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Treatment patterns and clinical outcomes with pazopanib in patients with advanced soft tissue sarcomas in a compassionate use setting: results of the SPIRE study*

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ABSTRACT

Background: A named patient program (NPP) was designed to provide patients with advanced soft-tissue sarcoma (aSTS) access to pazopanib, a multitargeted tyrosine kinase inhibitor. The SPIRE study was a retrospective chart review of participating patients.

Patients and methods: Eligibility criteria for the NPP and SPIRE mirrored those of the pivotal phase-III study, PALETTE, which compared pazopanib with placebo in patients ≥ 18 years with aSTS and whose disease had progressed during or following prior chemotherapy or were otherwise unsuitable for chemotherapy. Outcomes of interest included treatment patterns, treatment duration, relative dose intensity, progression-free survival (PFS), overall survival (OS), clinical benefit rate, adverse events (AEs) and reasons for treatment discontinuation.

Results: A total of 211 patients were enrolled (median age 56 years; 60% female). Most patients received pazopanib in second- and third-line therapy (28.0% and 28.4%, respectively), followed by fourth line (19.0%) and \geq fifth line (18.5%). The median duration of pazopanib treatment was 3.1 months (95% CI: 2.8–3.8), with a mean daily dose of 715 mg equating to 92% of recommended dose. Median OS was 11.1 months and clinical benefit rate was 46%. There was evidence of some clinical benefit across most histological subtypes. At study end, 40% of patients were alive and of these, 18% remained on pazopanib. Thirteen percent (13%) of patients discontinued pazopanib due to AEs.

Conclusions: The SPIRE study demonstrated activity of pazopanib in heavily pretreated aSTS patients in a compassionate use setting. No new safety concerns were noted. Reassuringly, the relative dose intensity of pazopanib was 92%.

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Introduction

Sarcomas are a rare group of solid tumors and over 80% of sarcomas are soft-tissue sarcomas (STS) [1,2]. STS include heterogeneous tumors, with over 40 malignant histological subtypes (defined by the current version of the World Health Organization's histopathological classification) which can occur throughout the body [2–4]. The heterogeneity of STS makes treating this disease a particular challenge. Prognostic factors for survival include: histological subtype and tumor site; tumor size; grade; age; performance status, and the presence of nodal or distant metastases [3,5]. Based on these

factors, treatment options may include surgery, radiotherapy and/or chemotherapy [6].

In locally advanced or metastatic disease, systemic therapy plays an important role [5,6]. Initial chemotherapy usually consists of an anthracycline with or without ifosfamide [5,6]. Treatment options in second line and beyond can vary according to histological subtypes and there is no standard chemotherapy in second line and beyond for patients who have progressed after an anthracycline-based treatment [5–7].

Pazopanib (Votrient[®]) has been approved for pretreated advanced STS (aSTS) in the USA, Europe and in Japan and

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 Supplemental data for this article can be accessed [here](#).

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is indicated for the treatment of adult patients with selective subtypes of aSTS who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after receiving adjuvant or neoadjuvant therapy. The recommended starting dose of pazopanib is 800 mg once daily [8].

Pazopanib is an oral anticancer agent and a multitargeted tyrosine kinase inhibitor, that targets VEGFR1,2,3, PDGFR alpha and beta and KIT, thereby blocking tumor growth and inhibiting angiogenesis [5,8–13]. Pazopanib has demonstrated activity in patients with aSTS following prior therapy [10,11]. In the phase-III PALETTE study, pazopanib demonstrated a significant advantage in median PFS compared with placebo, 4.6 months versus 1.6 months respectively (hazard ratio [HR]: 0.31, 95% CI: 0.24–0.40; $p < .0001$) [11]. Median OS was 12.5 months with pazopanib versus 10.7 months with placebo (HR: 0.86, 95% CI: 0.67–1.11; $p = .25$) [11]. Pazopanib was well tolerated, with the most common grade 3/4 adverse events being fatigue (13.7%), increased alanine transaminase (ALT) (9.6%) and lymphopenia (9.6%) [14].

