Original Article

The Clinical Outcome of Pazopanib Treatment in Japanese Patients With Relapsed Soft Tissue Sarcoma: A Japanese Musculoskeletal Oncology Group (JMOG) Study

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BACKGROUND: Because the efficacy and safety of pazopanib in Japanese patients with soft tissue sarcoma (STS) had not been evaluated previously in a large-scale cohort, the authors investigated the efficacy and safety of pazopanib in 156 Japanese patients with relapsed STS. This was a retrospective study based on the collection of real-life, postmarketing surveillance data. **METHODS:** Patients received pazopanib with the objective of treating local recurrence (n = 20), metastasis (n = 104), and both (n = 32). The patient median age was 53.8 years. The primary objective of this study was to clarify the efficacy of pazopanib for patients with STS. **RESULTS:** The median treatment duration was 28.7 weeks, and the average dose intensity of pazopanib was 609 mg. Adverse events occurred in 127 patients (81.4%). In addition to the main common toxicities, such as hypertension and liver disorder, pneumothorax (n = 11) and thrombocytopenia (n = 16) also were observed. The median progression-free survival for all patients was 15.4 weeks. The median progression-free survival for patients with leiomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma, and liposarcoma was 18.6 weeks, 16.4 weeks, 15.3 weeks, and 8 weeks, respectively. The median survival for all patients was 11.2 months. The median survival for patients with leiomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma, and liposarcoma was 20.1 months, 10.6 months, 9.5 months, and 7.3 months, respectively. **CONCLUSIONS:** There were apparent differences in the efficacy of pazopanib treatment among histologic types of STS. Pazopanib treatment is a new treatment option; however, adverse events like pneumothorax and thrombocytopenia, which did not occur frequently in the PALETTE study (pazopanib for metastatic soft-tissue sarcoma), should be taken into consideration. *Cancer* 2016;122:1408-16. © 2016 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of *American Cancer Society.* This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: efficacy, pazopanib, progression-free survival, soft tissue sarcoma, toxicity.

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INTRODUCTION

Soft tissue sarcomas (STSs) are a rare and heterogeneous group of tumors that include more than 50 histologic types.[1] From 5% to 30% of patients with STS have a local recurrence, and from 10% to 38% present with clinically detectable metastases.[2-5] The development of new systemic treatments for patients with STS has been limited in the past few decades. Thus, the median survival of patients with advanced STS remains >12 months.[6] Pazopanib is an orally available, multitarget tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptor 1 (VEGFR-1), VEGFR-2, and VEGFR-3 and against platelet-derived growth factor receptor α (PDGFR-α), PDGFR-α, and c-kit.[7] The European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (STBSG), in collaboration with GlaxoSmithKline (GSK), carried out a phase 3 study (pazopanib for metastatic soft-tissue sarcoma [PALETTE]) to evaluate the efficacy of pazopanib in patients with STS.[8] Three hundred sixty-nine patients were randomized (2:1) to pazopanib or placebo.

The study population included 47 Japanese patients. A significant 3-month advantage in progression-free survival (PFS) was observed in the pazopanib arm; however, it should be noted that patients who had liposarcoma (LPS) or some other types of STS were excluded from enrollment.[8] LPS was excluded based on results from a phase 2 trial that did not demonstrate a sufficient benefit from pazopanib treatment in patients with LPS.[9] In 2012, based on results from PALETTE, pazopanib was approved in Japan for the treatment of STS. However, the efficacy and safety of pazopanib in Japanese patients with advanced STSs remained to be evaluated in a large-scale cohort. In the current study, we investigated the clinical outcomes of 156 Japanese patients who had STS of the extremities or trunk and received treatment with pazopanib. The patients were treated by physicians from the Japanese Musculoskeletal Oncology Group (JMOG).

MATERIALS AND METHODS

Patients and Treatment

We retrospectively reviewed the postmarketing surveillance (PMS) data from the PALETTE study, and an independent questionnaire was administered to JMOG members. In Japan, PMS data have been used mainly to verify the safety of new medicines in practical use after they have been approved. As a requirement for its approval, a presentation of the PMS data from all patients who had received treatment with pazopanib since September 2012 was required by the Ministry of Health, Labor, and Welfare of Japan. At the cutoff date of October 27, 2014, in total, 539 patients were enrolled in the PMS system. Each institution approved the human protocol for this investigation, and that investigations were conducted in conformity with the ethical principles of research.

