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RESEARCH

Real-world outcomes of pazopanib in metastatic soft tissue sarcoma: a retrospective Turkish oncology group (TOG) study

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Abstract

Aim Description of patient characteristics, effectiveness and safety in Turkish patients treated with pazopanib for metastatic soft tissue sarcoma (STS).

Patients and methods This multicenter study is based on retrospective review of hospital medical records of patients (≥ 18 years) treated with pazopanib for non-adipocytic metastatic STS at 37 Oncology clinics across Turkey. Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) were evaluated with further analysis of data on the three most common histological subtypes (leiomyosarcoma [LMS], undifferentiated pleomorphic sarcoma [UPS], synovial sarcoma [SS]) in the cohort.

Results Data of 552 adults (57.6% women, median age: 52 years) were analyzed. DCR and ORR were 43.1% and 30.8%, respectively. Median PFS was 6.7 months and OS was 13.8 months. For LMS, UPS and SS, median PFSs were 6.1, 5.9 and 7.53 months and median OSs were 15.03, 12.87 and 12.27 months, respectively. ECOG ≥ 2 was associated with poor PFS and OS. Liver metastasis was only a factor for progression. Second-line use of pazopanib (vs. front-line) was associated with better PFS, its use beyond third line predicted worse OS. Adverse events (AE) occurred in 82.7% of patients. Most common AEs were fatigue (58.3%) and anorexia (52.3%) which were graded as ≥ 3 in 8.2% and 7.4% of patients, respectively.

Conclusion Pazopanib is effective and well-tolerated in treatment of non-adipocytic metastatic STS. Its earlier use (at second-line), good performance status may result in better outcomes. Worldwide scientific collaborations are important to gain knowledge on rarer STS subtypes by conducting studies in larger patient populations.

Keywords Pazopanib · Soft tissue sarcoma · Targeted therapy · Synovial sarcoma · Leiomyosarcoma · Metastatic soft tissue sarcoma

Introduction

Soft tissue sarcomas (STSs) are a group of rare mesenchymal tumors that arise in any anatomical region of the body and have different morphological, immunohistochemical and clinical features (Sbaraglia et al. 2021; Gronchi et al. 2021). The current ESMO-EURACAN-GENTURIS Soft Tissue and Visceral Sarcoma Clinical Practice Guidelines recommend using doxorubicin, alone or in combination with ifosfamide or dacarbazine, as a front-line regimen in patients with non-resectable or advanced/metastatic STS, regardless of tumor subtype. Few options have been shown to be efficacious in patients requiring further treatment (Gronchi et al. 2021). The 5-year survival rates for STSs locally advanced and metastatic at diagnosis are 56% and 16%, respectively, in the U.S (Siegel et al. 2023). Predictions for 2025 indicate that STS-related mortality will increase in many parts of the world (Pizzato et al. 2023).

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Pazopanib is an oral multitargeted agent that acts by selectively inhibiting vascular endothelial growth factor receptor (VEGFR) mediated angiogenesis and by blocking platelet-derived growth factor receptors (PDGFRs), fibroblast growth factor receptors (FGFRs), and c-kit (Kumar et al. 2007). The phase 2 European Organization for Research and Treatment of Cancer study (EORTC 62043) and the phase 3 PALETTE (EORTC 6072) study demonstrated the efficacy of pazopanib in non-adipocytic advanced STSs pretreated with standard chemotherapy (Sleijfer et al. 2009; van der Graaf et al. 2012). Although the overall survival (OS) gain achieved with pazopanib did not reach statistical significance versus placebo (median 12.5 vs. 10.7 months; HR 0.86; 95% CI 0.67–1.11, $p = 0.2514$ in the PALETTE study, the improved progression free survival (PFS) (median 4.6 vs. 1.6 months; HR 0.31; 95% CI 0.24–0.40; $p < 0.0001$) with an acceptable safety profile paved the way for the approval of the drug for use in selective types of STS by The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2012 followed by many other health authorities.

Real world data (RWD) are important sources of information on rare diseases where it is difficult to conduct traditional clinical research due to low number of patients (Jonker et al 2022). The SPIRE global named patient program (NPP) and several real-life studies from various populations have confirmed the beneficial effects and the acceptable tolerability of pazopanib in patients with various STS subtypes (Gelderblom et al. 2017; Karaagac et al. 2020; Nakamura et al. 2016; Oh et al. 2020; Seto et al. 2019; Yoo et al. 2015; Koca et al. 2021; Aykan et al. 2022; Alshamsan et al. 2021; Huang et al. 2018; Bajpai et al. 2021; Halim et al. 2021). This study aimed to describe the clinical features of mSTS patients treated with pazopanib and evaluate the effectiveness and safety of pazopanib in clinical practice.

Patients and methods

Patients

This multicenter, retrospective study is based on review of hospital medical records of patients treated with pazopanib for metastatic STS (mSTS) between 2013 and 2020 at 37 Oncology Centers across Turkey. Eligibility criteria included age ≥ 18 years, treatment with pazopanib for mSTS other than liposarcoma, at least one line of systemic treatment for metastatic disease before pazopanib unless a doxorubicin based front-line treatment was contraindicated.

