Received: 27 May 2020 | Revised: 19 June 2020 | Accepted: 26 June 2020

DOI: 10.1002/ijc.33201



IJC International Journal of Cancer

CANCER THERAPY AND PREVENTION

# Phase II clinical trial of pazopanib for patients with unresectable or metastatic malignant peripheral nerve sheath tumors

Yoshihiro Nishida[1,2] | Hiroshi Urakawa[1,3] | Robert Nakayama[4] | Eisuke Kobayashi[5] | Toshifumi Ozaki[6] | Keisuke Ae[7] | Yoshihiro Matsumoto[8] | Hiroyuki Tsuchiya[9] | Takahiro Goto[10] | Hiroaki Hiraga[11] | Norifumi Naka[12] | Shunji Takahashi[13] | Yuichi Ando[3] | Masahiko Ando[14] | Yachiyo Kuwatsuka[14] | Shunsuke Hamada[15] | Takafumi Ueda[16] | Akira Kawai[5]

[1]Department of Orthopaedic Surgery, Nagoya University, Nagoya, Japan

[2]Department of Rehabilitation, Nagoya University Hospital, Nagoya, Japan

[3]Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, Nagoya, Japan

[4]Department of Orthopaedic Surgery, Keio University School of Medicine, Tokyo, Japan

[5]Department of Musculoskeletal Oncology, National Cancer Center, Tokyo, Japan

[6]Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

[7]Department of Orthopaedic Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

[8]Department of Orthopaedic Surgery, Kyushu University, Fukuoka, Japan

[9]Department of Orthopaedic Surgery, Kanazawa University, Kanazawa, Japan

[10]Department of Musculoskeletal Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

[11]Department of Orthopaedic Surgery, Hokkaido Cancer Center, Sapporo, Japan

[12]Musculoskeletal Oncology Service, Osaka International Cancer Institute, Osaka, Japan

[13]Department of Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Japan

[14]Department of Advanced Medicine, Nagoya University Hospital, Nagoya, Japan

[15]Department of Orthopaedic Surgery, Aichi Cancer Hospital, Nagoya, Japan

[16]Department of Orthopaedic Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan

**Correspondence**
Yoshihiro Nishida, Department of Orthopedic Surgery, Rehabilitation, Nagoya University, 65 Tsurumai, Showa-ku, Nagoya, Aichi 466-8550, Japan.
Email: ynishida@med.nagoya-u.ac.jp

Akira Kawai, Department of Orthopaedic Surgery, National Cancer Center, Tokyo, Japan.
Email: akawai@ncc.go.jp

**Funding information**
Japanese Musculoskeletal Oncology Group; Novartis Pharmaceuticals Corporation

## Abstract

Malignant peripheral nerve sheath tumor (MPNST) often does not respond well to chemotherapy and develops against a background of NF1. The purpose of our study was to examine the efficacy of pazopanib against MPNST. Our study was designed as a physician-initiated phase II clinical trial in patients with advanced MPNST. Patients were registered from 11 large hospitals. The primary endpoint was set to clarify the clinical benefit rate (CBR) at 12 weeks according to response evaluation criteria in solid tumors (RECIST). Progression-free survival (PFS), overall survival (OS) and the CBR based on modified Choi evaluation at week 12 were set as secondary endpoints

**Abbreviations:** CBR, clinical benefit rate; CR, complete response; CTCAE, the Common Terminology Criteria for Adverse Events; DOX, doxorubicin; ECOG, the Eastern Cooperative Oncology Group; FNCLCC, Federation Nationale des Centers de Lutte le Cancer; HR, hazard ratio; IFO, ifosfamide; JMOG, the Japanese Musculoskeletal Oncology Group; MPNST, malignant peripheral nerve sheath tumor; NF1, neurofibromatosis type 1; OS, overall survival; PD, progressive disease; PDGFR, platelet derived growth factor receptor; PFS, progression-free survival; PR, partial response; PS, performance status; RECIST, response evaluation criteria in solid tumors; SD, stable disease; STS, soft tissue sarcoma; ULN, upper limit of normal; VEGFR, vascular endothelial growth factor receptor.

  

along with treatment-related safety. The study enrolled 12 patients. Median age was 49 years. Seven had Grade 2 and five Grade 3 according to the FNCLCC evaluation. Median follow-up period was 10.6 months. CBR at 12 weeks was both 50.0% (RECIST and Choi). The median PFS was 5.4 months for both RECIST and Choi, and the median OS was 10.6 months. Of special interest, the median PFS was 2.9 months for patients with FNCLCC Grade 2 and 10.2 months for Grade 3 (both RECIST and Choi). Grade 4 adverse events of neutropenia and lipase elevation were noted in one patient each. The results of this pazopanib therapy were generally better than those of any of the other single molecular targeted therapies reported previously. Although accumulation of more cases remains necessary, we conclude pazopanib treatment for MPNST to be a safe and promising treatment after doxorubicin-based chemotherapy.

**KEYWORDS**

clinical trial, malignant peripheral nerve sheath tumors, multicenter study, pazopanib

## 1 | INTRODUCTION

Malignant peripheral nerve sheath tumor (MPNST) is a rare malignancy, namely an aggressive soft tissue sarcoma (STS) that accounts for 2% of all STSs.[1] Approximately half of all MPNSTs occur in patients with neurofibromatosis type 1 (NF1), a common autosomal dominant and tumor-predisposing syndrome.[2,3] For unresectable disease or metastatic STS, doxorubicin (DOX) and ifosfamide (IFO) or DOX alone are generally considered the most effective chemotherapeutic agents.[4] STS are diverse groups of tumors that differ in genetic alterations, etiology and clinical behavior.[5] Therefore, the general information obtained from trials in all types of STS patients does not necessarily apply to MPNST. Moreover, because MPNST is an extremely rare disease, there is little useful information on second-line drug treatment for it.

Pazopanib is an orally ingestible angiogenesis tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR) -1, -2 and -3, platelet derived growth factor receptor (PDGFR) -α and -β and c-kit.[6] In patients with relapsed or refractory advanced STS, Pazopanib was found to provide an almost 3-fold increase in PFS over placebo, but the observed response rate was low (6%-9%), with an acceptable toxicity profile.[7,8] Despite the low response rate, some long-term responders are found among patients with advanced STS (PFS > 6 months, 36%; OS>18 months, 34%), including a few remaining progression-free for more than 2 years (3.5%).[9] Efficacy index and biomarker by histological subtype including MPNST in pazopanib treatment are required.