Among the patients identified, 199 patients had received treatment with pazopanib at 37 JMOG institutions. The inclusion criteria for the current study were as follows: 1) the primary tumor was an STS that arose at the extremities/trunk; and 2) patients had received pazopanib for an unresectable local recurrence and/or a metastatic lesion. In Japan, pazopanib is approved for all histologic types of STS by the drug-regulatory authority, because quite a few agents, including doxorubicin and ifosfamide, are available for the treatment of STS. For the same reason, pazopanib administration is also allowed for patients who have no history of chemotherapy. Thus, both patients with LPS and those without a history of chemotherapy were included in the current study. After applying the inclusion criteria, 43 patients were excluded from the study, and the data from 156 patients were analyzed (Fig. 1). The primary objective of this study was to clarify the efficacy of pazopanib for the treatment of STSs. Survival, PFS, and objective radiologic responses to pazopanib were analyzed by using a questionnaire was administered to the JMOG members. The best objective responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Stable disease (SD) was defined as a lack of disease progression for >8 weeks. This evaluation was done not on a fixed schedule but according to local institutional standards. We also evaluated the safety of pazopanib using the PMS data. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.0. This study was approved by the institutional review board of Mie University Hospital. Liver disorder included elevated serum levels of aspartate aminotransferase/alanine aminotransferase, hyperbilirubinemia, and liver failure. The mean follow-up after initiating pazopanib treatment was 11.4 months (range, 0.7-30.1 months).

Two abstracts/posters addressing this Japanese PMS cohort were presented previously at the European Cancer Congress and the Connective Tissue Oncology Society meeting.[10,11] The cohort included STSs that appeared at all sites, such as the uterus, bladder, skin, and soft tissue. The maximum duration of follow-up was 1 year after the initiation of pazopanib treatment. Those analyses did not include an evaluation of tumor response. The current
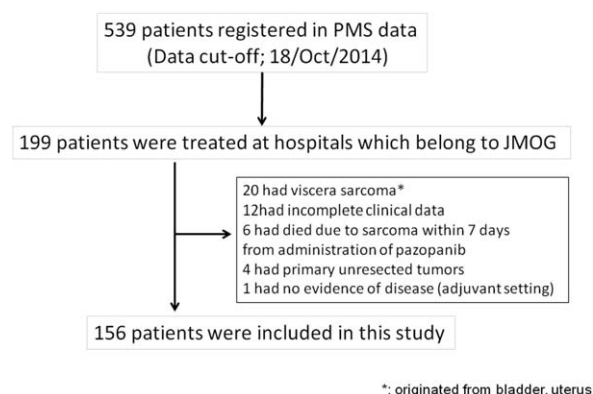
Figure 1. The study profile is illustrated. JMOG indicates Japanese Musculoskeletal Oncology Group; PMS, postmarketing surveillance.

study is different from the previous studies, in that we included only patients who had STSs of the extremities and trunk who were treated by JMOG members, had longer follow-up data about oncologic results, and had imaging data available on the response to pazopanib.

Statistical Analysis

Statistical associations of the clinicopathologic factors were evaluated using the Mann-Whitney U test (for quantitative data) and the chi-square test (for qualitative data). The Fisher least significant difference test was used to compare the mean duration of pazopanib treatment between each subtype. Correlations between the duration of pazopanib treatment and the clinical characteristics were tested using Spearman rank-correlation analysis. A statistically significant Spearman ρ value suggests a correlation in the population.

PFS was defined as the time from the initial administration of pazopanib to either the first instance of disease progression (according to RECIST version 1.1) or death from any cause. Overall survival (OS) was defined as the time from the initial administration of pazopanib to the date of either death or the last follow-up examination. Survival curves were constructed using the Kaplan-Meier method. A univariate Cox model was used to compare PFS and OS between patients. A multivariate analysis was performed using a Cox proportional-hazards model. The factors that were identified as significant in the univariate analysis were included as variables in the multivariate analysis. P values $< .05$ were considered significant in all statistical analyses. The StatView software program (version 5.0; SAS Institute Inc, Cary, NC) was used to perform all statistical analyses.

RESULTS

Patient Characteristics

In total, 156 patients with STS received treatment with pazopanib. Pazopanib was administered with the objective of treating local recurrence (n = 20), metastasis (n = 104), or both local recurrence and metastasis (n = 32) (Table 1). Lung and bone metastases developed in 113 and 32 patients, respectively. Table 1 lists the demographics and baseline characteristics of the patients. The median patient age was 53.8 years (range, 17-88 years). Twenty-two patients had not previously received systemic chemotherapy for advanced disease, and 134 had previously received systemic chemotherapy. The main reason that there was no history of chemotherapy in 22 patients was the estimated potential for age-dependent cardiac and renal toxicity, because they were aged >70 years.