This pazopanib NPP was launched during the pazopanib regulatory review process, upon request by physicians following the positive results of the PALETTE trial, to provide pazopanib treatment to appropriate patients with aSTS [13]. The results obtained from the SPIRE study (Sarcoma named Patient programme chart rEview) are described here.

Methods

This was a multicountry, multicenter, retrospective chart review study of treatment patterns and clinical outcomes in a subset of patients with aSTS who received pazopanib as part of the NPP. Prior to study conduct, ethics approvals were obtained in line with country-specific national regulations (further details provided in Supplementary section 1). Supplementary Figure 1 shows an overview of the patient identification, sampling and subject enrollment processes.

The pazopanib NPP included patients who were 18 years or older, with aSTS, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, with adequate organ system function and clinically normal cardiac function and had received prior systemic chemotherapy therapy for advanced disease unless it was considered unsuitable. Patients could not be treated concurrently with another anticancer therapy. Patients with STS histologies excluded from the PALETTE study were ineligible. Using a convenience sample of centers with higher numbers of NPP patients, all available patients from these study centers were included in the SPIRE study.

The primary objectives were to describe the number and type of prior and subsequent systemic treatments given to patients with aSTS who received pazopanib and to determine pazopanib treatment duration. Secondary objectives included relative dose intensity, dose modifications and reason for dose modifications, treatment discontinuation and reason for discontinuations for patients. Other outcomes of interest included PFS, OS, clinical benefit rate (complete response [CR] + partial response [PR] + stable disease [SD] + patients

receiving pazopanib for ≥ 12 weeks with unknown/undocumented benefit), AEs (measured by Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 or 4.0), and reasons for treatment discontinuation. PFS and OS were estimated by the Kaplan–Meier method. The analysis was mainly descriptive with appropriate statistical methods, further details are provided in the Supplementary section 1.

Results

The data were collected from patient medical charts for patients who received pazopanib between 26th August 2011 and 1st August 2013. The study was conducted at 24 sites across six countries (Australia, Greece, Israel, Italy, the Netherlands and the United Kingdom). The median study period from pazopanib initiation to date of death or date patient was last known to be alive was 6.9 months. The mean time from first diagnosis of aSTS until initiation of pazopanib therapy was 27.3 months.

Patient characteristics

Data were collected on 211 patients out of a total of 531 patients with aSTS who received at least one dose of pazopanib in the NPP. Supplementary Table 1 shows baseline patient characteristics where the median age was 56 years, all patients had stage IV (i.e., metastatic) disease, and the majority of patients had lung metastases (74%, 155/211).

The largest subset of histological subtypes was leiomyosarcoma (LMS) (41%, 87/211) which included uterine LMS, nonuterine LMS and LMS of unknown location. The second and third largest histological subtypes were synovial sarcoma (11%, 24/211) and undifferentiated sarcoma (9%, 19/211).

Treatment patterns and pazopanib treatment

Overall in the total observed population of 211 patients, 6% of patients (13/211) received pazopanib as a first-line therapy, while 28% (59/211), 28% (60/211), 19% (41/211) and 19% (39/211) received pazopanib as a second-, third-, fourth- and fifth-line or above therapy on the NPP, respectively. The frequencies of treatment, including pazopanib and other systemic therapies, by the line of therapy, are described in Figure 1. Thirty-nine percent (39%) of patients (83/211) received trabectedin either before or after pazopanib, 66% (55/83) of which had leiomyosarcoma.