Several studies have suggested that pazopanib may be effective against MPNST. VEGF expression has been reported to be significantly higher in MPNST tissues than in those of benign NF.[10-12] Holtkamp et al reported the presence of PDGFR-α expression in 21 of 28 MPNST patients (75%) and MPNST cell culture.[13] Analyses with gene expression microarray followed by confirmation with immunohistochemistry revealed that PDGFR-α protein expression is upregulated in MPNST as compared to plexiform neurofibroma.[14]

### What's new?

Malignant peripheral nerve sheath tumor (MPNST) is a rare, aggressive soft-tissue sarcoma (STS). Because STSs are very diverse, little has been learned about how to treat MPNST from STS studies. Here, the authors report results from a phase 2 trial of pazopanib, an orally administered angiogenesis inhibitor, tested in 12 patients with nonresectable advanced MPNST. Pazopanib showed a low response rate, but among responders, provided a 3-fold increase in progression-free survival. The safety profile was very manageable, and the drug achieved a better response than other molecular targeted therapies tested previously.

These reports suggest the potential efficacy of pazopanib targeting VEGFR and PDGFR. However, the efficacy of pazopanib for MPNST has not been well clarified,[15] while that for leiomyosarcoma and synovial sarcoma was evident in the PALETTE study.[8]

The responsiveness to drug treatment in MPNST may differ between the NF-based and sporadic types. Since NF1 deletion may lead to activation of Ras, pazopanib may be surmised to become less effective in NF1-related MPNST.[16] On the other hand, Ras activation is known to increase the dependence of cells on the VEGF-VEGFR pathway, and so it is also reasonable to expect that the efficacy of pazopanib would be enhanced in NF1-related MPNST.[17,18]

In the phase II study of STS, the significance of evaluation based on the clinical benefit rate (CBR) including complete or partial response (CR or PR) and stable disease (SD), which is synonymous with progression-free rate, has been described.[19] Therefore, clarifying the CBR to pazopanib at 12 weeks according to RECIST is important for the purpose of directly assessing the effectiveness of pazopanib, and was set as the primary endpoint of the present clinical trial as well.

Overall Survival (OS) is a true endpoint as it is an indicator of actual improvement in patient outcomes. On the other hand, the primary endpoint in the PALETTE trial was progression-free survival (PFS).[8] Keeping these points in mind, the PFS and OS were set as the secondary endpoints along with safety in our study. In STS, Choi criteria were reported to be more sensitive to the chemotherapy responsive[20,21] than RECIST criteria,[22] and the CBR by modified Choi criteria at 12 weeks was used also as a secondary endpoint in the present study.

## 2 | MATERIALS AND METHODS

### 2.1 | Trial oversight

This phase II, investigator-initiated, multi-institutional trial was supported by the Japanese Musculoskeletal Oncology Group (JMOG). JMOG is a multi-institutional joint research organization for bone and soft tissue tumors in Japan, started in 1981. A total of 82 facilities participate in it. Among them, in this trial, 11 major sarcoma treatment centers were selected as research facilities, because they are evenly distributed throughout Japan and treat a particularly high number of sarcoma cases. Novartis Pharmaceuticals Corporation financially supported JMOG for the operation of this trial.

**TABLE 1** Patient demographics

| Characteristics | Value (range) or No. of patients (%) |
|---|---|
| Sex | |
| Male | 6 (50.0%) |
| Female | 6 (50.0%) |
| ECOG performance status | |
| 0 | 5 (41.7%) |
| 1 | 7 (58.3%) |
| Age, years | |
| Median (range) | 49 (20-76) |
| Tumor status | |
| Unresectable | 5 (41.7%) |
| Metastasis | 11 (91.7%) |
| Size of primary tumor, cm | |
| ≦5 | 5 (41.7%) |
| >5 | 7 (58.3%) |
| Anatomic sites of primary tumors | |
| Extremity | 7 (58.3%) |
| Trunk | 3 (25.0%) |
| Other | 2 (16.7%) |
| Depth of primary tumors | |
| Superficial | 1 (8.3%) |
| Deep | 10 (83.3%) |
| Unknown | 1 (8.3%) |
| Histological grade (FNCLCC) | |
| Grade 2 | 7 (58.3%) |
| Grade 3 | 5 (41.7%) |
| Follow-up, months | |
| Median (range) | 10.60 (1.74-22.85) |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FNCLCC, The French Federation of Cancer Centers Sarcoma Group.

### 2.2 | Patient eligibility

Patients confirmed to have MPNST with histological Grade 2 or 3 according to the Federation Nationale des Centers de Lutte contre le Cancer (FNCLCC) system,[23] with locally advanced (unresectable) or metastatic lesions, which were measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1,[22] and those with progressive disease (PD) within 6 months before providing consent were considered eligible for the study. Experienced pathologists at each major center confirmed the diagnosis. Patients resistant to prior treatment including anthracyclines, or those who were determined to be intolerant of previous chemotherapy or who had not consented to receive previous chemotherapy could enter this trial. Details of eligibility are summarized in Table S1.

### 2.3 | Trial design

Since few data are available on the efficacy of pazopanib for MPNST, our study was designed as a phase II, single-arm, nonrandomized, multicenter study to determine it. After confirming that the eligibility

**TABLE 2** Summary of treatment outcomes

| Category | Value (range) or No. of patients (%) |
|---|---|
| Response to pazopanib at 12 weeks (RECIST), n = 12 | |
| PR | 1 (8.3%) |
| SD | 5 (41.7%) |
| PD | 6 (50.0%) |
| Response rate at 12 weeks (RECIST) | 8.3% |
| Clinical benefit rate at 12 weeks (RECIST) | 50.0% |
| Median PFS (RECIST), months | 5.38 |
| Response to pazopanib at 12 weeks (Choi), n = 12 | |
| PR | 3 (25.0%) |
| SD | 3 (25.0%) |
| PD | 5 (41.7%) |
| NE | 1 (8.3%) |
| Response rate at 12 weeks (Choi) | 25.0% |
| Clinical benefit rate at 12 weeks (Choi) | 50.0% |
| Median PFS (Choi), months | 5.37 |
| Median OS, months | 10.61 |

Abbreviations: Choi, modified Choi Criteria; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease.

criteria for patient selection were satisfied, the patient was registered with the secretariat before administration of the study drug.

Oral pazopanib (Votrient, Novartis Pharmaceuticals, Japan) 800 mg once/day was administered until the disease progressed, death or intolerable side effects occurred, or until the patient wished to discontinue the study for any other reason.

