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Original Article

Health-Related Quality-of-Life Results From PALETTE: A Randomized, Double-Blind, Phase 3 Trial of Pazopanib Versus Placebo in Patients With Soft Tissue Sarcoma Whose Disease Has Progressed During or After Prior Chemotherapy—A European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Global Network Study (EORTC 62072)

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BACKGROUND: Health-related quality of life (HRQoL) was an exploratory endpoint in the PALETTE trial, a global, double-blind, randomized, phase 3 trial of pazopanib 800 mg versus placebo as second-line or later treatment for patients with advanced soft tissue sarcoma (N = 369). In that trial, progression-free survival was significantly improved in the pazopanib arm (median, 4.6 vs 1.6 months; hazard ratio, 0.31; $P < .001$), and toxicity of pazopanib consisted mainly of fatigue, diarrhea, nausea, weight loss, and hypertension. **METHODS:** HRQoL was assessed using the 30-item core European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (EORTC QLQ-C30) at baseline and at weeks 4, 8, and 12 in patients who received treatment on protocol. The primary HRQoL endpoint was the EORTC QLQ-C30 global health status scale. **RESULTS:** Compliance with HRQoL assessments was good, ranging from 94% at baseline to 81% at week 12. Differences in scores on the EORTC QLQ-C30 global health status subscale between the 2 treatment arms were not statistically significant and did not exceed the predetermined, minimal clinically important difference of 10 points ($P = .291$; maximum difference, 3.8 points). Among the other subscales, the pazopanib arm reported significantly worse symptom scores for diarrhea ($P < .001$) loss of appetite ($P < .001$), nausea/vomiting ($P < .001$), and fatigue ($P = .012$). In general, HRQoL scores tended to decline over time in both arms. **CONCLUSIONS:** HRQoL did not improve with the receipt of pazopanib. However, the observed improvement in progression-free survival without impairment of HRQoL was considered a meaningful result. The toxicity profile of pazopanib was reflected in the patients' self-reported symptoms but did not translate into significantly worse overall global health status during treatment. *Cancer* 2015;121:2933-41. © *2015 American Cancer Society.*

KEYWORDS: advanced, pazopanib, quality of life, randomized clinical trial, soft tissue sarcoma.

INTRODUCTION

Soft tissue sarcomas (STS) are a rare and heterogeneous collection of mesenchymal cancers. Patients with advanced STS have a poor prognosis, with median overall survival (OS) of approximately 12 months from diagnosis of metastatic disease.[1] Therefore, treatment strategies should aim at more active treatments while also limiting treatment-related morbidity, controlling or alleviating symptoms, and retaining the performance of normal daily activities in as far as possible.

Patients with advanced STS often report difficulties with fatigue, pain, or respiratory symptoms, which can reduce their health-related quality of life (HRQoL) or restrict their independence.[2,3] These difficulties are caused not only by the disease itself but also by the treatment.

Because of the success of imatinib in producing a dramatic improvement in disease control by targeting KIT and platelet-derived growth factor (PDGF) in gastrointestinal stromal tumors,[4] there has been a major focus on identifying sarcoma subtypes with the appropriate targets for novel molecular-targeted agents. This has caused further fragmentation of treatment strategies in this already limited patient population.[5] STS growth is characterized by accelerated angiogenesis[6]; therefore, inhibiting this process could form an effective treatment strategy. Pazopanib (Votrient; GlaxoSmithKline Oncology, Uxbridge, UK) is a selective, multitargeted receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptor 1 (VEGFR-1), VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, and KIT. The PALETTE study, a global, double-blind, randomized, phase 3 trial that compared the efficacy of pazopanib versus placebo for the treatment of metastatic STS, investigated the HRQoL of patients in addition to progression-free survival (PFS) and OS. It is the only published phase 3 study to date of patients after failure on standard therapy for advanced STS.[7]

That study demonstrated that PFS was significantly prolonged with pazopanib (median, 18 weeks) compared with placebo (median, 6 weeks; hazard ratio, 0.31; 95% confidence interval [CI], 0.24-0.40; $P < .0001$).[8] The reported adverse events were representative of those expected for an angiogenesis inhibitor, with common on-therapy grade 3 and 4 toxicities in the pazopanib arm including fatigue (13%), hypertension (7%), anorexia (6%), and diarrhea (5%). Clinically relevant cardiac side effects were limited and manageable.