The mean daily dose of pazopanib was 715 mg, which translates to a mean relative dose intensity of 92% (Table 1). The mean starting daily dose was 738 mg, the majority of patients (179, 84.8%) started at a daily dose of 800 mg with 24 patients (11.4%) starting at daily doses $\leq 50\%$ of the labeled dose of 800 mg/day. Twenty-two percent (47/211) of patients had at least one dose reduction and 20% (42/211) of patients experienced at least one dose interruption. The reasons for either a dose reduction or interruption were: non-serious AEs (65%, 58/89); serious AEs (14%, 12/89); patient's

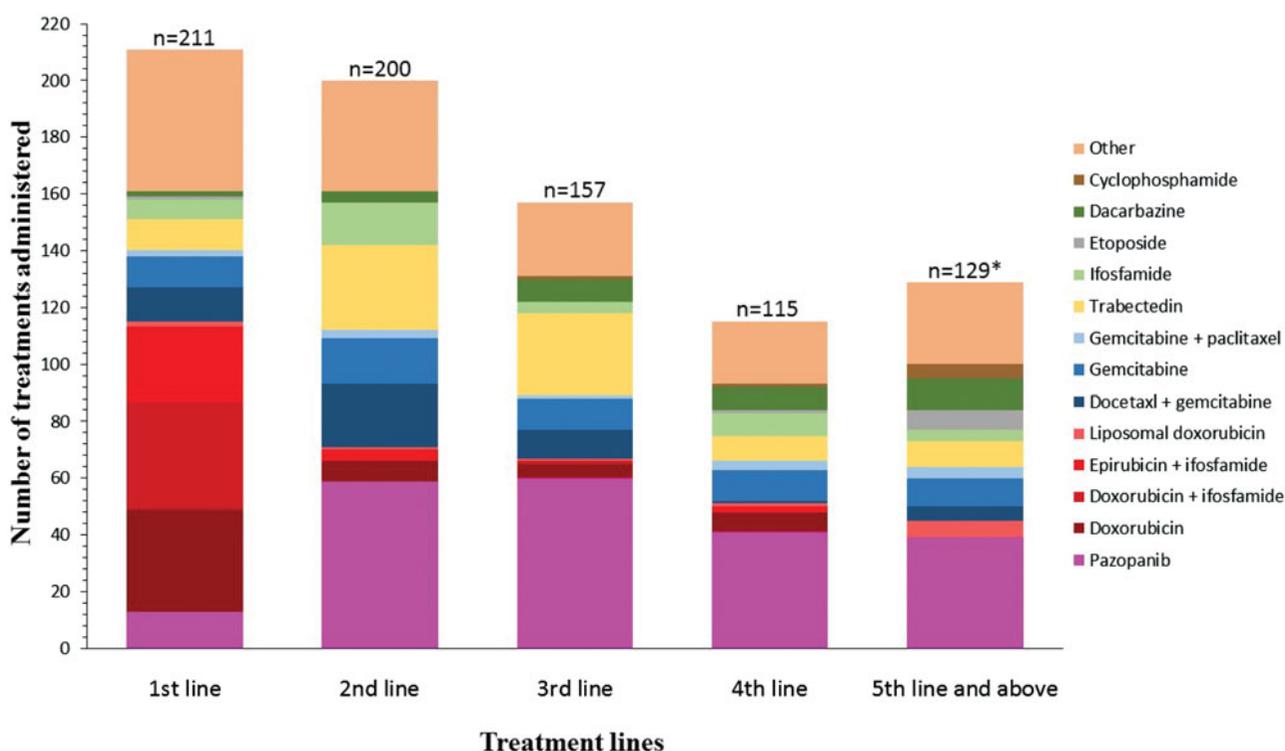


Figure 1. Treatment regimens by line of therapy (observed population). *There are 67 patients who had 5th line or above which =129 regimens.

Table 1. Pazopanib average daily dose and relative dose intensity.

	N = 211
Mean average daily dose (mg)	714.8
Mean relative dose intensity (%)	92.2
Mean starting dose (mg)	738.4
Starting dose (mg), n (%)	
200	9 (4.3)
400	15 (7.1)
600	8 (3.8)
800	179 (84.8)
Other	0

decision unrelated to AE (10%, 9/89) and other (11%, 10/89). The main AEs leading to dose reductions included hypertension (3%, 6/211), diarrhea and nausea (2%, 5/211 each) and fatigue (1%, 3/211).