The primary endpoint of the present clinical trial was set as CBR to pazopanib at 12 weeks according to RECIST. The PFS and OS were set as the secondary endpoint along with safety. The CBR by modified Choi evaluation at 12 weeks was also set as a secondary endpoint.[20,21] The severity of adverse events was evaluated according to CTCAE v4.03. If an adverse event suggesting a causal relationship to the study drug was observed, the study drug was withdrawn or the dose was reduced as needed. The dose of the study drug should be reduced to 600 mg first and then 400 mg. If dose reduction to 400 mg does not resolve the adverse event, further tapering to 200 mg can be considered.

Physical examinations, blood/urine tests and safety evaluation were performed within 14 days before the start of administration, 1, 3, 5, 7, 9, 12 weeks after the start of pazopanib, after 12 weeks and every 4 weeks thereafter. Image evaluation was performed at the base line and W3, W7, W12 and every 8 weeks thereafter. Individual data were collected by the doctor in charge of each facility. Regarding MRI evaluation and modified Choi, the participating staff at each research facility met twice before the start of the clinical trial and twice after the start of the trial to confirm the evaluation method and ensure that no discrepancy was present in the evaluation between the researchers. Those data were sent to the Department of Advanced Medicine in Nagoya University Hospital as an electronic data capture and analyzed (by Y. K. and M. A).

## 2.4 | NF1 status

NF1 was diagnosed according to the National Institutes of Health diagnostic criteria. An individual, who had two or more suggestive findings as follows, was diagnosed with NF1; (a) six or more café au lait macules >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals, (b) two or more neurofibromas of any type or one plexiform neurofibroma, (c) freckling in the axillary or inguinal regions, (d) optic glioma, (e) two or more Lisch nodules (iris hamartomas), (f) a distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis, (g) a first-degree relative (parent, sibling, or offspring) with NF1 as defined by the above criteria.

## 2.5 | Statistical analysis

Few studies have reported the rate of response to chemotherapy for MPNST in a large number of cases. Several studies reported single

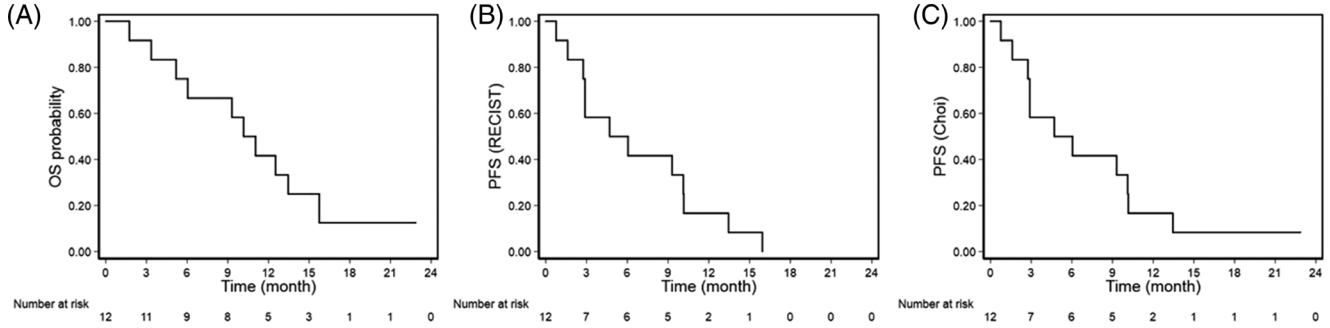


**FIGURE 1** Kaplan-Meier estimate of overall survival, progression free survival in all cases. A, Overall survival; B, progression free survival (RECIST); C, progression free survival (Choi)

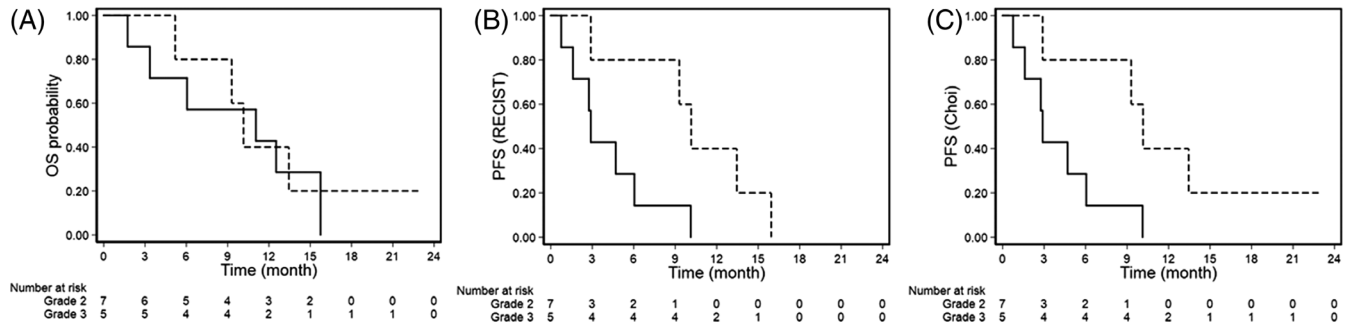


**FIGURE 2** Kaplan-Meier estimate of overall survival, progression free survival in cases with FNCLCC Grade 2 and Grade 3. Dotted line shows cases with Grade 3, solid line with Grade 2. A, Overall survival; B, progression free survival (RECIST); C, progression free survival (Choi)