Assessments

Treatment response and disease progression were evaluated based on the clinical and radiological judgment of the treating physician as per the RECIST 1.1 (Response Evaluation Criteria for Solid Tumors) criteria (Schwartz et al. 2016). Objective response rate (ORR) was calculated as the percentage of patients whose tumor regressed (partial response—PR) or disappeared (complete response—CR) with pazopanib. Disease control rate (DCR) was the percentage of patients with CR, PR or stable disease. PFS was defined as the length of time between the initiation of pazopanib and the progression of disease or death. OS was defined as the length of time between the initiation of pazopanib and death or last follow-up. Safety was evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) v.5.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Non-interventional Study Ethics Committee of the Medipol University Faculty of Medicine (10840098–604.01.01_E.8228; February 27, 2019).

Statistical analysis

Statistical analyses were performed using SPSS version 20 software. Descriptive summary statistics for continuous variables are presented as mean and standard deviation for normally distributed variables, and median and interquartile range (IQR) for non-normally distributed variables. Frequencies and percentages are given for categorical variables. The relationship between clinicopathological factors and survival was compared by the chi-squared Fisher's exact test or Mann–Whitney U test. The Kaplan–Meier method was used to estimate progression-free and overall survival. The data for patients lost to follow up were censored at the time of the last contact. Univariate and multivariate cox regression analysis was used to determine prognostic factors for survival. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided, and p values ≤ 0.05 were considered statistically significant.

Results

Demographic and clinical characteristics

A total of 552 patients (57.6% female) with a median age of 52 years (range: 18–86) were included in the study. The primary tumors were mostly located in extremities (39.9%;

n = 220). LMS (37.3%; n = 205), UPS (15.1%; n = 83), and SS (11.3%; n = 62) were the most common histological subtypes. ECOG performance status (PS) was 0–1 in 441 (79.9%) patients and ≥ 2 in 111 (20.1%) patients. Tumor grades were I/II and III in 143 (25.9%) and 227 (41.1%) patients, respectively, and were missing for 33% of the study population. Lungs were the most frequent metastatic sites (53.4%; n = 295) followed by liver (20.1%; n = 111) (Table 1).

Doxorubicin plus ifosfamide (42.9%) was the most preferred first-line regimen followed by gemcitabine plus docetaxel (17.9%). Overall, 7.8% of patients received pazopanib as the front-line treatment because of contraindication to doxorubicin. Pazopanib was the most commonly used therapeutic option in the second-line (67.3%) and third-line (62.3%) settings.

Response to pazopanib

Regardless of treatment line and histological subtype, 80 patients (14.5%) had a complete response (CR), 90 patients (16.3%) had partial response (PR), and 68 patients (12.3%) had stable disease (SD). The DCR and ORR were 43.1% and 30.8%, respectively. The ORRs in LMS, UPS, and SS were 26.4%, 27.7%, and 48.4%, respectively.

Progression free survival (PFS)

The median duration of pazopanib treatment was 5.81 months (IQR: 3.57–10.79; range: 1.03–84.67). Overall, 73.4% of patients progressed on pazopanib treatment, and the median PFS was 6.7 months (95% CI 5.974–7.426) (Fig. 1).

The median PFS was 6.1 months (95% CI 5.119–7.081), 5.9 months (95% CI 4.377–7.423) and 7.5 months in LMS, UPS and SS, respectively (Fig. 2).

Patients who progressed on pazopanib were older than those who did not ($p = 0.009$). Progression was more common among patients with ECOG PS ≥ 2 (87% vs. 71.2% in ECOG PS 0–1; $p = 0.004$), grade III tumors (78.4% vs. 68.5% in grade I-II; $p = 0.033$) and liver metastases (81.1 vs. 71.4%; $p = 0.040$). The number of prior lines of treatment also affected progression status ($p = 0.001$) (Table 2).

A cox univariate regression analysis showed that poor ECOG PS (≥ 2 vs. 0–1), high tumor grade (grade III vs. I-II) and presence of liver metastasis increased the crude hazard of progression in patients treated with pazopanib for metastatic STS. Moreover, the multivariate (adjusted) analysis revealed that poor ECOG PS ($p < 0.001, \geq 2$ vs. 0–1) ($p < 0.001$, HR:1.960, 95% CI 1.499–2.562), presence of liver metastasis ($p = 0.025$, HR 1.315, 95% CI 1.1035–1.671), and use of pazopanib at second-line versus first-line ($p = 0.044$, HR 0.682, 95% CI 0.470–0.989) were independent prognostic factors for progression (Table 3).