Most patients (132 of 156; 84.6%) had a good performance status (0 or 1). The distribution according to histologic subtype was as follows: undifferentiated pleomorphic sarcoma (UPS) (n = 30), LMS (n = 21), synovial sarcoma (SS) (n = 18), dedifferentiated LPS (n = 17), alveolar soft-part sarcoma (ASPS) (n = 12), myxoid LPS (n = 11), myxofibrosarcoma (MFS) (n = 8), malignant peripheral nerve sheath tumor (MPNST) (n = 7), pleomorphic LPS (n = 4), solitary fibrous tumor (n = 3), fibrosarcoma (n = 2), and others (n = 23). The primary major tumor sites were the thigh (n = 48) and the retroperitoneum (n = 30).

Adverse Events

Pazopanib initially was administered orally once daily at doses of 800 mg (n = 112), 600 mg (n = 12), 400 mg (n = 15), or 200 mg (n = 17) (Table 2). The median treatment duration was 28.7 weeks, and the average dose intensity of pazopanib was 609 mg. Adverse events occurred in 127 patients (81.4%). Age ($P = .78$; Mann-Whitney U test) and sex ($P = .40$; chi-square test) were not related to the occurrence of adverse events. The main common toxicities were hypertension (n = 60), liver disorder (n = 38), diarrhea (n = 35), hair hypopigmentation (n = 22), nausea (n = 20), anorexia (n = 19), fatigue (n = 18), and thrombocytopenia (n = 16). Younger patients were more likely to develop nausea and hand-foot syndrome ($P = .04$ and $P = .02$, respectively; Mann-Whitney U test), and female patients were more likely to develop anorexia and nausea ($P = .02$ and $P = .003$, respectively; chi-square test). Other adverse events, such as hypertension, liver disorder, and diarrhea, were not related to age or sex. Grade ≥ 3 adverse events were reported in 48 patients. The main common grade ≥ 3 toxicities were hypertension

TABLE 1. Patients and Tumor Background

Characteristic	No. of Patients
Age: Mean (range), y	53.8 (17–88)
Sex	
Male	97
Female	59
Primary tumor site	
Thigh	48
Retroperitoneum	30
Leg	13
Chest wall	13
Back	9
Neck	8
Others	37
WHO performance status	
0	42
1	90
2	19
3	3
4	2
Patients' status at the administration of pazopanib	
Local recurrence	20
Metastasis	104
Both	32
Site of metastasis	
Lung	113
Bone	32
Liver	13
Prior chemotherapy	
Yes	134
No	22
Treatment line	
First	30
Second	57
Third or more	69

Abbreviation: WHO, World Health Organization.

TABLE 2. Common Adverse Events

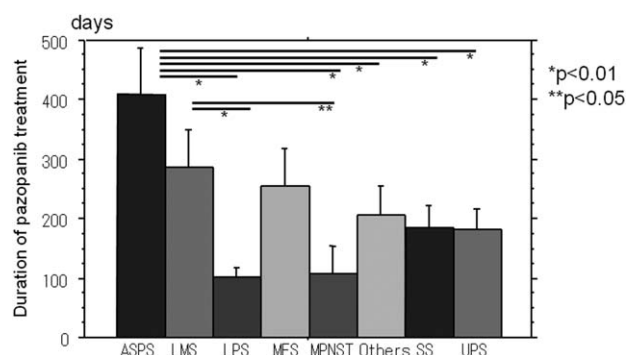|	No. of Patients (%)		
Events	All Grades	Grade3	Grade4
Hypertension	60 (38)	10 (6)	
Liver disorder	38 (24)	7 (4)	1 (<1)
Diarrhea	35 (22)	4 (3)	
Hair hypopigmentation	22 (14)		
Nausea	20 (13)	1 (<1)	
Anorexia	19 (12)		
Fatigue	18 (12)	2 (1)	
Thrombocytopenia	16 (10)	5 (3)	3 (2)
Protein urea	12 (8)	1 (<1)	
Pneumothorax	11(7)	5 (3)	3 (2)
Hand-foot syndrome	11(7)	2 (1)	

Figure 2. Correlations between the mean duration of pazopanib treatment and histology are illustrated (Fisher least significant difference test). Upper bars indicate the 95% confidence interval. ASPS indicates alveolar soft part sarcoma; LMS, leiomyosarcoma; LPS, liposarcoma; MFS, myxofibrosarcoma; MPNST, malignant peripheral nerve sheath tumor; SS, synovial sarcoma; UPS, undifferentiated pleomorphic sarcoma.

