to experience HRQoL deterioration, indicating informative censoring since the likelihood of censoring was dependent on the outcome. The higher dropout rate due to progression among patients receiving placebo would likely then result in patients with better HRQoL in the placebo group. Sensitivity analyses were conducted in this study where patients who progressed were assumed to have deteriorated HRQoL. The results showed that the reduction of risk of deterioration for pazopanib patients versus placebo patients was even larger. Therefore, the results presented here may underestimate the true difference in HRQoL between the pazopanib and placebo groups and may be biased in favour of the placebo group. If patients with disease progression had more HRQoL deterioration, then the present analysis would not capture particularly low values of HRQoL that may occur following progression. This would underestimate pazopanib's benefit in terms of HRQoL. It should be noted that the composite measure in this sensitivity analysis was a mixed end-point and while PD is a sufficient reason to discontinue treatment, deteriorated HRQoL may not be. Given the mixed nature of the measure, it may be difficult to interpret this particular finding in clinical practice.

6. Conclusions

Active cancer treatment may lead to considerable side-effects and thus negatively impact HRQoL, however, we found in a *post-hoc* analysis that there was a trend for patients treated with pazopanib to experience less HRQoL deterioration than the placebo patients, although the results were only statistically significant in a subset of analyses, namely for EQ-5D VAS. In addition, patients whose best response was CR/PR or SD experienced less HRQoL deterioration over the course of their treatment compared to patients whose best response was PD, and patients whose best response was CR/PR experienced less HRQoL deterioration than patients whose best response was SD. Significantly prolonged PFS and a generally well-tolerated safety profile for pazopanib were reported previously[4]; the benefit of pazopanib was further supported by evidence in this study that HRQoL was not compromised. As shown by the different validated methodologies, relative to placebo, pazopanib did not appear to impair the HRQoL of patients.

Conflict of interest and role of the funding source

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