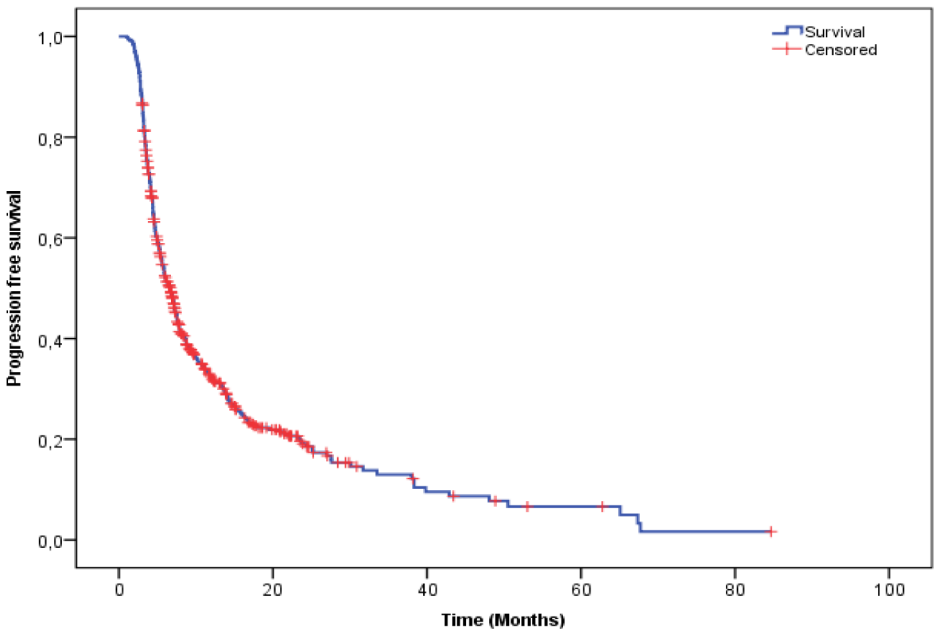
Table 1 Patients' characteristics

Characteristics*	Total ($n = 552$)
Sex	
Female	318 (57.6)
Male	234 (42.4)
Age at diagnosis (years)	
Median [IQR]	52 [40–62]
Range	18–86
Primary tumor site	
Extremities	220 (39.9)
Abdomen	121 (21.9)
Pelvis**	111 (20.1)
Thorax	72 (13.1)
Head and neck	26 (4.7)
Missing	2 (0.4)
Histological subtype	
LMS	205 (37.1)
UPS	83 (15.0)
SS	62 (11.2)
Others	200 (36.2)
Missing	2 (0.4)
ECOG performance status	
0–1	472 (85.5)
≥ 2	77 (13.9)
Missing	3 (0.5)
Tumor grade	
1	32 (5.8)
2	111 (20.1)
3	227 (41.1)
Missing	182 (33)
Lines of systemic chemotherapy for metastatic disease before pazopanib	
0	43 (7.8)
1	348 (63.1)
2	147 (26.6)
3 +	14 (2.5)
Metastatic site	
Lungs	295 (53.4)
Liver	111 (20.1)
Others	146 (26.5)

*Data are shown as *n* (%) unless otherwise specified

**Includes uterine (n = 108) and testicular (n = 3) tumors

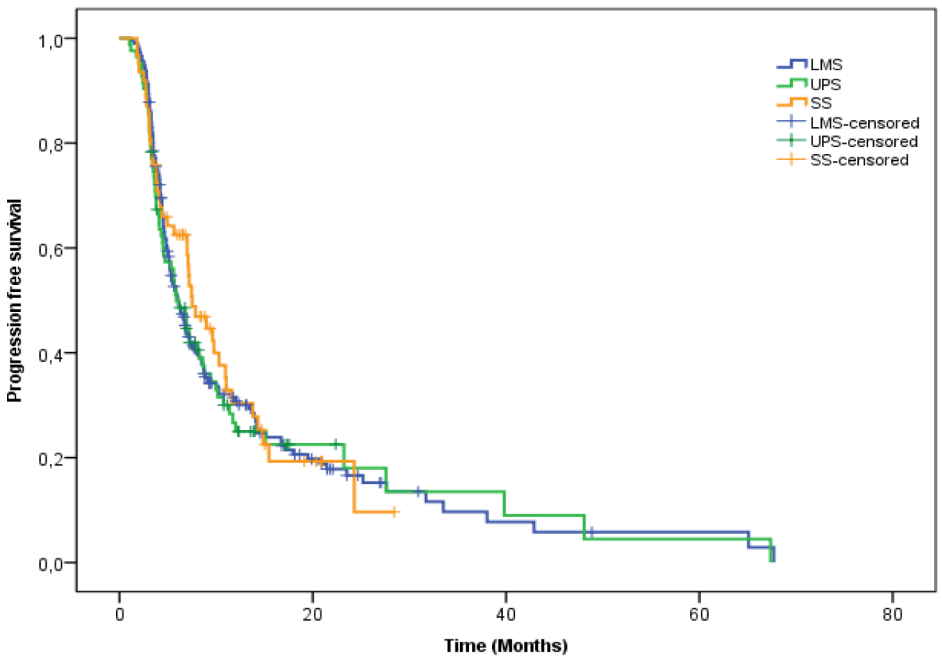
LMS leiomyosarcoma, *SS* synovial sarcoma, *UPS* undifferentiated pleomorphic sarcoma