An exploratory objective of this study was to compare HRQoL outcomes between the 2 treatment arms using 2 psychometrically validated instruments that are widely used in trials of cancer patients: the 30-item core European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (EORTC QLQ-C30),[9] and the EuroQol 5D instrument (EQ-5D).[10] The current article focuses on reporting detailed HRQoL results from the EORTC QLQ-C30 in line with the requirements established by the Consolidated Standards of Reporting Trials Patient-Reported Outcomes extension.[11] EQ-5D data were used for cost-effectiveness analyses reported elsewhere.[12,13]

MATERIALS AND METHODS

Patients

The PALETTE study (EORTC 62072, GlaxoSmithKline VEG110727, and European Clinical Trials Database [EudraCT] 2008-001307-33) enrolled patients who had metastatic STS with documented, measurable progressive disease (during the last 6 months before the start of study drug or 12 months in patients who had received prior adjuvant treatment). Patients were aged ≥ 18 years, had a World Health Organization (WHO) performance status 0 or 1, and had failed at least 1 anthracycline-containing regimen. Full details of the eligibility criteria are reported elsewhere.[8] HRQoL assessments were described for patients in the informed consent form. The study protocol was approved by the local ethics committees and registered at clinicaltrials.gov (NCT00753688).

Study Design

PALETTE was a randomized, double-blind, placebo-controlled, phase 3 trial conducted by the EORTC Soft Tissue and Bone Sarcoma Group across 72 sites worldwide. The primary objective was to demonstrate superiority in PFS (defined as the time from randomization to either the first documentation of Response Evaluation Criteria in Solid Tumors-defined disease progression [according to an independent radiology review] or death from of any cause) of pazopanib over placebo. Secondary objectives included comparisons of OS, radiologically confirmed objective responses, and safety profiles (results reported previously[7]). An additional objective was to compare HRQoL between treatment arms using the EORTC QLQ-C30 instrument. Patients were randomized to the treatment arms in a 2:1 ratio to receive either pazopanib 800 mg once daily or placebo using a central, stratified, permuted block procedure. The stratification factors were the number of previous lines of systemic therapy received for advanced disease (0-1 vs ≥ 2 lines) and WHO performance status (0 vs 1). Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or death. After discontinuation of study treatment, further treatment was applied at the discretion of the patients and their physicians. The treatment arm allocation remained blinded until the time of final analysis or at the physician's request upon disease progression or medical emergency. No cross-over was allowed.

Assessments

The EORTC QLQ-C30 (version 3.0) is a 30-item questionnaire that assesses HRQoL in cancer patients across 9

multi-item scales: global health status (GHS), physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, pain, and nausea and vomiting. It also contains single-item measures of dyspnea, insomnia, anorexia, constipation, diarrhea, and financial impact).[9] It has been translated into many languages.[14] Patients provide their answers on a 4-point scale (from 1 [not at all] to 4 [very much]), except for GHS, which has a 7-point scale (from 1 [very poor] to 7 [excellent]). A linear transformation is used to standardize the raw score, so that overall scores range from 0 to 100. For the EORTC QLQ-C30, a higher score on GHS or on a functioning scale represents a better level of quality of life and functioning, and a higher score on a symptom scale represents a worse level of symptoms.[15] Patients were asked to finish the questionnaires as completely as possible at the beginning of their hospital visit.