At the end of the study, 40% (84/211) of patients were still alive and of those patients still alive, 18% (15/84) remained on pazopanib. Reasons for pazopanib discontinuation are shown in Supplementary Figure 2, with the majority of patients (67%, 140/211) discontinuing due to disease progression.

The median treatment duration for pazopanib was 3.1 months (95% CI: 2.8–3.8) (Table 2(A)). There was considerable variation in treatment duration by histological subtype, with some patients remaining on therapy for an extended duration and other patients coming off therapy quickly (Table 2(A) and Supplementary Figure 2), although some of the histological subtypes had small numbers of patients. However, it was notable that some patients across most histological subtypes stayed on therapy for an extended duration. The histological subtypes with the longest median treatment duration included: PEComa (8.2 months);

aggressive fibromatosis (8.0 months); alveolar soft part sarcoma (7.1 months); desmoplastic small round cell tumor (5.7 months) and synovial sarcoma (5.1 months). Treatment duration also varied by ECOG PS, with the longest median treatment duration occurring in patients with a PS of 0 (4.5 months), followed by a PS of 1 (2.2 months), while patients with a PS of 2+ had a median treatment duration of 1.3 months and those of unknown PS had a median treatment duration of 3.3 months (Table 2(B)). The relationship between the PS and line of pazopanib therapy is shown in Supplementary Table 3(C), with patients with PS 0/1 receiving pazopanib across a range of therapy lines.

Effectiveness evaluations

Of the 211 patients, a clinical benefit at any time was experienced in 46% (97/211) of patients. Clinical benefit was observed in 62% (8/13) of first-line, 48% (28/59) of 2nd-line, 37% (22/60) of third-line, 58% (23/40) of fourth-line therapy and in 41% (16/39) of patients receiving pazopanib as a fifth-line therapy.

No CRs were observed. Patients with undifferentiated sarcoma (not otherwise specified (NOS)) had the highest percentage of PRs (26%, 5/19). Histological subtypes with the highest percentage of clinical benefit at any time, in sample sizes >10, included: nonuterine LMS (45%, 18/40) and uterine LMS (43%, 17/40), synovial sarcoma (54%, 13/24), undifferentiated sarcoma (NOS) (42%, 8/19), angiosarcoma (38%, 6/16) and solitary fibrous tumors (54%, 7/13) (Table 2(A)). In groups with smaller sample sizes ($5 \leq n < 10$), 85% (4/5) of patients with desmoplastic small round cell tumors and 71% (5/7) of

Table 2A. Pazopanib treatment duration and clinical benefit by histological subtype.