Number at risk:

Total	552	57	11	5	1

Fig. 1 Kaplan–Meier curve for progression free survival in the overall study population



Number at risk:

LMS	205	21	4	2
UMS	83	6	2	1
SS	62	5		

Fig. 2 Kaplan–Meier curve for progression free survival in patients with LMS, UPS and SS. *LMS* leiomyosarcoma, *SS* synovial sarcoma, *UPS* undifferentiated pleomorphic sarcoma

Overall survival (OS)

The median duration of follow-up as of initiation of pazopanib was 10.95 months (IQR 5.61–19.2; range: 0.97–84.67;). In total, 31.9% of patients were alive at last follow-up. The median OS for the overall study population was 13.83 months (95% CI 12.288–15.372) (Fig. 3).

Table 2 Key characteristics of patients regarding progression on pazopanib and survival status at last follow-up

	Progressed on pazopanib*		*p***	Alive at last follow-up*		*p***
	No	Yes		Yes	No	
Age, years						
Mean ± SD (range)	48.32 ± 15.30 (18–85)	51.91 ± 14.63 (19–86)	**0.009**	50.72 ± 14,26 (18–83)	51.07 ± 15.19 (18–86)	0.821
ECOG PS						
0–1	137 (28.8)	338 (71.2)	**0.004**	169 (35.6)	306 (64.4)	**< 0.001**
2 +	10 (13)	67 (87)		7 (9.1)	70 (90.9)	
Sex						
Female	85 (26.7)	233 (73.3)	0.951	102 (32.1)	216 (67.9)	0.910
Male	62 (26.5)	172 (73.5)		74 (31.6)	160 (68.4)	
Histological subtype						
LMS	47 (22.9)	158 (77.1)	0.437	70 (34.1)	135 (65.9)	0.115
UPS	19 (22.9)	64 (77.1)		18 (21.7)	65 (78.3)	
SS	19 (30.6)	43 (69.4)		19 (30.6)	43 (69.4)	
Tumor grade						
I-II	45 (31.5)	98 (68.5)	**0.033**	48 (33.6)	95 (66.4)	**0.019**
III	49 (21.6)	178 (78.4)		51 (22.5)	176 (77.5)	
Liver metastasis						
Absent	126 (28.6)	315 (71.4)	**0.040**	146 (33.1)	295 (66.9)	0.219
Present	21 (18.9)	90 (81.1)		30 (27)	81 (73)	
Lines of treatment before pazopanib						
None	11 (25.6)	32 (74.4)	**0.001**	22 (51.2)	21 (48.8)	**0.027**
1	106 (30.5)	242 (69.5)		110 (31.6)	238 (68.4)	
2	23 (15.6)	124 (84.4)		41 (27.9)	106 (72.1)	
3 +	7 (50)	7 (50)		3 (21.4)	11 (78.6)	

*Data are shown as *n* (%) unless otherwise specified

**Significant *p* values are shown in bold

Patients with LMS, UPS and SS had a median OS of 15.03 months (95% CI 11.696–18.364), 12.87 months (95% CI 9.661–16.079) and 12.27 months (95% CI 10.020–14.520), respectively (Fig. 4). Considering the histological subtype, 70 (34.1%), 18 (21.7%) and 19 (30.6%) patients with LMS, UPS and SS were alive at last follow-up.

The survival rates at last follow-up were higher in patients with good ECOG PS (0–1) (35.6% vs. 9.1% in ECOG PS ≥ 2; $p < 0.001$) and grade I-II tumors (33.6% vs. 22.5% in grade III, $p = 0.019$). Finally, the number of lines of chemotherapy for metastatic disease prior to pazopanib also affected survival status at last follow-up. The survival rates at last follow up decreased as the number of prior lines of treatment increased (Table 2). The cox univariate regression analysis showed that poor ECOG PS (≥ 2 vs. 0–1), high tumor grade (III vs. I-II) and having received ≥ 3 lines of chemotherapy (vs. none) for metastatic disease before pazopanib increased the crude hazard of death. In the multivariate cox regression analysis, after adjusting for PS and line of treatment, poor ECOG PS (≥ 2) and pazopanib treatment beyond third line (vs. first-line) remained unfavorable prognostic factors for overall survival (Table 3).

Adverse events

Overall, AEs of any grade occurred in 82.7% (n = 456) of patients during pazopanib treatment. The most common grade 3 AEs were fatigue (7.8%) and anorexia (7.4%). Most patients (n = 508, 92%) started pazopanib at a daily dose of 800 mg. In 98 patients (17.7%), pazopanib dose was reduced at least once. Pazopanib was interrupted in 8.1% of patients (n = 45) due to AEs. Cardiotoxicity was reported in four patients, one of which was grade 3. Two patients experienced pazopanib-associated hypothyroidism. There were two patients (0.4%) with grade 4 AEs (Table 4).