(n = 10), pneumothorax (n = 8), liver disorder (n = 8), diarrhea (n = 4), thrombocytopenia (n = 4), heart failure (n = 3), fatigue (n = 2), pneumonia (n = 2), and gastrointestinal perforation (n = 2). Age and sex were not related to the occurrence of grade ≥3 adverse events (P = .21 and P = .31, respectively; Mann-Whitney U test). Dose reductions and/or treatment interruptions because of the occurrence of an adverse event were required in 70 patients (48%). The mean time (± standard error) of the first dose reduction or treatment interruption because of the occurrence of an adverse event was 38 ± 6.2 days. The main reasons for an interruption or reduction in pazopanib treatment were liver disorder (n = 13), diarrhea (n = 12), hypertension (n = 11), thrombocytopenia (n = 10), and nausea (n = 6). At the time of analysis, 11 patients were still receiving pazopanib. Among the remaining 145 patients, treatment was terminated because of tumor progression (n = 87), toxicity (n = 44), or other reasons (n = 14). The types of toxicity that prompted treatment discontinuation were liver disorder (n = 9), fatigue (n = 7), pneumothorax (n = 5), and diarrhea (n = 3). The

mean ± standard error duration of pazopanib treatment discontinuation was 109 ± 18.6 days. Figure 2 illustrates the correlation between the mean duration of pazopanib treatment and histology. The duration of pazopanib treatment was relatively long in patients who had ASPS and LMS (Fisher least significant difference test).

Tumor Responses

Among all 156 patients in the study population, an evaluable tumor response (according to RECIST) occurred in 125 patients. Thirty-one patients were excluded from this evaluation for the following reasons: discontinuation of treatment because of adverse events before the evaluation (n = 14), tumor progression before the evaluation (n = 9), and admission to hospital for another reason (n = 8). Table 3 lists the best overall responses to pazopanib treatment. Thirteen patients achieved a partial response (PR),

TABLE 3. Best Overall Response for Pazopanib Treatment

Histology	No. of Patients					
	Total No.	PR	SD (Long SD)	PD	PR + Long SD [%]	NE
LPS	33	0	9 (3)	13	3/22 [14]	11
UPS	30	3	19 (6)	4	9/26 [35]	4
LMS	21	0	12 (8)	6	8/18 [44]	3
SS	18	2	10 (5)	4	7/16 [44]	2
ASPS	12	4	4 (3)	1	7/9 [78]	3
MFS	8	0	6 (2)	2	2/8 [25]	0
MPNST	7	0	3 (0)	2	0/5 [0]	2
Others	27	4	11 (5)	6	9/21 [43]	6
Total	156	13	74 (32)	38	45/125 [36]	31

Abbreviations: ASPS, alveolar soft part sarcoma; LMS, leiomyosarcoma; Long SD, stable disease for >6 months; LPS, liposarcoma; MFS, myxofibrosarcoma; MPNST, malignant peripheral nerve sheath tumor; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SS, synovial sarcoma; UPS, undifferentiated pleomorphic sarcoma.
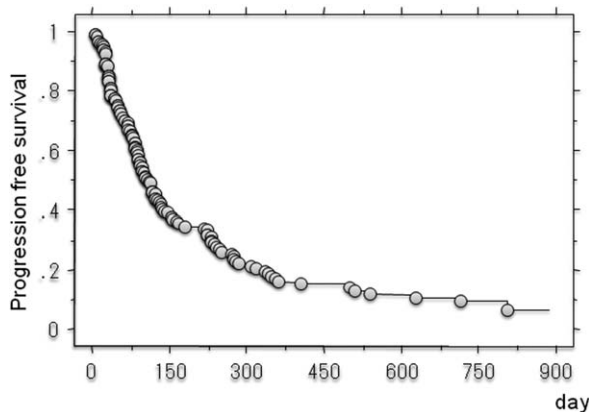

Figure 3. This Kaplan-Meier curve illustrates progression-free survival for all 156 patients in the current study.

which also was observed in patients with ASPS (n = 4), UPS (n = 3), epithelioid sarcoma (n = 2), SS (n = 2), malignant granular cell tumor (n = 1), and malignant ossifying fibromyxoid tumor (n = 1). Seventy-four patients achieved SD, which was maintained for a period of >6 months (long SD) in 32 of 74 patients. Thus, a PR or long SD was observed in 36% of the 125 patients. Histologically, a PR or long SD was achieved in patients with ASPS (78%), LMS (44%), and SS (44%). Few patients with LPS (14%) or MPNST (0%) achieved PR or long SD.

The median PFS for all patients was 15.4 weeks (95% confidence interval [CI], 13-18.9 weeks) (Table 3, Fig. 3). Age, sex, PS, treatment line, treatment target, and primary tumor site were not significantly correlated with PFS (data not shown). The median PFS in 33 patients who had LPS was 8 weeks. In contrast, the median PFS in patients who had non-LPS was 17.7 weeks. The median PFS in patients who had LMS, SS, and UPS was 18.6 weeks, 16.4 weeks, and 15.3 weeks, respectively (Table 4).