**TABLE 3** Patients characteristics and treatment outcomes for individual patients

| Case | Age/sex | ECOG PS | Histological grade | Primary tumor with NF-1 (Plexiform neurofibroma) | Site of primary tumor | Metastatic sites | Response to pazopanib at 12 weeks (RECIST) | PFS, months (RECIST) | Response to pazopanib at 12 weeks (Choi) | PFS, months (Choi) | OS, months | Final status |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 54/F | 1 | Grade 3 | – | Shoulder | Lung<br>Lymph nodes<br>Pancreas | SD | 15.94 | SD | 22.85 | 22.85 | AWD |
| 2 | 69/M | 1 | Grade 3 | – | Axilla | Bone<br>Lymph nodes<br>Lung | PD | 2.89 | PD | 2.89 | 5.19 | DOD |
| 3 | 41/M | 0 | Grade 3 | + (+) | Neck | Lung | SD | 13.45 | PR | 13.45 | 13.45 | DOD |
| 4 | 20/F | 1 | Grade 3 | + (–) | Peritoneal | None | SD | 9.30 | SD | 9.30 | 9.30 | DOD |
| 5 | 76/M | 0 | Grade 3 | – | Shoulder-axilla | Lung | PR | 10.16 | PR | 10.16 | 10.16 | DOD |
| 6 | 45/F | 1 | Grade 2 | + (–) | Thigh | Lung | PD | 0.76 | PD | 0.76 | 1.74 | DOD |
| 7 | 34/F | 0 | Grade 2 | + (+) | Lumbar | Lung | PD | 1.61 | PD | 1.61 | 3.35 | DOD |
| 8 | 70/M | 1 | Grade 2 | – | Thigh | Lung | SD | 4.70 | PR | 4.70 | 15.15 | AWD |
| 9 | 64/M | 0 | Grade 2 | – | Shoulder | Lung<br>Lymph nodes<br>Liver | PD | 2.76 | PD | 2.76 | 12.52 | DOD |
| 10 | 53/M | 1 | Grade 2 | – | Thigh | Bone | SD | 10.12 | SD | 10.12 | 15.75 | DOD |
| 11 | 33/F | 0 | Grade 2 | – | Chest wall | Pancreas<br>Lung | PD | 2.89 | PD | 2.89 | 11.05 | DOD |
| 12 | 36/F | 1 | Grade 2 | + (+) | Abdominal wall | Bone | PD | 6.05 | PD[a] | 6.05 | 6.05 | DOD |

Abbreviations: AWD, alive with disease; Choi, modified Choi Criteria; DOD, dead of disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

[a]Clinically judged to show exacerbation, and so pazopanib was discontinued before 12 weeks.

agent chemotherapy to have a response rate of 4.0% to 18% and PFS of 2.0 to 3.0 months for locally advanced/metastatic STS.[24-26] The response rate of second-line chemotherapy was 6% to 8%, which is lower than that of first-line chemotherapy,[27] and most of the patients in this trial would be treated with or after second-line chemotherapy. Threshold CBR at 12 weeks was set at 15%, expected CBR with pazopanib at 40%. With a single arm design for pazopanib treatment, significance level of 10% on both sides, and power of 80%, it is necessary to accumulate at least 22 cases. The target number of cases was set at 23 in anticipation of possible dropout. PFS and OS were estimated by Kaplan-Meier method, and statistically analyzed by Log rank test. Statistical analyses were performed using Stata version 15.0 (StataCorp, College Station, TX) and JMP version 12.2 (SAS Institute Inc, Cary, NC).

## 3 | RESULTS

Our study enrolled 12 patients with MPNST. Evaluable tumors progressed in all patients within 3 months before enrollment. Demographics of enrolled patients including sex, tumor size, anatomic site, histological grade (FNCLCC) and follow-up duration were shown in Table 1. The number of prior chemotherapy was 3 lines for 1 patient, 2 lines for 1, 1 line for 8 and 0 lines for 1. Evaluation at 12 weeks according to RECIST was PR in 1, SD in 5, PD in 6 (one patient was not evaluable with image analyses because she was clinically judged to show exacerbation, and so pazopanib was discontinued before 12 weeks). CBR according to RECIST at 12 weeks (primary endpoint) and modified Choi evaluation, median PFS (RECIST), PFS (Choi) and OS were shown in Table 2 and Figure 1. On a waterfall plot, a marked suppressive effect on target tumor growth was observed. Only 2 cases showed PD (Figure S1). Detailed patient demographics including prior treatment were listed in Table 3 and Table S2.

One of the interesting results of the present study was that PFS and CBR differed according to FNCLCC grade. CBR (RECIST) at 12 weeks was 28.6% in Grade 2 and 80.0% in Grade 3. CBR (Choi) at 12 weeks was 14.3% in Grade 2 and 40.0% in Grade 3 (Table S3). A waterfall plot indicated that target lesions in Grade 3 cases were well-controlled, with 0 cases evaluated as PD at 12 weeks (Figure S1). Median PFS (RECIST) was 2.9 months for Grade 2 and 10.2 months for Grade 3 by Kaplan-Meier analysis, with this difference significant ($P$ = .02). The median PFS (Choi) was 2.9 months for Grade 2 and 10.2 months for Grade 3, showing a significant difference between them ($P$ = .02). The median OS was 11.1 months for Grade 2 and 10.2 months for Grade 3, with this difference not significant ($P$ = .76) (Figure 2).

Whether the effect of pazopanib differs between patients with NF1-related and sporadic MPNST is another intriguing issue. Median PFS of RECIST and modified Choi were both 6.1 months for NF1-MPNST and both 4.7 months for sporadic MPNST, indicating the absence of any significant difference ($P$ = .59 for both RECIST and modified Choi). CBR at 12 weeks of RECIST and modified Choi were both 40.0% for NF1-MPNST and both 57.1% for sporadic MPNST. In contrast, median OS for NF1 and sporadic MPNST were 6.1 months and 12.5 months, respectively, showing a significant difference ($P$ = .048) (Table S4, Figure S2). Pazopanib may have been effective even for NF1-related MPNST for response with RECIST and modified Choi.

The adverse events of Grade 4 were neutropenia and lipase elevation in one person each. As Grade 3 adverse events, aspartate aminotransferase/alanine aminotransferase increase was observed in 2 cases, white blood cell decrease in two, and left ventricular systolic dysfunction, leading to discontinuation of the therapeutic drug in one (Table S5). Six patients (50%) received either interruption or dose reduction because of adverse events. Regarding these six cases, RECIST at 12 weeks was PR 1, SD 4 and PD 1, with the dose reduction not seeming to diminish the efficacy of pazopanib.

The reason for discontinuation of pazopanib leading to cessation of participation in the pazopanib study was disease progression in eight cases, and disease progression during discontinuation due to side effects, heart failure, malaise and patient preference in one case each. The subsequent anticancer therapy after this trial in individual patients was as follows. When liver dysfunction occurred, participation in the clinical trial was discontinued due to patient request (Case 1). Thereafter, however, pazopanib was restarted, with the patient still showing SD at 18 months after the restart of pazopanib treatment. Three patients showed PD with administration of eribulin (Case 3, 8 and 12), with one case showing PD with administration of DOX and then PD with gemcitabine and docetaxel (Case 10). One case showed PD with eribulin and then PD with trabectedin (Case 11). Except for the pazopanib restart cases, all cases receiving post-study treatment after pazopanib cessation showed PD.