	Total (N)	Median Treatment Duration ^a (months) [95% CI] ^b	T _x Duration Min	T _x Duration Max ^d	Cen-sored n	CR ^c	PR ^c	SD ^c	≥12w T _x UNK ^c	<12w T _x UNK ^c	PD ^c
All Subtypes	211	3.1 [2.8, 3.8]	0.0	29.7+	22	0	15	38	44	28	86
Leiomyosarcoma (LMS), nonuterine	40	3.2 [2.2, 4.5]	0.0	23.2+	5	0	3	6	9	6	16
Leiomyosarcoma (LMS), uterine	40	2.8 [2.2, 3.7]	0.5	20.0	2	0	1	5	12	4	18
Synovial sarcoma	24	5.1 [3.8, 6.3]	0.0	16.6+	2	0	1	6	6	1	10
Undifferentiated sarcoma (NOS)	19	2.4 [1.4, 5.5]	0.0	24.2+	5	0	5	1	2	3	8
Angiosarcoma	16	2.6 [1.8, 5.5]	0.4	15.5+	1	0	2	2	2	2	8
Solitary fibrous tumor	13	4.7 [1.7, 11.9]	0.3	21.1+	1	0	0	5	2	3	3
Leiomyosarcoma (LMS), unknown location	7	3.5 [2.3, 5.1]	1.2	7.4	0	0	0	2	3	1	1
Hemangioendothelioma	6	1.8 [1.3, 3.1]	0.6	9.3	0	0	0	0	2	1	3
Desmoplastic small round cell tumor	5	5.7 [0.5, 9.3]	0.5	9.3	0	0	1	3	0	0	1
Fibrosarcoma	5	2.9 [0.4, 21.2]	0.4	21.2	0	0	0	1	0	1	3
Malignant peripheral nerve sheath tumor (MPNST)	5	3.6 [0.5, 14.0]	0.5	14.0	0	0	0	0	2	1	2
Myxofibrosarcoma	5	3.6 [0.1, -]	0.0	26.7+	2	0	1	0	1	1	2
Epithelioid sarcoma	4	1.9 [1.4, -]	1.4	25.4+	1	0	0	1	0	1	2
Fibromyxoid sarcoma	3	- [2.8, -]	2.8	29.7+	2	0	0	2	0	0	1
Rhabdomyosarcoma	3	0.6 [0.1, 3.0]	0.1	3.0	0	0	0	0	1	1	1
Spindle cell sarcoma	3	1.7 [1.1, 2.1]	1.1	2.1	0	0	0	0	0	0	3
Endometrial stromal cell sarcoma	2	1.4 [0.5, 2.2]	0.5	2.2	0	0	0	0	0	1	1
Fibromatosis	2	8.0 [3.8, 12.2]	3.8	12.2	0	0	0	1	1	0	0
PEComa	2	8.2 [6.8, 9.7]	6.8	9.7	0	0	0	1	1	0	0
Alveolar soft part sarcoma	1	7.1 [-, -]	7.1	7.1	0	0	0	1	0	0	0
Clear cell sarcoma	1	1.2 [-, -]	1.2	1.2	0	0	0	0	0	1	0
Mesenchymal sarcoma	1	- [-, -]	25.2	25.2+	1	0	0	1	0	0	0
Sarcomatoid carcinoma	1	2.1 [-, -]	2.1	2.1	0	0	0	0	0	0	1

^aBased on Kaplan–Meier estimates.

^bUsing the methodology of Brookmeyer and Crowley.

^cBased on the number of patients treated with pazopanib overall and for each histological listed in the table.

^d+Censored maximum treatment duration (treatment ongoing or end date unknown); N=number of observations.

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; CI: confidence interval; PEComa: Neoplasms with perivascular epithelioid cell differentiation; t_x: treated; w: weeks.

Table 2B. Treatment duration by performance status (PS).

Performance status	N	Median treatment duration (months) [95% CI]
PS 0	41	4.5 [3.3, 5.9]
PS 1	47	2.2 [1.9, 3.1]
PS 2+	9	1.3 [1.1, 2.3]
PS unknown	114	3.3 [2.8, 4.9]

CI: confidence interval; N: number of observations; PS: performance status.

patients with LMS (of unknown location) experienced clinical benefit with pazopanib.

The median PFS was 3.0 months (95% CI: 2.7–3.5) (Table 3 and Supplementary Figure 3(A)). PFS decreased with a poorer PS, similar outcomes were observed for the PFS relating to each line therapy (Table 3). Median OS from first palliative treatment was 31.6 months (95% CI: 24.9–35.4) and from initiation of pazopanib therapy was 11.1 months (95% CI: 7.8–13.8) (Table 3, Supplementary Figure 3(B)).

The OS from time of pazopanib initiation varied by histological subtypes, where the median OS (months) was similar for subjects with nonuterine LMS (12.9, CI: 6.1–17.3), synovial sarcoma (13.8, CI: 8.8–) and solitary fibrous tumor (13.2, CI: 4.5–25.7) and appears slightly longer for subjects with uterine LMS (16.5, CI: 5.5–24.7) and leiomyosarcoma of unknown location (17.6, CI: 4.7–NR) (Supplementary Table 4).

Adverse events

The most common AEs (>10%) with pazopanib (any grade) included: gastrointestinal disorders (i.e., diarrhea, nausea, vomiting, etc.) (28%, 60/211); general disorders (i.e., fatigue,

Table 3. Progression-free survival (PFS) and overall survival (OS) for pazopanib therapy and survival status at end of study.