Administration of the HRQoL questionnaires followed the clinical assessment schedule of the trial: the EORTC QLQ-C30 was completed at baseline (from 2 weeks before randomization to the start of treatment) and at weeks 4, 8, and 12 after starting treatment for patients who received protocol-specified treatment, allowing a 1-week window before and after the scheduled visit for questionnaire completion. If a patient discontinued protocol treatment or was unblinded, then HRQoL was no longer assessed. Guidelines for administering questionnaires were provided, ensuring standardization of HRQoL data by all personnel.[16]

Statistical Methods

The prespecified primary HRQoL outcome was GHS on the EORTC QLQ-C30 to test the hypothesis that patients who receive pazopanib would have improved HRQoL compared with patients in the placebo arm. To accommodate the repeated nature of the data, a linear mixed-effects model was constructed with treatment, time-effect and time-treatment interactions as fixed effects, and a patient-specific random effect. This model was applied to the data from all randomized patients, and the most suitable covariance structure was determined on the basis of Akaike Information Criterion.[17] Score estimates, standard errors, associated CIs, and subsequent tests were obtained from the resulting model. The primary test consisted of a general overall postbaseline test for no differences between the 2 treatment arms at all postbaseline time points using an overall F test statistic at a 5% level of significance. Because missing data are a problem in most HRQoL studies, sensitivity analyses were preplanned and performed investigating the informative

dropout by graphic evaluation and assessing the relation between selected variables (sex and the stratification factors: performance status and number of previous lines) and questionnaire compliance using logistic regression. In these analyses, factors that were associated with the missing data process were included as additional covariates in the mixed model. In addition, a linear regression model was used to predict the value of these missing data and to subsequently impute the data.[18] The main analysis was then repeated on this augmented data set. Further sensitivity analyses included limiting patient selection to the safety or per-protocol population, applying the primary model to the other scales of the EORTC QLQ-C30, and the use of summary statistics. For GHS, the difference between the baseline assessment and subsequent assessments was calculated 1) until the last available score, 2) until the lowest available score, and 3) as the average of all postbaseline scores. A final summary statistic was the percentage of patients reporting a change from baseline of ≥10-points at any time on the GHS scale. Differences of at least 10 points (on a 0-100 scale) were chosen because these correspond to the minimum clinically meaningful change in the HRQoL parameter).[19]

In post-hoc exploratory analyses, factor analysis and linear regression models were used to explore the correlations between HRQoL scores. Linear regression also was used to link relative dose intensities (ie, the amount of drug administered proportional to the protocol drug schedule) with HRQoL parameters. Prognostic factor analyses of PFS and OS were performed using Kaplan-Meier techniques and Cox proportional hazards regression. The exploratory tests were stratified for treatment allocation when possible. All analyses were done using the statistical software package SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Patients

In total, 369 patients (123 in the placebo arm and 246 in the pazopanib arm) were randomized in 16 months (October 2008 to February 2010) and represented the intent-to-treat population. Baseline demographics and clinical characteristics were well balanced between the 2 arms (Table 1). Additional data are reported elsewhere.[8]

HRQoL Completion Rates and Baseline Scores

Completion rates for HRQoL questionnaires in the intent-to-treat population are listed in Table 2. Compliance with HRQoL assessment was good, and 94% of patients completed the questionnaires at baseline. Compliance rates slowly decreased over time, with the lowest

rate reported at week 12 (78% and 81% for the placebo and pazopanib arms, respectively). No statistically significant differences in compliance rates between the 2 arms were observed at any time point, but patients in the placebo arm tended to complete fewer questionnaires, largely because of a higher progression rate. The median number of completed questionnaires was 3 for the pazopanib group and 2 for the placebo group. The mean and median HRQoL scores at baseline for the EORTC QLQ-C30 scales were comparable between the 2 treatment arms. Overall, compared with other studies, the compliance rates in our trial were within all acceptable limits.[20]

GHS Modeling

The overall test for postbaseline differences between the 2 treatment arms resulting from the repeated measures mixed effect with an unstructured covariance was not significant ($P = .291$). Differences in GHS between the 2 treatment arms assessed at each of the week-4, week-

8, and week-12 assessments were not statistically significant and did not reach the predetermined minimal clinically important difference of 10 points (Table 3). The maximum observed difference occurred at week 4 and was -3.8 points (95% CI, -9.0, 1.3), indicating a lower score in the pazopanib arm, but it was not beyond the 10-point threshold for clinical significance. Figure 1 illustrates the mean GHS scores estimated according to the model and the corresponding 95% CIs. In both arms, the mean GHS scores tended to decline over time.