## 4 | DISCUSSION

This trial was conducted to determine whether pazopanib would be effective as a histology-tailored drug treatment for MPNST. CBR at 12 weeks were 50.0% with both RECIST and Choi, and median PFS and OS were 5.4 (both RECIST and Choi), and 10.6 months, with these results generally more favorable than the mostly disappointing ones of previous studies with molecular targeted drugs used as a single agent for MPNST patients.[28-31] However, alisertib, a novel oral selective inhibitor of aurora kinase A, showed good PFS for advanced/metastatic MPNST[29] (Table 4). Combination use of the mTOR inhibitor everolimus with a recombinant humanized anti-VEGF monoclonal antibody, bevacizumab, for patients with refractory MPNST revealed a CBR of 12% (3/25) according to the WHO evaluation, and the combination of everolimus and bevacizumab was considered inactive.[32] Combination use of genetespib, an injectable potent small molecule inhibitor of Hsp90, with sirolimus, an oral mTOR inhibitor, achieved no response in 13 patients with refractory MPNST.[33] Regarding pazopanib, three retrospective studies showed the outcomes for MPNST cases, indicating no PR patients although the numbers of cases were up to 5.[34-36] Nakamura et al reported that patients with MPNST had a poorer response to pazopanib than other

**TABLE 4** Reports of molecular targeted therapy for MPNST

| Drug | Author | Number of patients | Efficacy (tumor growth) | Efficacy (PFS, OS) |
|---|---|---|---|---|
| Imatinib | Chugh et al[28] | 7 (5 evaluable) | SD: 1, PD: 4 | PFS:1.92M |
| Sorafenib | Maki et al[30] | 15 (12 evaluable) | SD: 6, PD: 6 | PFS: 1.7M |
| Dasatinib | Schuetze et al[31] | 14 | SD: 2, PD: 12 | PFS: 14% (2M), 7% (4M) |
| Alisertib | Dickson et al[29] | 10 | PR: 0 | PFS: 3M, PFS (2.8M); 60%, OS: 15.9M |
| Pazopanib | Yoo et al[36] | 5 | PR: 1, SD: 4 | PFS: 6.5M, OS: 8.9M |
| Pazopanib | Seto et al[35] | 7 | SD: 4, PD: 3 | NA |
| Pazopanib | Nakamura et al[34] | 7 (5 evaluable) | SD: 3, PD: 2 | PFS: 1.7M |
| Pazopanib | Present study | 12 (11 evaluable) | PR:1, SD; 5, PD; 5 | PFS: 5.4M, PFS (2.8M); 50%, OS; 10.6M |

Abbreviations: M, month; NA, not available; OS, overall survival (median); PD, progressive disease; PFS, progression free survival (median); PR, partial response; SD, stable disease; W, week.

histotypes based on the postmarketing surveillance (PMS) data.[34] Furthermore, the median PFS in patients with MPNST was 7.4 weeks (1.7 months), which was much worse than that in the present study (5.4 months) (Table 4). Their study was retrospective, based on PMS data. For this reason the diverse treatment policies adopted by the individual facilities and vague data collection methods used precluded the drawing of any firm conclusions. The results of the PALETTE study showed that the PFS of all STSs was 4.6 months, comparable to the PFS of MPNST (5.4 months) in the present study, and data that can be acquired online of the PALETTE study indicated that the CBR for MPNST patients was 50% (PR 1, SD3, among 8 cases: http://www.pmda.go.jp/files/000153553.pdf), which is identical to the results of the present study, Together, MPNST could be a good target for pazopanib among the many histological types of STSs, and there are unlikely to be major discrepancies in the effects of pazopanib between Westerners and Japanese. Among the molecular targeted drugs reported thus far, pazopanib can be recommended for MPNST from the perspective of PFS and CBR.

Due to the rarity of MPNST, there are few consistent data on their sensitivity to traditional chemotherapy. DOX and IFO or DOX alone are generally considered to be the most effective chemotherapeutic agents in unresectable disease or metastatic STS.[4] Few Phase II or III trials have been specifically conducted on advanced or metastatic MPNST. Recently, the results of an international, randomized, controlled, phase 3 study investigating histotype-tailored neoadjuvant chemotherapy vs standard chemotherapy for sarcoma subtypes were reported.[37] In MPNST, this comparative study was conducted to compare the efficacy of IFO + etoposide and that of epirubicin + IFO. Disease free survival was significantly better in the cohort of epirubicin + IFO than that of IFO + etoposide. Another study documented that neoadjuvant use of epirubicin + IFO for MPNST achieved a CBR of 100%,[38] suggesting that anthracyclin + IFO can still be regarded as the standard chemotherapy regimen.

A review of 12 pooled nonrandomized and randomized European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trials, comparing the results of 175 MPNST and 2500 other histological types demonstrated similar outcomes for MPNST and other STS histotypes (PFS; MPNST: 17.0 weeks, other STS: 16.1 weeks, $P = .830$, response rate; MPNST: 21%, other STS: 22%, $P = .84$).[39] On the other hand, Ferrari et al reported that MPNST had the worst prognosis, with various regimens for 304 STSs including 71 MPNSTs in children.[40] This highlights the present reality in which devising effective second line drug treatment after standard chemotherapy for MPNST remains an urgent task. Pazopanib may be promising as a candidate for a second line drug treatment for MPNST. Cesne et al reported that the median PFS with pazopanib was longer in patients who had had only 1 prior line vs 2 or more lines of therapy.[41] To clarify the efficacy of pazopanib use as a first line therapy for MPNST, further study and data accumulation are required.

In the present study, we adopted not only RECIST but also modified Choi evaluation to determine the effects of pazopanib. In the sorafenib study,[30] the authors were impressed by a discovery made subsequent to evaluation of the RECIST response; namely two patients with MPNST showed regression or cystification of metastatic disease without a RECIST response. Previous clinical trials in MPNST have used imaging end points with MRI or CT using WHO,[42] RECIST,[22] or Choi[20] criteria. Although the number of cases was small, there was no significant difference between the results of RECIST and those of modified Choi evaluation in the present study of MPNST. Which evaluation better reflects the prognosis of MPNST will require future case accumulation.