Among the 33 patients with LPS, 17 patients a dedifferentiated type, and 11 had a myxoid type. The median PFS for these patients was 8 weeks and 8.3 weeks, respectively. The median PFS for the patients with MPNST and MFS was 7.4 weeks and 16.7 weeks, respectively (Table 4). Although the patients with ASPS had better PFS than those with non-ASPS (ASPS vs non-ASPS: HR, 0.225; 95% CI, 0.091-0.052; $P = .001$), the patients with LPS or MPNST had poorer PFS than those with non-LPS (LPS vs non-LPS: HR, 1.753; 95% CI, 1.147-2.679; $P = .01$) or non-MPNST (MPNST vs non-MPNST: HR, 2.24; 95% CI, 1.035-4.849; $P = .03$), respectively.

Finally, we divided the patients into 2 groups according to eligibility criteria for PALETTE as far as possible. Therefore, the "PALETTE group" (n = 63) consisted of the patients with an inclusion histology type, a PS of 0 or 1, a history of previous chemotherapy containing an anthracycline for metastatic disease, and age ≥18 years. The "non-PALETTE group" (n = 93) consisted of patients who had at least an exclusion histology type (eg, LPS, extraskeletal osteosarcoma), had a PS from 2 to 4, had received pazopanib as first-line treatment, had brain metastasis, or were aged <18 years). The median PFS for patients in the "PALETTE group" and the "non-PALETTE group" was 13.8 weeks and 16.7 weeks ($P = .90$), respectively (Fig. 4).

OS

The median OS was 11.2 months (95% CI, 9.1-14.1 months) (Table 4, Fig. 5). At the final follow-up, pazopanib was still being received by 11 patients. One hundred three patients died of their sarcoma. We also analyzed the OS of patients based on their histologic subtypes (Table 4) The median survival for patients with LMS, SS, UPS, and LPS was 20.1 months, 10.6 months, 9.5

TABLE 4. Survival of Patients With Various Histologic Subtypes

Histology	No. of Patients	Median PFS, wk	6-Month PFS, %	Median Survival, mo	1-Year OS, %
LPS	33	8	14.8	7.3	44.2
UPS	30	15.3	36	9.5	41.6
LMS	21	18.6	38.6	20.1	61.8
SS	18	16.4	42.8	10.6	41.4
ASPS	12	76.6	83.3	NA	90
MFS	8	16.7	25	8.3	29.2
MPNST	7	7.4	0	2.5	28.6
Others	27	14.6	37	7.2	37
Total	146	15.4	34.5	11.2	47.2

Abbreviations: ASPS, alveolar soft part sarcoma; LMS, leiomyosarcoma; LPS, liposarcoma; MFS, myxofibrosarcoma; MPNST, malignant peripheral nerve sheath tumor; NA, not applicable; OS, overall survival; PFS, progression-free survival; SS, synovial sarcoma; UPS; undifferentiated pleomorphic sarcoma.
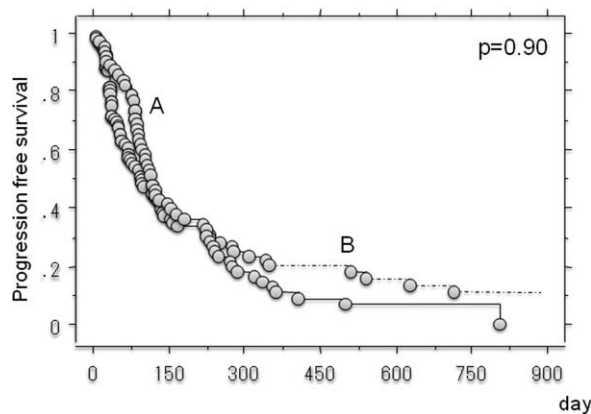

Figure 4. Kaplan-Meier curves illustrate progression-free survival for all 156 patients divided into 2 groups according to eligibility criteria for the PALETTE study (pazopanib for metastatic soft-tissue sarcoma) as far as possible. Line A indicates the PALETTE group; line B, the non-PALETTE group.
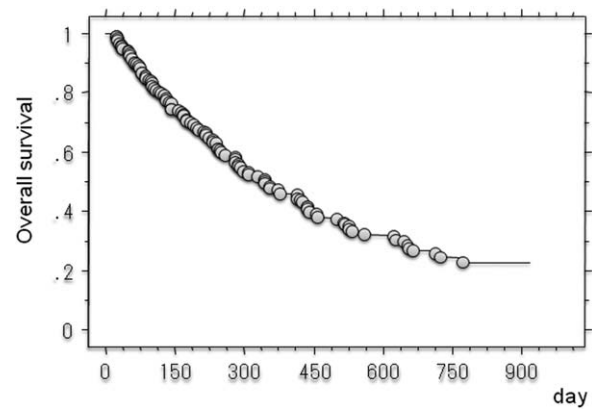

