Original Article

Efficacy and safety of apatinib in patients with untreated or chemotherapy-refractory soft tissue sarcoma: a multicenter, phase 2 trial

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Background: Anti-angiogenic agents have been reported to exert promising clinical activity for advanced soft tissue sarcoma (STS). Apatinib, a vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor, is effective and safe for various solid tumors, but its role in STS remains unclear. The aim of this study was to explore the efficacy and safety of apatinib in patients with untreated or chemotherapy-refractory STS.

Methods: In this multicenter, single-arm, phase 2 trial, patients aged 18–70 years with untreated or chemotherapy-refractory STS were enrolled and received 500 mg apatinib per day. During treatment, patients were followed up with imaging every 8 weeks. The primary endpoint was the 6-month progression-free survival (PFS) rate. The secondary endpoints were objective response rate (ORR), overall survival (OS), and adverse events (AEs), which were graded following the National Cancer Institute common terminology criteria for AEs version 4.03.

Results: From June 2017 to October 2018, 53 patients were enrolled, 51 of whom received at least one dose of apatinib. Of the 53 patients, 41 (77.4%) had chemotherapy-refractory disease. The median follow-up was 13.3 months. The 6- and 12-month PFS rates were 46.8% and 25.2%, respectively, with a median PFS of 5.6 months [95% confidence interval (CI): 3.8–9.2 months]. The median PFS was 5.5 months for chemotherapy-refractory patients, 9.1 months for untreated patients, 13.9 months for patients with alveolar soft part sarcoma (ASPS), and 3.7 months for patients with clear cell sarcoma (CCS). The 12- and 24-month OS rates were 58.6% and 44.9%, respectively, with a median OS of 20.0 months (95% CI: 9.2–31.1 months). The median OS was 10.7 months for chemotherapy-refractory patients and not estimated for untreated, ASPS, nor CCS patients. In 50 evaluable patients, the ORR was 18.0% and the disease control rate was 86.0%. These results were similar to those of the per-protocol set. The most common grade 3 or 4 AEs included hypertension [30 (58.8%) of 51 patients], leukopenia [12 (23.5%)], proteinuria [8 (15.69%)], and hematuria [8 (15.69%)]. One patient died of unknown cause.

Conclusions: This study suggested that apatinib might be effective and tolerable in patients with untreated or chemotherapy-refractory STS (NCT03064243).

Keywords: Soft tissue sarcoma (STS); neoplasm drug resistance; apatinib; angiogenesis

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Introduction

Soft tissue sarcomas (STSs) are a heterogeneous group of rare, solid cancers of mesenchymal or connective tissue origin (1-4). STSs commonly develop in the extremities, trunk, viscera, retroperitoneum, or head and neck. More than 50 different histologic subtypes of STS have been identified (1,3), with the 7 most common subtypes representing about 75% of all STSs (1,3). The reported annual incidence worldwide is approximately 1.8–5 per 100,000, but the incidence may be underestimated due to the exclusion of gastrointestinal stromal tumors in tumor registry databases before 2001 (1,3-5). STS is commonly found in adults older than 55 years, and the median age at diagnosis is 65 years. About 10% of STS patients have metastases at presentation (3), and more than 33.3% will die from the disease, mostly likely due to lung metastases (3,4). Prognosis varies depending on the histological subtype, resection margins, and tumor characteristics including tumor grade, size, and anatomical site (3,4).

The first-line treatment for advanced STS is chemotherapy, but the evidence-based treatment options after progression are limited (2,6,7). Furthermore, alveolar soft part sarcoma (ASPS) and clear cell sarcoma (CCS) are generally not sensitive to cytotoxic chemotherapy (8,9). Therefore, there is an urgent need for novel treatment therapies for STS (7,10).

Angiogenesis is a crucial process in the development, progression, and spread of STS (11). Several studies have shown that multi-kinase angiogenesis inhibitors, such as pazopanib (12) and anlotinib (13), have yielded positive results in patients with STS. The vascular endothelial growth factor receptor-2 (VEGFR-2) plays a major role in angiogenesis (14). VEGFR-2 can be targeted by tyrosine kinase inhibitors (TKIs) such as apatinib (11). Clinical trials have demonstrated the efficacy and safety of apatinib in the treatment of various solid tumors (15-18). A phase 2 clinical trial (NCT03121846) reported that apatinib was well-tolerated and demonstrated promising antitumor activity, with a median progression-free survival (PFS) of 7.9 months in patients with metastatic STS who had failed chemotherapy (19,20). However, selective bias might not be obviated since this was a single-center study.