Missing Data Mechanism

An investigation into the reported reasons for missing data revealed that the main documented reason was administrative failure (either the patient or the staff forgetting to complete the assessment), which accounted for 63% of all reported reasons for missing data. Missingness was not related to selected clinical prognostic variables.

Sensitivity Analyses

The mixed-effect model was replicated in the safety population (overall test for difference, $P = 282$) and in the per-protocol population ($P = .315$). In addition, although no variable was significantly linked to compliance, sex and the stratification factors were added as extra fixed-effects covariates ($P = .302$). All of these models yielded very similar results. Explicit regression imputation with imputed values predicted from a regression model that included certain variables (time, treatment group, sex, age, WHO performance score, the number of previous lines of systemic treatment for advanced disease) also confirmed that there were no significant differences (Supporting Table 1; see online supporting information). The change in GHS scores from baseline between the 2 treatment arms in terms of average or last reported scores were not clinically significant. However, a difference in terms of the minimum number and proportion of patients experiencing a 10-point decrease was reported, both in favor of the placebo arm (Table 4).

TABLE 1. Baseline Characteristics

	No. of Patients (%)	
	Placebo Arm, N = 123	Pazopanib Arm, N = 246
Age: Median [range], years	51.9 [18.8-78.6]	56.7 [20.1-83.7]
WHO performance status		
0	56 (45.5)	113 (45.9)
1	67 (54.5)	133 (54.1)
Histology, local		
Leiomyosarcoma	50 (40.7)	115 (46.7)
Synovial sarcoma	14 (11.4)	30 (12.2)
Other type	59 (48)	101 (41.1)
Grade, local[a]		
Low	3 (2.4)	24 (9.8)
Intermediate	30 (24.4)	63 (25.6)
High	90 (73.2)	159 (64.6)
Prior (neo)adjuvant therapy	36 (29.3)	58 (23.6)
Number of prior lines of therapy for advanced disease	110 (89.4)	232 (94.3)
0-1	52 (42.3)	110 (44.7)
2-4	71 (57.7)	136 (55.3)

Abbreviations: WHO, World Health Organization.
[a] Local grade at the time of initial diagnosis is indicated.

TABLE 2. Summary of QLQ-C30 Completion Rates

Treatment Arm	Compliance: No. of Forms Received/Expected (%)[a]			
	Baseline	Wk 4	Wk 8	Wk 12
Placebo arm	115/123 (93.5)	96/103 (93.2)	55/67 (82.1)	31/40 (77.5)
Pazopanib arm	232/246 (94.3)	194/220 (88.2)	148/179 (82.7)	126/155 (81.3)

[a] No statistically significant differences in compliance were observed between the 2 arms.

TABLE 3. Summary of the Health-Related Quality-of-Life Results

QLQ-C30 Scales						
Primary Scale of Interest	Secondary Scales of Interest					Sensitivity Analysis
GHS	Diarrhea	Loss of Appetite	Nausea/Vomiting	Fatigue	Role Functioning	Imputed GHS
P-value for test of overall difference						
.291	< .001	< .001	< .001	0.012	0.039	0.272
Difference between treatment arms (95% CI)[a]						
Baseline 1.4 (−3.7, 6.4)	1.9 (−2.1, 5.8)	0.1 (−6.1, 6.3)	−0.2 (−3.2, 2.8)	−1.0 (−6.6, 4.7)	1.4 (−5.7, 8.5)	1.7 (−3.0, 6.3)
Wk 4 −3.8 (−9.0, 1.3)	19.0 (12.4-25.6)	15.3 (7.9-22.6)	8.3 (3.8-12.8)	10.1 (3.9-16.2)	−9.5 (−17.1, −1.9)	−2.9 (−7.6, 1.8)
Wk 8 −2.3 (−8.3, 3.7)	26.4 (18.3-34.6)	17.1 (7.9-26.3)	11.0 (5.1-16.8)	7.6 (1.0-14.3)	−8.1 (−16.8, 0.6)	−3.2 (−8.3, 1.9)
Wk 12 −1.6 (−8.4, 5.1)	20.9 (10.4-31.5)	13.2 (3.3-23.2)	12.3 (5.8-18.9)	4.5 (−3.3, 12.4)	−4.9 (−14.5, 4.6)	−0.7 (−6.3, 4.9)