Discussion

This study retrospectively assessed clinical effectiveness and safety of pazopanib in 552 adults with mSTS, more than 90% of whom had previously received standard cytotoxic chemotherapy. To the best of our knowledge, this is the largest pazopanib real-life study investigating the survival outcomes and associated factors in this clinical

Table 3 Univariate (crude) and multivariate (adjusted) cox regression analyzes for PFS and OS

	Progression free survival (PFS)				Overall survival (OS)			
	Crude HR (95%.CI)	*p**	Adjusted HR (95%. CI)	*p**	Crude HR (95%.CI)	*p**	Adjusted HR (95%. CI)	*p**
Age								
< 50 years	Ref		Ref		Ref		Ref	
≥ 50 years	1.108 (0.909–1.350)	0.311	1.064 (0.871–1.299)	0.545	0.971 (0.792–1.190)	0.776	0.913 (0.743–1.123)	0.390
ECOG PS								
0–1	Ref		Ref		Ref		Ref	
≥ 2	1.921 (1.475–2.502)	**< 0.001**	1.960 (1.499–2.562)	**< 0.001**	2.235 (1.720–2.904)	**< 0.001**	2.384 (1.823–3.119)	**< 0.001**
Tumor grade								
I-II	Ref				Ref			
III	1.291 (1.008–1.654)	**0.043**	**	**	1.330 (1.036–1.709)	**0.025**	**	**
Liver metastasis								
Absent	Ref		Ref		Ref		Ref	
Present	1.398 (1.105–1.769)	**0.005**	1.315 (1.035–1.671)	**0.025**	1.210 (0.946–1.549)	0.129	1.089 (0.847–1.401)	0.504
Lines of treatment before pazopanib								
None	Ref		Ref		Ref		Ref	
1	0.733 (0.507–1.062)	0.733	0.682 (0.470–0.989)	**0.044**	1.104 (0.706–1.725)	0.665	1.021 (0.651–1.600)	0.929
2	1.017 (0.690–1.501)	1.017	0.981 (0.664–1.451)	0.925	1.406 (0.880–2.246)	0.154	1.395 (0.872–2.233)	0.165
3 +	0.923 (0.407–2.092)	0.923	0.919 (0.403–2.097)	0.840	2.384 (1.148–4.953)	**0.020**	2.499 (1.195–5.228)	**0.015**

CI Confidence interval, *HR* Hazard ratio, *Ref* Reference

*Significant *p* values are shown in bold

**Grades were missing in 182 patients (33%) and were therefore not included in the multivariate analysis to avoid reducing the number of patients in the adjusted analysis