	Total (N = 211)
Median PFS, in months [95% CI]	
Overall	3.0 [2.7, 3.5]
By performance status (PS)	
PS 0	3.9 [3.2, 5.6]
PS 1	2.5 [2.0, 2.9]
PS 2+	1.1 [0.3, 1.3]
PS Unknown	3.5 [2.8, 4.4]
By line of therapy	
2nd line	3.1 [2.2, 5.0]
3rd line	2.5 [1.8, 2.9]
4th line	3.7 [3.1, 5.3]
5th line+	2.8 [2.3, 4.2]
Median OS, in months [95% CI]	
From initiation of pazopanib therapy	11.1 [7.8, 13.8]
From 1st palliative treatment	31.6 [24.9, 35.4]

asthenia, etc.) (27%, 56/211); skin and subcutaneous tissue disorders (18%, 38/211); and vascular disorders (i.e., hypertension, DVT and flushing) (11%, 24/211); however, none of these were of CTCAE version 4 grade 4 or 5 severity. Table 4 shows the AEs of special interest. Thirteen percent (27/211) of patients discontinued due to AEs (Supplementary Table 5).

Discussion

The results of this retrospective chart review study demonstrate the activity of pazopanib in a mostly heavily pretreated aSTS patient population. The median duration of treatment of 3.1 months reflects the underlying condition of the

Table 4. Adverse events of special interest while on pazopanib therapy.

Category of AESI	N = 211 Severity (CTCAE grades), n (%)						Total
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Unknown	
Diarrhea	22 (10.4)	11 (5.2)	0	0	0	6 (2.8)	39 (18.5)
Nausea	13 (6.2)	8 (3.8)	6 (2.8)	0	0	6 (2.8)	33 (15.6)
Vomiting	6 (2.8)	5 (2.4)	2 (0.9)	0	0	9 (4.3)	22 (10.4)
Tumor pain	1 (0.5)	1 (0.5)	2 (0.9)	0	0	4 (1.9)	8 (3.8)
Pneumothorax	0	2 (0.9)	2 (0.9)	0	0	0	4 (1.9)
Heart/cardiac failure	0	0	1 (0.5)	0	1 (0.5)	0	2 (0.9)
Pulmonary Embolism	0	0	0	0	1 (0.5)	1 (0.5)	2 (0.9)
DVT	0	1 (0.5)	0	0	0	0	1 (0.5)

AESI: adverse events of special interest; CTCAE: Common Terminology Criteria for Adverse Events version 3.0 or 4.0: 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = fatal; DVT: deep vein thrombosis.

patients receiving pazopanib therapy in this compassionate use setting, including patients that are quite often in poorer condition than in clinical studies, and receiving treatments that are not fully aligned with ESMO guidelines [6] and therefore needs to be interpreted accordingly. Median treatment duration of pazopanib therapy varied considerably both by, and within, histological subtype.

Effectiveness was observed across a wide range of histological subtypes as demonstrated by extended duration of therapy in some patients, across most histological subtypes. While some patients having prolonged treatment were suffering from diseases with an indolent pattern of disease progression, for example, alveolar soft part sarcoma, the median duration of treatment in synovial sarcoma (5.1 months, $n = 24$) and desmoplastic small round cell tumor (5.7 months, $n = 5$), both aggressive, rapidly progressing diseases, is noteworthy. The small numbers make it difficult to draw firm conclusions about any specific subtype. It should also be noted that fibromatosis ($n = 2$) and sarcomatoid carcinoma ($n = 1$) are not strictly sarcomas, fibromatosis because it is a clonal connective tissue tumor that does not metastasize, but can be locally aggressive and occasionally fatal, and sarcomatoid carcinoma because it has epithelial differentiation but nevertheless may behave like a sarcoma and is often treated as one. However, these results are in accordance with previous publications in several case series of patients which have shown some patients with certain subtypes benefit from using pazopanib, including LMS, synovial sarcoma, angiosarcoma, UPS, MPNST, SFT, epithelioid hemangioendothelioma, hemangiopericytoma, rhabdomyosarcoma, desmoplastic small round cell and desmoid tumor/aggressive fibromatosis [15–27]. Overall, in this study, 46% of patients experienced clinical benefit at any time while on pazopanib. However, it should be noted that response rate and PFS can be difficult to measure in the context of a retrospective study due to heterogeneity in scanning frequency and incomplete information in medical charts. The 1.3 month (range 1.1–2.3) treatment duration in ECOG PS 2+ patients echoes the limited role of chemotherapy in aSTS in these patients [28]. Many patients (54%) had unknown PS in this study because this variable was not recorded in the medical charts. However, it is likely that this unknown PS was 0 or 1, aligned with the NPP recruitment requirements.