Abbreviations: GHS, general health status; QLQ-C30, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30.
[a] Estimates for the differences between treatment arms were calculated using linear mixed modelling and are expressed in absolute score points on the scale. For the GHS and role functioning scales, positive numbers indicate a higher value (better quality of life) for pazopanib compared with placebo. For the symptom scales (diarrhea, loss of appetite loss, nausea/vomiting, and fatigue), positive numbers indicate a higher level of symptoms (worse quality of life) for pazopanib compared with placebo.
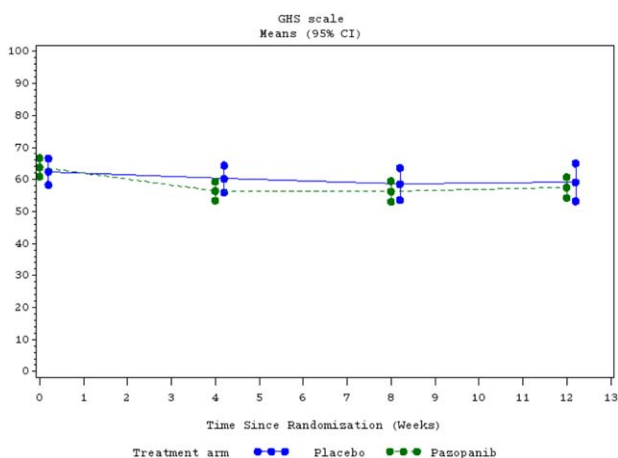

Figure 1. Mean global health status (GHS) scores and corresponding 95% confidence intervals (CIs) were estimated using the model. In both treatment arms, the GHS scores tended to decline over time.

Other Scales

Among the other scales of the EORTC QLQ-C30, there were both statistically and clinically significant differences in scores between the 2 treatment arms for diarrhea, loss of appetite, nausea/vomiting, and fatigue (Table 3). Patients who reported at least 1 minimally important worsening (ie, an increase ≥10 points) in any of those 4 symptom scales are summarized in Table 4. No significant differences were observed in scores on any of the functioning scales (physical, emotional, role, social and cognitive functioning), although the results for role functioning were statistically but not clinically significant. All differences were in favor of the placebo arm.

Exploratory Post-Hoc Analyses

Exploratory factor analysis revealed that GHS scores were associated mainly with functioning scales (physical, role, and social) and less with symptom scales, with the exception of fatigue. Linear regression of the various EORTC QLQ-C30 scales on the GHS score revealed that current GHS was linked with role functioning, social functioning, fatigue, and pain. Future GHS (ie, the GHS score reported at the next assessment) was linked with role functioning, social functioning, and fatigue only. Pazopanib dose intensity before week 4 was significantly related to the fatigue score at week 4 ($P = .006$). However, no correlations with HRQoL parameters were observed at the week-8 or week-12 time points.

The results of prognostic factor analyses of the effects of baseline GHS scores and changes in GHS scores from baseline to the week-4 assessment on PFS and OS are summarized in Table 5. A statistically significant effect was observed for the baseline GHS score on OS, in which patients who had GHS scores ≤50 had poorer survival (9.1 months vs 13.7 months; $P = .0002$) (Fig. 2).