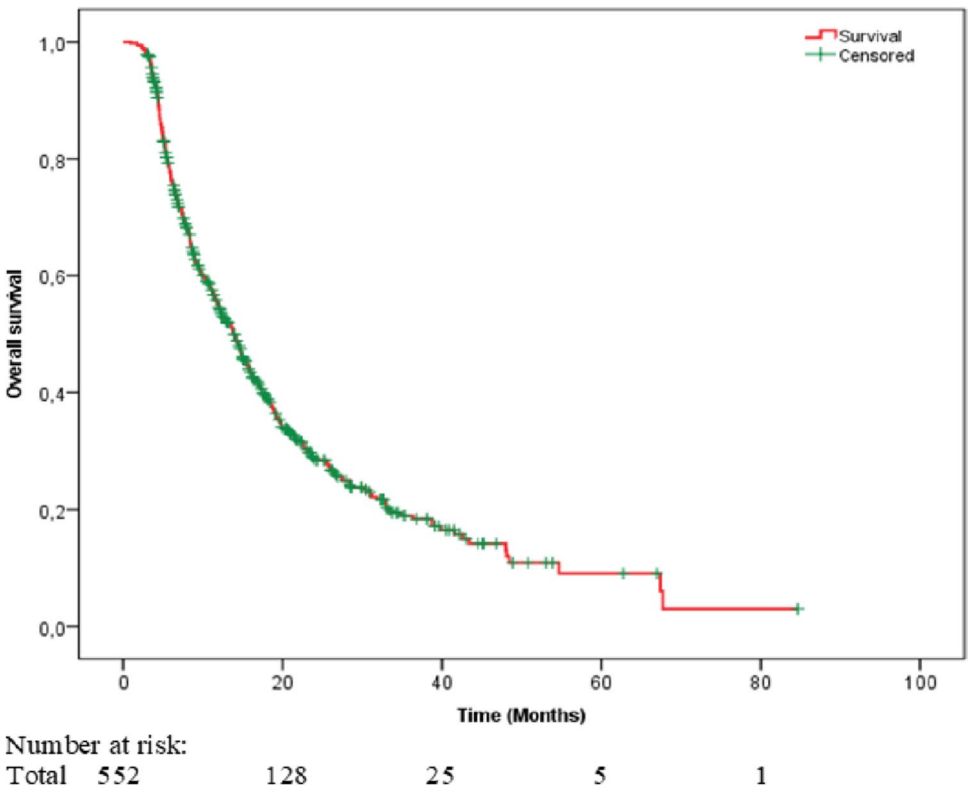


Fig. 3 Kaplan–Meier curve for overall survival in the study population

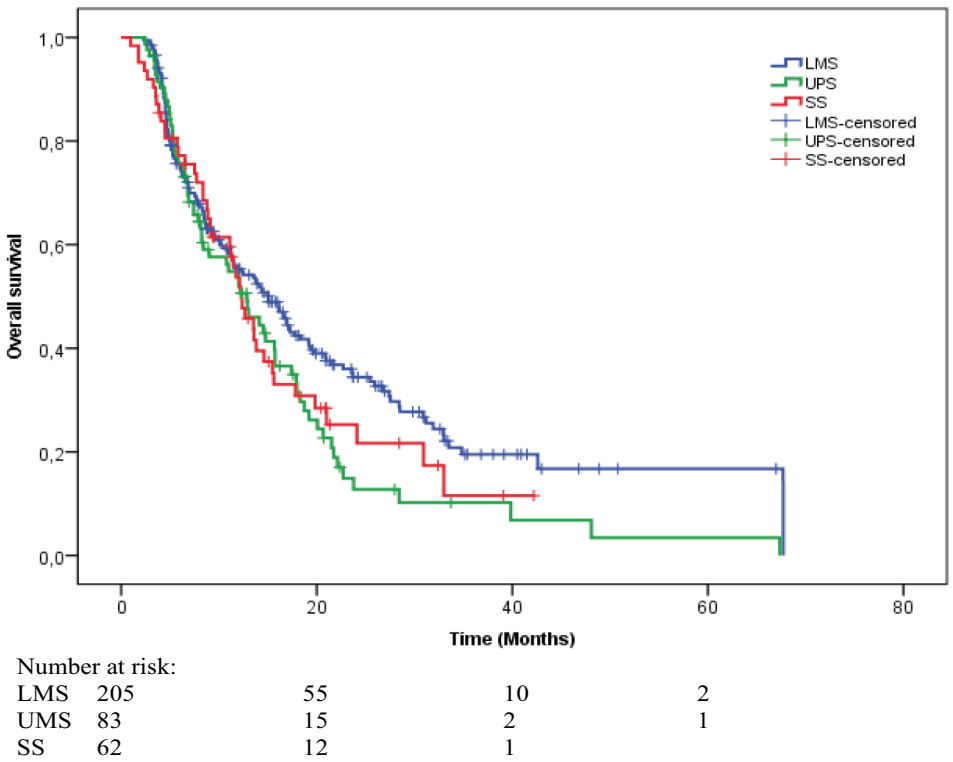


Fig. 4 Kaplan–Meier survival curves for LMS, UPS and SS. *LMS* leiomyosarcoma, *SS* synovial sarcoma, *UPS* undifferentiated pleomorphic sarcoma

Table 4 Adverse events reported in ≥ 1% of study population

Adverse events	Grades, *n* (%)*		
	All grades	Grade 3	Grade 4
Fatigue	322 (58.3%)	43 (7.8%)	2 (0.4%)
Anorexia	289 (52.3%)	41 (7.4%)	
Weight loss	211 (38.2%)	5 (0.9%)	
Hair hypopigmentation	208 (37.6%)		
Nausea	145 (26.2%)	6 (1.1%)	
Vomiting	118 (21.3%)	2 (0.4%)	
Hypertension	113 (20.4%)	6 (1.1%)	
Diarrhea	89 (16.1%)	6 (1.1%)	
Abnormal liver function test	48 (8.7%)	5 (0.9%)	
Skin toxicity	43 (7.7%)	2 (0.4%)	
Taste changes	33 (5.9%)		
Anemia	25 (4.5%)	5 (0.9%)	
Mucositis	12 (2.1%)		

*Data are shown as number and % of patients

setting. The study also evaluated the outcomes in LMS, UPS, and SS, which affected approximately two-thirds of the cohort. Pazopanib improved PFS and OS with an acceptable tolerability in patients with non-adipocytic mSTS. Line of treatment and ECOG PS were predictors of both PFS and OS. Additionally, the presence of liver metastasis was an independent factor for progression.

In the current study, the majority of patients treated with pazopanib for advanced/metastatic STS patients were middle-aged and older (median: 52 years) consistent with real-life data from various geographies (44.5–60 years) (Gelderblom et al. 2017; Karaagac et al. 2020; Nakamura et al. 2016; Oh et al. 2020; Seto et al. 2019; Yoo et al. 2015; Koca et al. 2021; Aykan et al. 2022; Alshamsan et al. 2021; Huang et al. 2018; Bajpai et al. 2021). As with the phase 3 PALETTE (PALETTE) trial and most large ($n > 100$ patients) real-life pazopanib STS studies, the study population was predominantly female (57.6%) (van der Graaf et al. 2012; Oh et al. 2020; Seto et al. 2019; Huang et al. 2018). This might be due to the high percentage of patients with LMS (27.4–44%), a tumor known to originate mostly from uterus (Byar and Fredericks 2022), in these studies. In the present study, LMS affected 37.1% of patients and the primary tumor site was uterus in 19.6%. On the other hand, male predominance (62.2%) was reported in a post-marketing surveillance study from Japan (n = 156) where liposarcoma (LS), a tumor which is more common in men, affected one fifth of the study subjects (Nakamura et al. 2016). The present study did not include patients with LS since pazopanib is not approved for treating adipocytic tumors.