Figure 5. This Kaplan-Meier curve illustrates overall survival for all 156 patients in the current study.

months, and 7.3 months, respectively. A Cox univariate analysis revealed that the favorable prognostic factors in patients who received pazopanib were a good PS, female sex, the number of previous systemic chemotherapy lines, and a longer duration of pazopanib treatment (Table 5). The significance of a PS of 0 (0 vs 2-4: HR, 0.297; 95% CI, 0.155-0.567; P = .0009), female sex (female vs male: HR, 0.623; 95% CI, 0.394-0.984; P = .04), the number of previous systemic chemotherapy lines (0-1 vs $\geq$2 lines: HR, 0.619; 95% CI, 0.413-0.927; P = .02), and a longer duration of pazopanib treatment (per day: HR, 0.995; 95% CI, 0.994-0.997; P < .0001) remained in the multivariate analysis.

There was a significant association between the duration of pazopanib treatment and PFS (Spearman ρ = 0.631; P < .0001). Although 31 patients were excluded from the multivariate analysis because of a lack of RECIST information, a better tumor response was associated with longer survival.

OS was compared between the patients who met eligibility criteria for the PALETTE study as far as possible and those who did not. The OS of patients in the "PALETTE group" and "non-PALETTE group" was 11.4 months and 10.8 months (P = .48), respectively (Fig. 6).

Among the 145 patients who stopped pazopanib treatment, 47 received postpazopanib treatment, which consisted of chemotherapy in 21 patients and radiotherapy in 17 patients. The remaining 98 patients received only best supportive care.

DISCUSSION

Pazopanib is the first antiangiogenic drug for STS that has been approved on the basis of the PALETTE study results.[8] The median treatment duration and the relative dose intensity of pazopanib (in the PALETTE study) were 16.4 weeks and 96%, respectively. In the current multicenter study, the median treatment duration was 28.7 weeks, and the average dose intensity of pazopanib was 609 mg. These results suggest that, although 48% of patients required either a reduction in dose intensity or the interruption of pazopanib treatment, the treatment

TABLE 5. Prognostic Factors for Overall Survival

Variable	HR (95% CI)	P
Age, y	1.007 (0.995–1.019)	.24
Sex: Female vs male	0.445 (0.287–0.69)	.0003
PS		
0 vs 2–4	0.219 (0.115–0.415)	< .0001
1 vs 2–4	0.53 (0.323–0.869)	.01
No. of lines of previous systemic chemotherapy:	0.645 (0.44–0.947)	.03
0–1 vs ≥2		
Bone mets: No vs yes	0.896 (0.563–1.423)	.64
Lung mets: No vs yes	0.868 (0.554–1.361)	.17
Liver mets: No vs yes	0.66 (0.343–1.271)	.21
Duration of pazopanib, d	0.995 (0.994–0.997)	< .0001

Abbreviations: CI, confidence interval; HR, hazard ratio; mets, metastasis; PS, performance status.
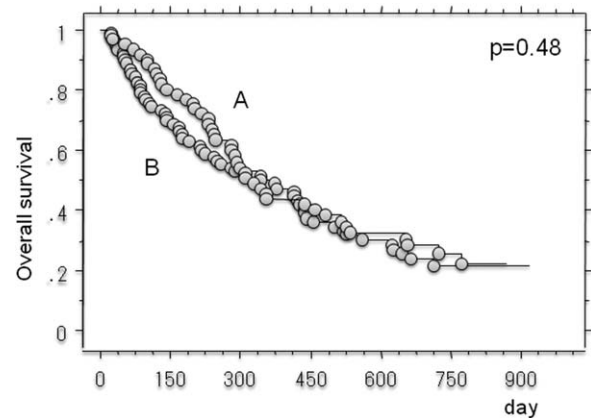

Figure 6. Kaplan-Meier curves illustrate overall survival for all 156 patients divided into 2 groups according to eligibility criteria for the PALETTE study (pazopanib for metastatic soft-tissue sarcoma) as far as possible. Line A indicates the PALETTE group; line B, the non-PALETTE group.

was relatively tolerable. Therefore, pazopanib is likely to become a new treatment option for patients with STSs. Although some patients may continue pazopanib treatment with stable disease control, they should be informed of the exhausting symptoms, which include diarrhea, anorexia, and fatigue.