Systematic Review

We searched the PubMed database using the search terms "pazopanib," and "soft tissue sarcoma," and

TABLE 4. Sensitivity Results on General Health Status Summary Statistics

		Placebo Arm, N = 123	Pazopanib Arm, N = 246
	GHS score		
Change from baseline until last score	Median	0.0	0.0
	Mean (SD)	−5.13 (15.27)	−6.82 (22.43)
Change from baseline to minimum score	Median	−8.3	−16.7
	Mean (SD)	−8.61 (16.12)	−14.83 (23.55)
Change from baseline to average score	Median	−2.8	−8.3
	Mean (SD)	−5.01 (17.15)	−7.82 (21.99)
10-Points decrease from baseline	event/evaluable[a]	30/91	107/191
	%	33	56
	Clinically relevant deterioration from baseline in any key symptom scale (diarrhea, loss of appetite , nausea/vomiting or fatigue)		
At week 4	event/evaluable[a]	53/90	162/186
	%	58.9	87.1
At week 8	event/evaluable[a]	30/51	121/142
	%	58.8	85.2
At week 12	event/evaluable[a]	16/28	102/121
	%	57.1	84.3
Overall	event/evaluable[a]	63/93	184/195
	%	67.7	94.4

Abbreviations: GHS, general health status; SD, standard deviation.

[a] An event is defined as having experienced at least one score that is at least 10 points higher than the score reported at baseline (ie. indicating a clinical relevant deterioration in that symptom). Patients are evaluable if they have a valid baseline, at least one follow-up assessment and on-treatment at the time-point of interest.

TABLE 5. Prognostic Value of the Global Health Status Score

Variable	No. of Patients	No. of Observed Events	HR (95% CI)	Wald P	Median Survival, mo
PFS					
Baseline GHS score			0.89 (0.69-1.15)	.381	
≤50	132	99			2.7
>50	206	154			2.8
Change in GHS score			0.90 (0.68-1.21)	.502	
≤ −10	93	71			2.9
> −10	175	134			2.8
OS					
Baseline GHS score ≤50/>50			0.58 (0.44-0.77)	<.001	
≤50	132	91			9.1
>50	206	108			13.7
Change in GHS score			0.98 (0.69-1.37)	.886	
≤ 10	93	51			13.1
> −10	175	98			12.3

Abbreviations: CI, confidence interval, GHS, global health status; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

"quality of life," and "patient-reported outcome" up to March 2013, restricting the search to English-language publications. We then reviewed the abstracts to exclude articles that did not evaluate HRQoL in detail. Only 2 relevant articles were identified: the 2012 publication of the phase 3 PALETTE trial by van der Graaf et al[8] and a review article by Deeks[21] that mainly reiterates the PALETTE results.

DISCUSSION

HRQoL was an important exploratory endpoint of the phase 3 PALETTE trial. The results obtained from the prespecified analysis demonstrated that pazopanib had no significant impact on GHS. Various sensitivity analyses (using different populations, methodologies, or outcomes) supported the primary analysis, indicating that pazopanib can be administered in this patient population
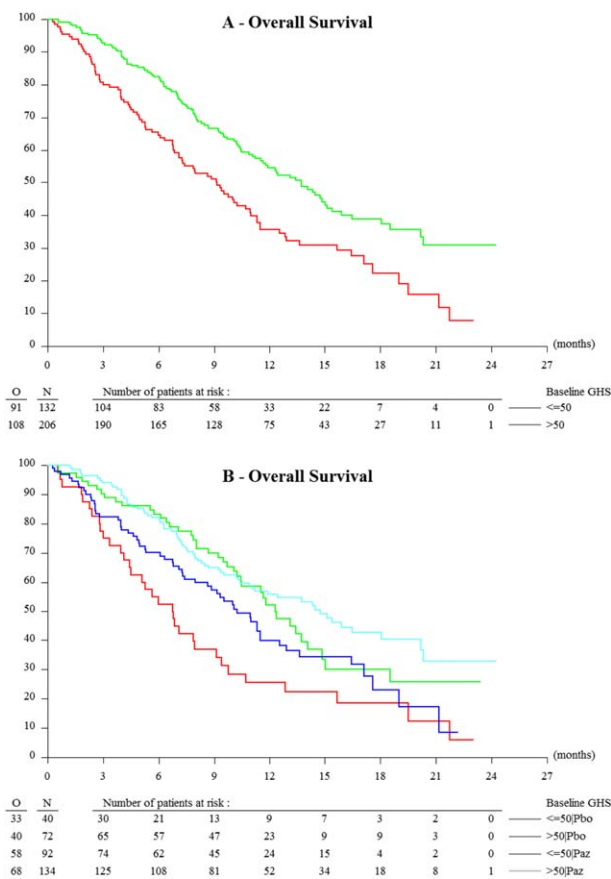
Figure 2. Overall survival is illustrated according to baseline global health status (GHS) scores in (A) all patients and (B) per treatment arm, the placebo arm (Pbo) versus the pazopanib arm (Paz). A statistically significant effect on overall survival was observed for the baseline score, in which patients who had GHS scores ≤50 had poorer survival. N indicates the number of patients; O, number of observed events.