The ORR in this study (30.8%), consistent with previous pazopanib real-life studies about advanced/metastatic STS (7.1–45%) (Gelderblom et al. 2017; Karaagac et al. 2020; Nakamura et al. 2016; Oh et al. 2020; Seto et al. 2019; Yoo et al. 2015; Koca et al. 2021; Aykan et al. 2022; Alshamsan

et al. 2021), was higher than that in the PALETTE trial (6%) (van der Graaf et al. 2012). However, the reverse was true for DCR, which was 73% in the PALETTE trial (van der Graaf et al. 2012), and varied between 25.1% and 70% in real-life studies (Gelderblom et al. 2017; Karaagac et al. 2020; Nakamura et al. 2016; Oh et al. 2020; Seto et al. 2019; Yoo et al. 2015; Koca et al. 2021; Aykan et al. 2022; Alshamsan et al. 2021) including the current one (43.1%). In addition, in the present study, both PFS (6.7 months) and OS (13.8 months) were longer than in the PALETTE trial (PFS: 4.6 months and OS: 12.5 months) and other real-life studies (PFS: 3–5.73 months and OS: 8.2–12.4 months) (Gelderblom et al. 2017; Karaagac et al. 2020; Nakamura et al. 2016; Oh et al. 2020; Seto et al. 2019; Yoo et al. 2015; Koca et al. 2021; Aykan et al. 2022; Alshamsan et al. 2021; Huang et al. 2018; Bajpai et al. 2021; Halim et al. 2021). Characteristics (e.g., histology, molecular profiles, location, metastatic sites, burden, grade), patient demographics including ethnic/racial characteristics, ECOG PS, availability and accessibility of pazopanib and other therapeutic options, prior systemic therapies, as well as study design, size, duration, eligibility criteria can be potential reasons for the varying treatment responses and survivals in these studies. All these factors make a comparative assessment difficult and need to be considered when evaluating the study results. Several factors might help interpret survival outcomes in this study. It has been reported that the length of interval between radiological evaluations may affect PFS in the absence of overt clinical worsening in clinical studies (Korn and Crowley 2013). In clinical practice, patients' assessment plans are not as strict as in interventional studies making it difficult to compare response and PFS rates between real-world studies. The current retrospective study did not consider assessment intervals which might have differed across study sites.

In the current study, LMS and SS patients constituted almost half the study population. Good outcomes with pazopanib treatment reported in patients with these two tumor types, might have affected overall PFS and OS. SS and LMS were the leading histological types (54%) in long-term responders (PFS ≥ 6 months) and survivors (OS ≥ 18 months) in a pooled analysis of the EORTC 62,043 (phase 2) and 62,072 (phase 3-PALETTE) clinical trials (Kasper et al. 2014; van der Graaf et al. 2012). It should be noted, however, that due to the very low numbers of long responders and survivors in the EORTC trials, these observations should be interpreted with caution.

In this study, cox univariate regression analyses revealed that ECOG PS, tumor grade, and line of pazopanib treatment were factors affecting both PFS and OS but liver metastasis was only a factor for progression. We did not include tumor grade in subsequent multivariate analyses, as the large amount of missing data (33%) for this variable would limit the number of patients in the analyses. Good ECOG PS (0–1) remained to be a favorable factor for PFS and OS in the multivariate analyses and liver metastasis was a predictor for worse PFS. In addition, second-line use of pazopanib (vs. front-line) was associated with better PFS, while its use beyond third line (vs. front-line) was a factor for worse OS. The prognostic factors for better PFS in the present study, other than absence of liver metastasis, were consistent with those of the PALETTE study where low-intermediate histological grade (vs. high grade), ECOG PS 0 (vs. 1), less line of systemic treatment before pazopanib (0–1 vs. 2–4) were related to better PFS. Presence of liver metastasis did not affect PFS in the PALETTE trial (HR: 0.98; CI 95% 0.68–1.41; *p*: 0.9056). The PALETTE trial did not provide information about prognostic factors for OS since pazopanib was not superior to placebo for this outcome (van der Graaf et al. 2012).