In the current study, grade ≥3 adverse events, including serious or fatal events, were reported in 48 patients (33%). Remarkably, pneumothorax occurred in 11 of 113 patients (9.7%) who had lung metastasis; and, in 8 of those patients, the severity of the event was grade 3 or 4. This incidence is higher than that observed in the PALETTE study (3%). In the current study, 72% of 156 patients had lung metastasis, which may cause pneumothorax after pazopanib administration. Verschoor and Gelderblom reported that 6 of 43 patients (14%) with lung metastasis who received pazopanib developed pneumothorax.[12] It is difficult to compare that study directly with the PALETTE trial, because the proportion of patients with lung metastasis was not described in the PALETTE study. However, patients should be informed of the risk of pneumothorax before the administration of pazopanib. Thrombocytopenia is another adverse event that is worthy of discussion. Thrombocytopenia was observed in 16 patients (10%); and, in 4 of those patients, the severity was grade 3. Moreover, an interruption or reduction of pazopanib was required in 10 patients because of thrombocytopenia. Nakano et al reported that 28% of Japanese patients with STS (13 of 47 patients) developed grade 1 or 2 thrombocytopenia, although there were no patients who required an interruption or reduction of pazopanib treatment.[13] Physicians should be alert to the occurrence of pneumothorax and thrombocytopenia as well as other well known adverse events.

Radiologic evaluations using RECIST indicated that 13 patients achieved PR and that 32 of 74 patients achieved long SD. From 35% to 78% of patients with ASPS, UPS, LMS, and SS achieved a PR or long SD. The patients with LPS and MPNST had a poorer response to pazopanib. Furthermore, the median PFS in patients with LPS and MPNST was 8 weeks and 7.4 weeks, respectively. The median PFS in all patients was 15.4 weeks. This result was poorer than that reported in the PALETTE study (4.6 months for the pazopanib group). The short PFS in our patients with LPS may have affected the results, because the PALETTE study excluded LPS. Actually, the median PFS for patients with non-LPS sarcoma was 17.7 weeks in the current study, which is almost identical to data from the PALETTE study. Furthermore, we compared PFS and OS between the PALETTE and non-PALETTE groups, and there was no significant difference between them. Although there were only 2 patients with epithelioid sarcoma, the best response that was achieved in such patients was a PR. Patients who had LMS, SS, ASPS, and vascular tumors reportedly were the main long-term responders and survivors.[13,14] In particular, the activity of antiangiogenic agents, such as bevacizumab, sunitinib, and cediranib, was reported previously in ASPS.[15-17] In addition to these tumors, we suggest that pazopanib may have the potential to allow patients with UPS and epithelioid sarcoma to achieve long SD and that there is less potential to achieve long SD in patients with LPS and MPNST. Our results concerning LPS support the findings of the EORTC phase 2 study, which did not demonstrate a sufficient benefit from pazopanib

treatment in patients with LPS.[9] These results suggest that the indications for pazopanib should be carefully decided.

We also demonstrated that the duration of pazopanib treatment was significantly associated with PFS and that a longer duration of pazopanib administration was associated with a longer OS. However, in patients who have progressive disease, all available systemic treatments should be considered after pazopanib is discontinued, because 32% of the patients in this study received postpazopanib treatment.

The median survival of 11.2 months is in line with findings from the PALETTE study (12.5 months in the pazopanib group).[8] A good PS and female sex also were favorable prognostic factors for OS. Kasper et al reported that a good PS and a normal hemoglobin level were favorable factors for long-term survival (OS, $\geq$18 months).[14] Sex and soluble VEGFR2 and placental-derived growth factor levels at week 12 also reportedly were identified as prognostic factors.[18,19] In addition to histologic diagnosis, these clinical factors should be taken into account when deciding the indications for pazopanib treatment. However, more international research will be required to precisely identify the prognostic factors that are associated with survival.

The current study was associated with some limitations. The study population was relatively small for considering the relation between different histologic tumors and clinical outcomes. Also, the study was retrospective in nature. It may be difficult to compare this study directly with previous phase 2[9] and 3[8] trials because of differences according tumor subtype in inclusion criteria, eligibility criteria, and follow-up procedures. For example, in the previous study, the scheduled time points for tumor evaluations were fixed according to RECIST. In the current study, the time points depended on the physician. Moreover, although the median PFS was 15.4 weeks, the median pazopanib treatment duration was 28.7 weeks. The may be because pazopanib treatment was continued depending on the physician's decision despite disease progression.

In conclusion, there were apparent differences in the radiographic efficacy of pazopanib treatment among the histologic types of STS. A PR or long SD may be expected in patients with ASPS, LMS, SS, and UPS who receive pazopanib. Pazopanib treatment is a new, tolerable treatment option; however, adverse events, such as pneumothorax and thrombocytopenia, which did not occur frequently in the PALETTE study, should be taken into consideration.