without relevant deterioration in perceived overall health or HRQoL status. The objective of the current study was to demonstrate whether GHS could be improved by the administration of pazopanib, which was not the case. However, achieving a delay in PFS without an impairment in GHS is considered a meaningful result.

Significantly worse outcomes in the pazopanib arm were observed for 4 symptoms scales: diarrhea, appetite loss, nausea/vomiting, and fatigue. These results are in line with the known toxicity profile of pazopanib and angiogenesis inhibitors in general. The most frequently cited side effects of pazopanib treatment in patients with STS include hypertension, skin reactions, gastrointestinal disturbances, and fatigue.[6,8,22] Similar observations are reported in other cancers, most notably renal cell carcinoma.[23,24] However, a notable point is that, despite their

impact on these 4 symptom scales, the side effects did not translate into worse GHS or functional scale scores. Only the role-functioning scale, which measures the ability to continue daily tasks and work, was borderline worse in the pazopanib arm. Its maximum observed difference of 9.5 points (95% CI, 17.1-1.9 points), which occurred at week 4, was just short of clinical significance. There also did not seem to be any strong evidence that HRQoL affected treatment compliance, with fatigue at the week-4 time point the only event related to pazopanib dose intensity. This may be because patients became accustomed to the pazopanib dosing and side effects early in their treatment period. However, it should be noted that these results stem from an exploratory, post-hoc analysis and may not be reliable.

Currently, there is limited information in the literature on the HRQoL impact of pazopanib administration in patients with advanced STS. Even general information on HRQoL in advanced STS after first-line treatment is scarce: only 6 randomized trials (this study and 5 phase 2 trials) have been published since 1980.[7] HRQoL results are more common in extremity STS in patients with early/localized disease.[25-27] For this population, surgical options and impairment in physical functioning are obviously the dominant issues, as is the lack of patient input in decisions regarding treatment.[27] Reichardt et al[2] recently reported on HRQoL and health state utilities specifically among patients with metastatic STS and bone sarcoma (excluding gastrointestinal stromal tumors) who had attained a favorable response to chemotherapy, whereas Shingler et al[3] reported on STS health state utilities in general. Their observations are similar to those obtained in our current study, with the authors reporting fatigue as a major driver in reduced overall HRQoL. Both groups reported a general decline in HRQoL over time, most likely caused by the underlying disease burden. Moreover, their results highlighted the significant negative impact of disease progression, because patients who developed progressive disease consistently reported lower HRQoL.

Beyond STS, there have been other studies examining the impact of pazopanib on HRQoL. Most notably, Cella et al[28] investigated the HRQoL of patients who were receiving pazopanib for advanced renal cell carcinoma. Those authors observed a favorable risk-benefit profile with pazopanib, leading to a delay in HRQoL deterioration compared with placebo. This delay in HRQoL deterioration was related to a delay in PFS; because, in that study, the development of disease progression was considered HRQoL deterioration by definition. Recently, a direct comparison of sunitinib versus

pazopanib in metastatic renal cell carcinoma demonstrated similar efficacy but safety and quality-of-life profiles in favor of pazopanib.[29] This was confirmed in a patient preference study in which patients preferred pazopanib over sunitinib, citing quality of life in general and fatigue in particular as important reasons.[30]

The prognostic value of the baseline GHS scores for OS confirm previous reported findings that baseline HRQoL scores can act as a universal prognostic factor across many cancer disease sites.[31] Patients who had GHS scores <50 at baseline had lower OS but similar PFS, independent of the treatment arm. Normative scores for GHS are typically approximately 65 to 70, depending on age, sex, and other chronic diseases.[32,33] Similar values were observed at baseline in this trial, but the outcomes tended to decline slightly to <60 over time.