Few real-life studies have investigated the association between various variables and survival outcomes in mSTS patients treated with pazopanib. These studies invariably associated good PS (ECOG PS 0–1) with better PFS and OS. In the present study, 85% of patients had ECOG PS 0–1 which can explain the better survival outcomes. While female sex (Karaagac et al. 2020), response to pazopanib (CR, PR and SD) (Karaagac et al. 2020; Alshamsan et al. 2021), pazopanib-induced hypothyroidism (Karaagac et al. 2020; Alshamsan et al. 2021) were reported to be associated with better PFS, Yoo et al. reported that SD or progression (vs. PR) with prior doxorubicin was a poor prognostic factor for pazopanib treatment regarding PFS (Yoo et al. 2015). Studies have reported that response to first-line treatment (Karaagac et al. 2020) or to pazopanib (Karaagac et al. 2020; Alshamsan et al. 2021) and pazopanib-induced hypothyroidism (Alshamsan et al. 2021) were determinants of better OS. In line with the current study, Oh et al. reported that delayed pazopanib treatment (≥ 3 vs. 1 prior line) was associated with worse OS (Oh et al. 2020). Interestingly, Huang et al. reported that hand–foot skin reactions was also an independent predictive factor for better treatment outcomes (Huang et al. 2018). Considering these data, the low percentage of heavily pre-treated patients (≥ 2 lines), the high proportion of patients with good PS (ECOG 1–2) might be other explanations for the good survival outcomes in this study. Unlike most studies, including the PALETTE trial, 70% of patients in the current cohort had at most one prior line of chemotherapy (7.8% none). Ray-Coquard et al. reported that the outcomes of patients with mSTS (other than GIST tumors and LS) worsened with increasing line of treatment (Ray-Coquard et al. 2017). Furthermore, analysis of patients in the pazopanib in the PALETTE study revealed longer mPFS in patients who had 1 line of chemotherapy (24.7 weeks) compared to those who received ≥ 2 prior lines (18.9 weeks) (van der Graaf et al. 2012). Contrastingly, PFS for patients

treated with pazopanib at fourth-line in the SPIRE study had the longest PFS (3.7 months) (Gelderblom et al. 2017).

Although liver metastasis, which occurred in 20% of patients in the current study, was found to be associated with progression on pazopanib treatment, there have been no studies in this clinical setting to support this observation. In two studies, liver metastasis was evaluated as a predictor of survival in pazopanib-treated patients for mSTS (van der Graaf et al. 2012; Oh et al. 2020). These studies, where approximately 25% of patients had liver metastases, did not show a relationship between survivals and the presence of liver metastasis. Assessment of the impact of this variable on PFS and OS in future studies will be valuable.

LMS, UPS, and SS, the three most common tumor subtypes in the current study, affecting almost two-thirds of the study population, were also evaluated for survival outcomes. These tumors did not differ from each other regarding PFS and OS. In the PALETTE study, the comparison of SS, LMS and other sarcomas did not reveal a significant difference in terms of PFS. However, the PFS for SS and the OS for LMS were longer than those of the overall study population (van der Graaf et al. 2012). The OS for LMS and SS with pazopanib were slightly longer in a large real-life study from South Korea than in the current study (16 vs. 15 months for LMS and 14 vs. 12.3 months for SS) (Oh et al. 2020). In a meta-analysis of 7 studies investigating outcomes of patients treated with pazopanib for metastatic SS beyond first line, median OS was 10.5 (95% CI 8.2–13.4) months in studies which included ≥ 10 patients (Carroll et al 2022). Pokras et al. reported that time to treatment discontinuation and time to next treatment decreased with subsequent lines of treatment, in patients with metastatic SS (Pokras et al. 2022). The longer OS in the current study might be related to early use of pazopanib.

The overall safety and tolerability of pazopanib was good in the current study in line with most previous studies conducted in patients with mSTS (Gelderblom et al. 2017; Karaagac et al. 2020; Nakamura et al. 2016; Oh et al. 2020; Seto et al. 2019; Yoo et al. 2015; Koca et al. 2021; Aykan et al. 2022; Alshamsan et al. 2021; Huang et al. 2018; Bajpai et al. 2021; Halim et al. 2021). Grade > 3 toxicities were infrequently reported and the most common grade 3 AEs regarding pazopanib were fatigue (7.8%) and anorexia (7.4%), respectively. Hypothyroidism and cardiac toxicity were rare. Although more than half of patients in the study population had lung metastases, none of the patient's experienced pneumothorax.

Due to the retrospective design of this study, which was the major limitation of this study, our analyses used the available data in the hospital records. Because many patients' tumor grades were not reached, we did not include this variable in our multivariate model to avoid analyzing data from a smaller group of patients. Our results may not be valid for very rare histological types of STS which were not adequately represented in the study population. For these tumors, it would be valuable to conduct multinational studies combining data from countries with similar STS treatment guidelines and pazopanib indications. Despite these limitations, we think that the results of this large study may help the decision-making process in clinical practice.

Conclusion

Pazopanib is a suitable treatment option with its positive impact on PFS and OS and has an acceptable tolerability in patients with non-adipocytic mSTS. Earlier use of pazopanib in patients with good PS may result in better clinical outcomes. The clinical value of liver metastasis as an indicator of poor PFS in patients treated with pazopanib therapy should be investigated in future studies. Worldwide scientific collaboration would be valuable to evaluate clinical outcomes and associated factors in larger patient populations, increasing the presentation of rarer histological subtypes of STS.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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