AUTHOR CONTRIBUTIONS

Tomoki Nakamura: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, and visualization. **Akihiko Matsumine:** Conceptualization, methodology, writing–review and editing, supervision, and project administration. **Akira Kawai:** Investigation and writing–review and editing. **Nobuhito Araki:** Resources. **Takahiro Goto:** Conceptualization, methodology, validation, investigation, and writing–review and editing. **Tsukasa Yonemoto:** Resources. **Hideshi Sugiura:** Resources. **Yoshihiro Nishida:** Resources, data curation, and writing–review and editing. **Hiroaki Hiraga:** Conceptualization, validation, investigation, resources, writing–review and editing, supervision, and project administration. **Kanya Honoki:** Investigation, resources, and data curation. **Taketoshi Yasuda:** Investigation and resources. **Shogen Boku:** Investigation. **Akihiro Sudo:** Writing–review and editing, supervision, project administration, and funding acquisition. **Takafumi Ueda:** Conceptualization, methodology, validation, investigation, writing–review and editing, supervision, and project administration.

REFERENCES

1. Clark MA, Fisher C, Judson I, et al. Soft-tissue sarcomas in adults. *N Engl J Med.* 2005;353:701-711.
2. Zager GK, Ballo MT, Pesters PW, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy; an analysis of 1225 patients. *Cancer.* 2003;97:2530-2543.
3. Weiss SW, Goldblum JR. Local recurrence. In: Enzinger F, Goldblum JR, eds. Soft Tissue Tumors. 4th ed. St. Louis, MO: Mosby; 2001:28-32.
4. Kane JM, Finley JW, Driscoll D, et al. The treatment and outcome of patients with soft tissue sarcomas and synchronous metastases. *Sarcoma.* 2002;6:69-73.
5. Pollock RE, Karnell LH, Menck HR, et al. The National Cancer Data Base report on soft tissue sarcoma. *Cancer.* 1996;87:2247-2257.
6. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of

advanced or metastatic soft-tissue sarcoma: a randomized controlled phase 3 trial. *Lancet Oncol.* 2014;15:415-423.

7. Schutz FA, Choueiri TK, Sternberg CN. Pazopanib: clinical development of a potent anti-angiogenic drug. *Crit Rev Oncol Hematol.* 2011;77:163-171.

8. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2012;379:1879-1886.

9. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC 62403). *J Clin Oncol.* 2009;27:3126-3132.

10. Kawai A, Araki Y, Ando K, et al. Post marketing surveillance (PMS) in Japan for soft tissue sarcoma (STS) patients treated with pazopanib [abstract]. *Eur J Cancer.* 2015;51(suppl 3):S701.

11. Nakano K, Kawai K, Araki A, et al. Clinical outcome of pazopanib for liposarcoma patients from post-marketing surveillance sub-analysis. Poster presented at: Connective Tissue Oncology Society 20th Annual Meeting; November 4-7, 2015; Salt Lake City, UT.

12. Verschoor AJ, Gelderblom H. Pneumothorax as adverse event in patients with lung metastases of soft tissue sarcoma treated with pazopanib: a single reference centre case series [serial online]. *Clin Sarcoma Res.* 2014;4:14.

13. Nakano K, Motoi N, Inagaki L, et al. Difference in the response to pazopanib and the prognosis of soft tissue sarcoma by their histological eligibility for the PALETTE study. *Jpn J Clin Oncol.* 2015;45:449-455.

14. Kasper B, Sleijfer S, Litiere S, et al. Long-term responders and survivors on pazopanib for advanced soft tissue sarcomas: subanalysis of 2 European Organization for Research and Treatment of Cancer (EORTC) clinical trials 62043 and 62072. *Ann Oncol.* 2014;25:719-724.

15. Azizi AA, Haberler C, Czech T, et al. Vascular-endothelial-growth-factor (VEGF) expression and possible response to angiogenesis inhibitor bevacizumab in metastatic alveolar soft part sarcoma. *Lancet Oncol.* 2006;7:521-523.

16. George S, Merriam P, Maki RG, et al. Multicenter phase II trial of sunitinib in the treatment of nongastrointestinal stromal tumor sarcomas. *J Clin Oncol.* 2009;27:3154-3160.

17. Kummar S, Allen D, Monks A, et al. Cediranib for metastatic alveolar soft part sarcoma. *J Clin Oncol.* 2013;31:2296-2302.

18. Duffaud F, Sleijfer S, Litiere S, et al. Hypertension (HTN) as a potential biomarker of efficacy in pazopanib-treated patients with advanced non-adipocytic soft tissue sarcoma. A retrospective study based on European Organisation for Research and Treatment of Cancer (EORTC) 62043 and 62072 trials. *Eur J Cancer.* 2015;51: 2615-2623.

19. Sleijfer S, Gorlia T, Lamers C, et al. Cytokine and angiogenic factors associated with efficacy and toxicity of pazopanib in advanced soft-tissue sarcoma: an EORTC-STBSG study. *Br J Cancer.* 2012; 107:639-645.