Our study was not without limitations. A major constraint was the lack of HRQoL collection after progression, especially because the treatment effect on PFS did not translate into a significant OS benefit. Therefore, the question remains: How significant was the overall benefit of pazopanib in terms of quality-adjusted life-years? In addition, the PFS benefit in the pazopanib arm caused lower attrition rates and, thus, a longer HRQoL observation period compared with the placebo arm. Combined with a general decline in HRQoL scores over time, lower scores in the pazopanib arm may have been influenced by the higher number of HRQoL observations in the treatment arm.

Missing data constitute a common challenge to HRQoL assessment in clinical trials.[34] Compliance in the PALETTE trial was good and remained within acceptable limits to allow the performance of analyses as intended. Sensitivity analyses confirmed the results, and an investigation into the causes of missing data revealed no systematic bias. Although the QLQ-C30 is often cited currently as 1 of the most commonly used and validated measures applied within the oncology clinical trials setting, when applied to this particular study, several side-effect scales/items or symptoms common to angiogenesis inhibitors are lacking. Most notably absent are symptoms related to hand-foot syndrome or skin reactions. These symptoms represent a severe limitation to the patient when performing normal daily activities. Similar to hair loss for cytotoxic regimens, dermatologic problems may be considered more important by patients because of their chronicity, obvious appearance, and social impact, thus affecting daily activities more than might be apparent from a clinical perspective.

It should be noted that there is no questionnaire specific for patients with advanced STS; and, given the heterogeneity of this disease, the development of such an instrument may be challenging. The EORTC Quality-of-Life Group uses a module-based approach to questionnaire development, in which the core questionnaire (EORTC QLQ-C30) is supplemented with disease-specific, treatment-specific, or symptom-specific modules. Currently, no STS-specific module exists, but a symptom-based module on targeted therapies is under construction.[35] Fatigue-specific instruments, such as the EORTC QLQ-FA13[36] or the Functional Assessment of Cancer Treatment-Fatigue,[37] could be a valuable consideration for future trials with angiogenesis inhibitors.

Conclusion

HRQoL was an important exploratory endpoint in this comparison between pazopanib and placebo in patients with advanced STS. The primary selected scale, the EORTC QLQ-C30 GHS, revealed no statistically or clinically significant differences between the 2 treatment arms at any time point. Sensitivity analyses confirmed this finding. The toxicity profile of pazopanib was reflected in patients' self-reported symptoms (fatigue, nausea/vomiting, appetite loss, and diarrhea) but did not translate into significantly worse overall global health during treatment. HRQoL scores tended to decline over time in both arms, at least in part reflecting the underlying disease burden in this patient population.

CONFLICT OF INTEREST DISCLOSURES

Prof. van der Graaf reports speaker's fee from GlaxoSmithKline (GSK) outside the submitted work. Prof. Blay reports research support and honoraria from GSK, Novartis, PharmaMar, MSD Pharmaceuticals, and Roche outside the submitted work; Ms Manson and Rachel Hodge are employed by and hold shares in GSK; Dr. Lugowska reports personal fees from Roche, Bristol Myers Squibb, and GSK outside the submitted work; Dr. Sanfilippo reports grants and personal fees from GSK outside the submitted work. Dr. Judson reports personal fees from GSK, during the conduct of the study; personal fees from Bayer, Ariad, and Merck-Serono, outside the submitted work. Dr. Chawla has been a consultant for Amgen, Roche, Cytrx, Threshold, GSK and Berg Pharma outside the submitted work.

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