It would be of interest to clarify whether a difference exists in the effect of pazopanib between FNCLCC Grade 2 and Grade 3 in MPNST. Histological grade is commonly associated with life prognosis in STS, although the importance of grading classification in MPNST staging is controversial. Some institutions consider all MPNSTs to be of high grade reflecting the lack of consensus on histological grade and may not perform regular grading as FNCLCC does.[12] However, several studies have reported that the histological grade of MPNST makes a difference in life prognosis. In the study of Stucky et al, when grade was classified into 4 grades (NCI), high grade was a significantly poor prognostic factor in disease specific survival (DSS) with univariate ($P = .017$), and also hazard ratio (HR) 3.8 in multivariate analyses.[43] Valentin et al also showed that FNCLCC Grade 3 was a poor prognostic factor in multivariate analysis in DFS.[44] Kolberg et al analyzed 179 cases from three European centers, and found that there was a

significant difference in prognosis between low grade and high grade MPNST in not only the entire cohort, but also the NF1 cohort or non-NF1 cohort considered separately.[45] Regarding analysis using the FNCLCC classification, Anghileri et al reported that the prognosis of patients with Grade 3 was poor with regard to cause-specific mortality (HR 1.83) compared to 1 and 2, but not significantly so ($P$ = .091).[46] In the present study, patients with FNCLCC Grade 3 had better outcomes in both CBR and PFS according to both RECIST and Choi criteria compared to those with Grade 2. Given that median OS was comparable between Grades 2 and 3, pazopanib may be more effective in Grade 3 MPNST. However, since the small number of cases may have affected the results obtained, it will be necessary to increase the number of cases in future studies to see if these results can be reproduced.

We also need information on whether the efficacy of pazopanib differs between NF1 related MPNST and sporadic MPNST. Previously reported studies documented discordant survival rates for sporadic MPNST and MPNST NF1 patients. NF1 patients had a lower survival rate than non-NF1 ones in some reports,[47-49] while others noted no difference.[12,46,50,51] The meta-analyses[45] including data from a total of 48 studies and >1800 patients revealed a significantly higher odds ratio (OR) for OS and DSS in the non-NF1 group (OR of OS = 1.75, 95% confidence interval [CI] = 1.28-2.39, and OR of DSS = 1.68, 95% CI = 1.18-2.40). However, studies published over the past decade show improved outcomes, especially in the NF1 group, with the survival rates for the two patient groups thereby becoming similar. In the report on the responsiveness to chemotherapy in NF1-related and sporadic MPNST, phase II study for AJCC3-4 MPNST patients with DOX + IFO and IFO + etoposide demonstrated response rates of 17.9% in NF1-related MPNST and 44.4% in sporadic cases.[52] The response of NF-MPNST was also reported to be worse than that of sporadic MPNST in pediatric MPNST.[40] In the present study, median PFS of RECIST and Choi were not significantly different between NF1 related and sporadic -MPNST, and CBR was also similar between the 2 cohorts, suggesting that NF1-related MPNST may respond to pazopanib. In contrast, the median OS for NF1-related MPNST was significantly worse than that for sporadic cases. Since NF1-related MPNST may have multiple complicated genetic alterations, combination therapy with pazopanib and other drugs may need to be considered to prolong not only PFS, but also OS.

The profile of adverse events of pazopanib in the present study was not different from that in the PALETTE study[8] and retrospective real-world data.[34] In the PALETTE study, the most common adverse events were fatigue, diarrhea, nausea, weight loss and hypertension. Increased concentrations of liver enzymes were observed in 20% to 30% of the patients. A drop in the left ventricular ejection fraction occurred in 16 patients (6.7%). These results of adverse events are not significantly different from those of the present study. Results of the retrospective study based on PMS data showed Grade 3 adverse events in 31% of the patients. The most common Grade 3 toxicities were hypertension (6%), pneumothorax (5%), liver disorder (5%), diarrhea (3%), thrombocytopenia (3%), heart failure (2%), fatigue (1%), pneumonia (1%) and gastrointestinal perforation (1%).[34] In their study, dose reductions and/or treatment interruptions because of the occurrence of adverse events were required in 48% of the patients, which is consistent with the results of the present study in which six patients (50%) needed either dose reduction or interruption of pazopanib because of adverse events. These results indicate that pazopanib is tolerable in patients with MPNST, similar to the experience with other histotypes of STS.

Regarding the relationship between adverse events and effects of pazopanib, one of the most common toxicities of pazopanib, hypertension, has been previously investigated.[53] That study concluded that pazopanib-induced hypertension did not correlate with outcome in pazopanib-treated STS patients. Other studies indicated that there was no association between the occurrence of pazopanib-induced proteinuria, hypothyroidism and cardiotoxicity and outcome.[54] In the present study, regarding six patients (50%) who required either discontinuation or dose reduction due to adverse events, efficacy was not inferior to that of the noninterruption cohort. Together, toxicity cannot be used as a predictor of pazopanib activity in patients with MPNST just like in other advanced STS.

A limitation of the present study is that the number of cases comprising the study cohort was lower than expected. The reason for the slow enrollment may be that pazopanib is not novel, and is already being used to treat MPNST at nonspecialist centers as well under standard medical insurance coverage in Japan. In addition, the study period was predetermined as a condition for receiving support for the study, and no extension was permitted to continue enrolling patients beyond August 2018. However, the number of MPNST cases is not small compared to clinical trials using other molecular targeted agents, and the results of the present study provide much useful information.

In conclusion, this multicenter, physician-initiated phase II clinical trial of pazopanib in patients with malignant peripheral nerve sheath tumors with unresectable disease or distant metastases revealed that pazopanib achieved favorable outcomes similar to those of other STSs. Pazopanib may show particularly good efficacy against tumors with higher grades of malignancy, and thereby prolong life.

## ACKNOWLEDGMENTS

We thank the patients who participated in our study, members of JMOG participating institutions and members to collect data (Dr K. Kikuta, Dr M. Endo, Dr J. Hasei, Dr T. Ota, Dr T. Sakai), Data and Safety Monitoring Committee (Dr H. Sugiura, Dr A. Nagano, and Dr Y. Shido), and Department of Advanced Medicine in Nagoya University Hospital (Ms F. Sugiura, and Ms M. Ito), and employees of Novartis Pharmaceuticals Corporation (Mr T. Yonezu, Ms M. Endo, Mr R. Kano, and Ms M. Machida) for their contributions to our study. We thank also Ms Y. Kawai, Ms T. Naganuma, Ms M. Yoshino for secretarial assistance. Our study is financially supported by JMOG. The operation of JMOG is financially supported by Novartis Pharmaceuticals Corporation.