This NPP was not a controlled prospective clinical trial, and therefore, the experience with pazopanib in this study represents real-world effectiveness and safety of pazopanib

used in a compassionate use setting in a heavily pretreated aSTS population. In addition, the absence of central radiological and pathological review due to the retrospective chart review methodology contributes uncertainty toward the outcomes reported here. The median OS (11.1 months) and PFS (3.0 months) observed supplement the results observed in the rigidly controlled phase-III PALETTE clinical trial study (OS of 12.5 months and PFS of 4.6 months), demonstrating that the activity with pazopanib translates into the compassionate use setting. It is important to remember that the effectiveness of the drug must be balanced with its cost [29].

The extent and nature of the adverse events were consistent with the known safety profile of pazopanib with 13% of patients discontinuing due to adverse events [5,8,10,11,13]. The adverse events that occurred were typically managed by temporary dose reductions of pazopanib. Although fewer AEs were reported in this study compared with PALETTE, this could be related to the retrospective nature of the study, as not all AEs may be fully captured in the charts. The tolerability of pazopanib was reassuring with a 92% relative dose intensity achieved, allowing most patients to receive close to the full 800 mg daily dose. However, this figure could have been influenced by failure to record all dose changes in the medical chart.

The results from the SPIRE study support the information generated from clinical trials showing pazopanib to be active in heavily pretreated patients and specifically after previous chemotherapy failure [11,13]. In this study, from a compassionate use program, 66% (139/211) of patients received pazopanib as a third or later line of therapy. Interestingly, many patients receiving treatment in the fourth line and fifth line and beyond setting still experienced a clinical benefit with pazopanib. In the present study, there was a distinct difference in treatment patterns for first-line compared to second and later lines of therapy. The dominant first-line treatment regimens were anthracyclines with or without ifosfamide, which is consistent with the recommendations in the guidelines for the treatment of aSTS, although this was also a prerequisite according to the eligibility criteria [6]. In the second- and later-line settings, pazopanib was the dominant treatment regimen.

At time of chart abstraction for the SPIRE study, the majority of patients (60%, 127/211) received no further systemic treatment. Eighteen percent (15/84) of patients alive at the time of chart abstraction continued with pazopanib therapy.

Conclusions

The SPIRE study is one of the first datasets describing the activity of pazopanib in patients with aSTS outside of a clinical trial setting, building on the evidence from the small series of specific histological subtypes previously reported. Activity was evident across a wide range of histological subtypes which was encouraging in the context of this rare, heterogeneous group of diseases. No new safety concerns were noted and pazopanib was well tolerated with a dose intensity of 92%, equating to 715 mg daily dose. It is important to consider that this study was conducted in a patient population that received treatment exclusively in a compassionate use setting where patients typically have received multiple lines of treatment and have limited therapeutic options. Despite this, the data are reassuring and complement the existing clinical trial data, supporting the use of pazopanib in routine clinical practice.

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Disclosure statement

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Role of the funding source and contributors

Study investigators and GlaxoSmithKline were involved in writing the report and in the decision to submit for publication. GlaxoSmithKline employees (listed as authors) were involved in study design, data collection, interpretation, and analysis and writing of the report. This article was reviewed and approved by all authors. The corresponding author had full access to all the data in the study, was involved in report preparation and had final responsibility for the decision to submit for publication.

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