## CONFLICT OF INTEREST

Yoshihiro Nishida: research funding from Zimmer-Biomet, personal fees from Eisai Co., Ltd., Eli Lilly Japan K.K., Kaken Pharmaceutical Co. Ltd., Hisamitsu Pharmaceutical Co. Inc., Kyowa Hakko Kirin Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiici Sankyo Company Ltd, Novartis Pharma K. K., Asahi Kasei Pharma Corporation, consultant

for Seikagaku corp. Akira Kawai: personal fee from Novartis Pharma K. K. Yuichi Ando: grants and personal fees from Chugai Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Nippon Kayaku, Yakult Honsha, Eli Lilly Japan, Mochida Pharmaceutical, Taiho, Daiici Sankyo Company Ltd, Eisai, and personal fees from Novartis Pharma K. K., Bayer Holding, BMS, Sawai, Tsumura, Shionogi, Otsuka Holding, AstraZeneca, Roche Diagnostics, Insertion Healthcare Japan. Shunji Takahashi: grants and personal fees from Novartis Pharma K. K., Eisai, Taiho, Ono pharmaceutical. Eisuke Kobayashi: honorarium from Novartis Pharma K. K. Hiroaki Hiraga: lecture fee from Novartis Pharma K. K.

## CLINICAL TRIALS REGISTRATION

This trial was registered as UMIN000019303 in the UMIN Clinical Trials Registry and as jRCTs041180114 in the Japan Registry of Clinical Trial since the enforcement of the Clinical Trials Act in Japan.

## ETHICS STATEMENT

Our study was approved by the Ethics Committee of Nagoya University Graduate School of Medicine in January 2016 (registration number: 2015-0371), and subsequently approved by the respective ethics committees in each of the participating 11 centers. All patients provided written informed consent to participate in it.

## DATA AVAILABILITY STATEMENT

The research data is available in a data base repository in our institution (Nagoya University), and can be available upon reasonable request.

## ORCID

*Yoshihiro Nishida* https://orcid.org/0000-0002-7511-6388
*Hiroshi Urakawa* https://orcid.org/0000-0003-2961-1238

## REFERENCES

1. Ng VY, Scharschmidt TJ, Mayerson JL, Fisher JL. Incidence and survival in sarcoma in the United States: a focus on musculoskeletal lesions. *Anticancer Res*. 2013;33:2597-2604.
2. Evans DG, Baser ME, McGaughran J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. *J Med Genet*. 2002;39:311-314.
3. Uusitalo E, Rantanen M, Kallionpää RA, et al. Distinctive cancer associations in patients with neurofibromatosis type 1. *J Clin Oncol*. 2016;34:1978-1986.
4. 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 randomised controlled phase 3 trial. *Lancet Oncol*. 2014;15:415-423.
5. Van Glabbeke M, van Oosterom AT, Oosterhuis JW, et al. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with anthracycline-containing first-line regimens—a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. *J Clin Oncol*. 1999;17:150-157.
6. Harris PA, Boloor A, Cheung M, et al. Discovery of 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl] amino]-2-methyl-benzenesulfonamide (Pazopanib), a novel and potent vascular endothelial growth factor receptor inhibitor. *J Med Chem*. 2008;51:4632-4640.
7. 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 the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol*. 2009;27:3126-3132.
8. van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, Schöffski P, Aglietta M, Staddon AP, Beppu Y, Le Cesne A, Gelderblom H, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (Lond, Engl)* 2012;379:1879-86.
9. Kasper B, Sleijfer S, Litière S, et al. Long-term responders and survivors on pazopanib for advanced soft tissue sarcomas: subanalysis of two European Organisation for Research and Treatment of Cancer (EORTC) clinical trials 62043 and 62072. *Ann Oncol*. 2014;25:719-724.
10. Gesundheit B, Parkin P, Greenberg M, et al. The role of angiogenesis in the transformation of plexiform neurofibroma into malignant peripheral nerve sheath tumors in children with neurofibromatosis type 1. *J Pediatr Hematol Oncol*. 2010;32:548-553.
11. Wasa J, Nishida Y, Suzuki Y, et al. Differential expression of angiogenic factors in peripheral nerve sheath tumors. *Clin Exp Metastasis*. 2008;25:819-825.
12. Zou C, Smith KD, Liu J, et al. Clinical, pathological, and molecular variables predictive of malignant peripheral nerve sheath tumor outcome. *Ann Surg*. 2009;249:1014-1022.
13. Holtkamp N, Okuducu AF, Mucha J, et al. Mutation and expression of PDGFRA and KIT in malignant peripheral nerve sheath tumors, and its implications for imatinib sensitivity. *Carcinogenesis*. 2006;27:664-671.
14. Grobmyer SR, Reith JD, Shahlaee A, Bush CH, Hochwald SN. Malignant peripheral nerve sheath tumor: molecular pathogenesis and current management considerations. *J Surg Oncol*. 2008;97:340-349.
15. Gelderblom H, Judson IR, Benson C, et al. Treatment patterns and clinical outcomes with pazopanib in patients with advanced soft tissue sarcomas in a compassionate use setting: results of the SPIRE study. *Acta Oncol (Stockholm, Sweden)*. 2017;56:1769-1775.
16. Bollag G, Clapp DW, Shih S, et al. Loss of NF1 results in activation of the Ras signaling pathway and leads to aberrant growth in haematopoietic cells. *Nat Genet*. 1996;12:144-148.
17. Lapinski PE, Kwon S, Lubeck BA, et al. RASA1 maintains the lymphatic vasculature in a quiescent functional state in mice. *J Clin Invest*. 2012;122:733-747.
18. Munchhof AM, Li F, White HA, et al. Neurofibroma-associated growth factors activate a distinct signaling network to alter the function of neurofibromin-deficient endothelial cells. *Hum Mol Genet*. 2006;15:1858-1869.
19. Van Glabbeke M, Verweij J, Judson I, Nielsen OS. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. *Eur J Cancer (Oxford, Engl: 1990)*. 2002;38:543-549.
20. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol*. 2007;25:1753-1759.
21. Stacchiotti S, Collini P, Messina A, et al. High-grade soft-tissue sarcomas: tumor response assessment—pilot study to assess the correlation between radiologic and pathologic response by using RECIST and Choi criteria. *Radiology*. 2009;251:447-456.
22. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer (Oxford, Engl: 1990)*. 2009;45:228-247.
23. Coindre JM. Grading of soft tissue sarcomas: review and update. *Arch Pathol Lab Med*. 2006;130:1448-1453.

24. Borden EC, Amato DA, Rosenbaum C, et al. Randomized comparison of three adriamycin regimens for metastatic soft tissue sarcomas. *J Clin Oncol*. 1987;5:840-850.
25. García-Del-Muro X, López-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol*. 2011;29:2528-2533.
26. Lorigan P, Verweij J, Papai Z, et al. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. *J Clin Oncol*. 2007;25:3144-3150.
27. van Oosterom AT, Mouridsen HT, Nielsen OS, et al. Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients. *Eur J Cancer (Oxford, Engl: 1990)*. 2002;38:2397-2406.
28. Chugh R, Wathen JK, Maki RG, et al. Phase II multicenter trial of imatinib in 10 histologic subtypes of sarcoma using a bayesian hierarchical statistical model. *J Clin Oncol*. 2009;27:3148-3153.
29. Dickson MA, Mahoney MR, Tap WD, et al. Phase II study of MLN8237 (Alisertib) in advanced/metastatic sarcoma. *Ann Oncol*. 2016;27:1855-1860.
30. Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. *J Clin Oncol*. 2009;27:3133-3140.
31. Schuetze SM, Wathen JK, Lucas DR, et al. SARC009: phase 2 study of dasatinib in patients with previously treated, high-grade, advanced sarcoma. *Cancer*. 2016;122:868-874.
32. Widemann BC, Lu Y, Reinke D, et al. Targeting sporadic and neurofibromatosis type 1 (NF1) related refractory malignant peripheral nerve sheath tumors (MPNST) in a phase II study of everolimus in combination with bevacizumab (SARC016). *Sarcoma*. 2019;2019:7656747.
33. Kim A, Lu Y, Okuno SH, et al. Targeting refractory sarcomas and malignant peripheral nerve sheath tumors in a phase I/II study of sirolimus in combination with ganetespib (SARC023). *Sarcoma*. 2020;2020:5784876.
34. Nakamura T, Matsumine A, Kawai A, et al. The clinical outcome of pazopanib treatment in Japanese patients with relapsed soft tissue sarcoma: a Japanese Musculoskeletal Oncology Group (JMOG) study. *Cancer*. 2016;122:1408-1416.
35. Seto T, Song MN, Trieu M, et al. Real-world experiences with pazopanib in patients with advanced soft tissue and bone sarcoma in northern California. *Med Sci (Basel, Switzerland)*. 2019;7.
36. Yoo KH, Kim HS, Lee SJ, et al. Efficacy of pazopanib monotherapy in patients who had been heavily pretreated for metastatic soft tissue sarcoma: a retrospective case series. *BMC Cancer*. 2015;15:154.
37. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol*. 2017;18:812-822.
38. Hirbe AC, Cosper PF, Dahiya S, Van Tine BA. Neoadjuvant ifosfamide and epirubicin in the treatment of malignant peripheral nerve sheath tumors. *Sarcoma*. 2017;2017:3761292.
39. Kroep JR, Ouali M, Gelderblom H, et al. First-line chemotherapy for malignant peripheral nerve sheath tumor (MPNST) versus other histological soft tissue sarcoma subtypes and as a prognostic factor for MPNST: an EORTC soft tissue and bone sarcoma group study. *Ann Oncol*. 2011;22:207-214.
40. Ferrari A, Miceli R, Rey A, et al. Non-metastatic unresected paediatric non-rhabdomyosarcoma soft tissue sarcomas: results of a pooled analysis from United States and European groups. *Eur J Cancer (Oxford, Engl: 1990)*. 2011;47:724-731.
41. Cesne AL, Bauer S, Demetri GD, et al. Safety and efficacy of Pazopanib in advanced soft tissue sarcoma: PALETTE (EORTC 62072) subgroup analyses. *BMC Cancer*. 2019;19:794.
42. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer*. 1981;47:207-214.
43. Stucky CC, Johnson KN, Gray RJ, et al. Malignant peripheral nerve sheath tumors (MPNST): the Mayo Clinic experience. *Ann Surg Oncol*. 2012;19:878-885.
44. Valentin T, Le Cesne A, Ray-Coquard I, et al. Management and prognosis of malignant peripheral nerve sheath tumors: the experience of the French Sarcoma Group (GSF-GETO). *Eur J Cancer (Oxford, Engl: 1990)*. 2016;56:77-84.
45. Kolberg M, Høland M, Agesen TH, et al. Survival meta-analyses for >1800 malignant peripheral nerve sheath tumor patients with and without neurofibromatosis type 1. *Neuro Oncol*. 2013;15:135-147.
46. Anghileri M, Miceli R, Fiore M, et al. Malignant peripheral nerve sheath tumors: prognostic factors and survival in a series of patients treated at a single institution. *Cancer*. 2006;107:1065-1074.
47. Carli M, Ferrari A, Mattke A, et al. Pediatric malignant peripheral nerve sheath tumor: the Italian and German soft tissue sarcoma cooperative group. *J Clin Oncol*. 2005;23:8422-8430.
48. Porter DE, Prasad V, Foster L, Dall GF, Birch R, Grimer RJ. Survival in malignant peripheral nerve sheath tumours: a comparison between sporadic and neurofibromatosis type 1-associated tumours. *Sarcoma*. 2009;2009:756395.
49. Sordillo PP, Helson L, Hajdu SI, et al. Malignant schwannoma—clinical characteristics, survival, and response to therapy. *Cancer*. 1981;47:2503-2509.
50. Okada K, Hasegawa T, Tajino T, et al. Clinical relevance of pathological grades of malignant peripheral nerve sheath tumor: a multi-institution TMTS study of 56 cases in northern Japan. *Ann Surg Oncol*. 2007;14:597-604.
51. Yu J, Deshmukh H, Payton JE, et al. Array-based comparative genomic hybridization identifies CDK4 and FOXM1 alterations as independent predictors of survival in malignant peripheral nerve sheath tumor. *Clin Cancer Res*. 2011;17:1924-1934.
52. Higham CS, Steinberg SM, Dombi E, et al. SARC006: phase II trial of chemotherapy in sporadic and neurofibromatosis type 1 associated chemotherapy-naive malignant peripheral nerve sheath tumors. *Sarcoma*. 2017;2017:8685638.
53. Duffaud F, Sleijfer S, Litière 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 (Oxford, Engl: 1990)*. 2015;51:2615-2623.
54. Vos M, Sleijfer S, Litière S, et al. Association of pazopanib-induced toxicities with outcome of patients with advanced soft tissue sarcoma; a retrospective analysis based on the European Organisation for Research and Treatment of Cancer (EORTC) 62043 and 62072 clinical trials. *Acta Oncol (Stockholm, Sweden)*. 2019;58:872-879.


## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Nishida Y, Urakawa H, Nakayama R, et al. Phase II clinical trial of pazopanib for patients with unresectable or metastatic malignant peripheral nerve sheath tumors. *Int. J. Cancer*. 2020;1–10. https://doi.org/10.1002/ijc.33201