Therefore, the present multicenter, phase 2 clinical trial was conducted to assess the efficacy and safety of apatinib in patients with untreated or chemotherapy-refractory STS. We present the following article in accordance with the TREND reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4229/rc).

Methods

Study design and participants

This was a multicenter, single-arm, phase 2 clinical trial conducted in nine centers in China (Table S1). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Ethics Committee of the Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University (lead center, No. 2016-133). All participating centers were informed and agreed the study. All participants provided written informed consent before enrollment. The study was registered on ClinicalTrials.gov (Identifier: NCT03064243).

The following inclusion criteria were applied. (I) Patients were pathologically diagnosed with advanced STS, with at least one measurable lesion. These included synovial sarcoma, leiomyosarcoma, ASPS, undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma, liposarcoma, fibrosarcoma, CCS, epithelioid sarcoma, angiosarcoma, and spindle cell sarcoma, but excluded malignant peripheral nerve sheath tumor, chondrosarcoma, dermatofibrosarcoma protuberans, gastrointestinal stromal tumor, inflammatory myofibroblastic sarcoma, and malignant mesothelioma. The final pathological types were confirmed centrally at the Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University. (II) Patients showed no indication of surgical treatment for the target lesion or the patient refused surgery. (III) Within the last 6 months, the patient failed at least one chemotherapy regimen (anthracycline included) or could not tolerate treatments (except for ASPS and CCS). Treatment failure

was defined as an unacceptable toxicity reaction that occurs during the treatment or within 3 months of the last treatment, clear progressive disease (PD), or clear recurrence after treatment. Drugs may be administered in combination or separately in prior therapy, may be used as neoadjuvant/adjuvant therapy, or for the treatment of metastatic disease or both. Sequential therapy and neoadjuvant/adjuvant therapy in combination with the drug are denoted as a linear chemotherapy regimen. (IV) Patients are aged 18–70 years of age. (V) The patient's Eastern Cooperative Oncology Group (ECOG) performance status (PS) score is 2 or less. (VI) The patient's expected survival is greater than 3 months. (VII) There is no previous use of antiangiogenic drugs. Other targeted agents whose mechanism of action is different from that of apatinib, such as mTOR inhibitors or gefitinib/erlotinib/icotinib, and withdrawal for more than 1 month was allowed. Patients who had used antiangiogenic drugs for <2 weeks and stopped treatment for more than 1 month were also eligible. (VIII) Patients demonstrated adequate organ function, including blood, liver, and kidney function.

The key exclusion criteria were as follows: (I) uncontrolled hypertension, New York Heart Association (NYHA) ≥II, arrhythmia (including QTc interval increased to >450 ms in men and >470 ms in women), or heart failure; (II) diseases that affect the absorption of oral drugs; (III) risk of gastrointestinal bleeding (e.g., active gastrointestinal ulcer lesions, feces occult blood (++), or a medical history of black stool or hematemesis within 3 months); (IV) abnormal coagulation function (international normalized ratio >1.5 × the upper limit of normal (ULN) or activated partial thromboplastin time >1.5 × ULN) with bleeding tendency; (V) active bleeding or patient underwent a major operation within 30 days; (VI) intracranial metastasis; (VII) other malignancies in the past 3 years; (VIII) large metastatic/recurrent tumor foci and imaging findings indicating that the foci is mainly necrotic tissues; and (IX) patients with malignant pleural effusion or ascites causing grade ≥2 Common Terminology Criteria for Adverse Events (CTCAE) dyspnea.

Treatment

Patients were administered 500 mg apatinib half an hour after a meal, once a day, and continuously from day 1 to day 28 (one cycle). Apatinib treatment continued until PD, death, or intolerable toxicity. The drug dosage could be reduced to 250 mg after a grade 4 hematologic adverse event (AE) or 2 occasions of a non-hematologic AE grade ≥3. If a patient required a second dosage adjustment, the study treatment was discontinued.

Endpoints and assessment

The primary endpoint was the 6-month PFS rate, assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. The secondary endpoints were the objective response rate [ORR; defined as the proportion of patients with a complete response (CR) or partial response (PR)], overall survival (OS) and safety.

All imaging evaluations with contrast-enhanced computerized tomography (CT) or magnetic resonance imaging (MRI) were performed every 8 weeks (i.e., every two cycles). Electrocardiograms and laboratory tests (including blood, biochemistry, urine and coagulation examinations) were done on days 7 and 28 of the first cycle and every 4 weeks thereafter. Survival was followed up every 2 months either by telephone or in hospital after treatment discontinuation. Safety assessments, including monitoring for adverse events (AEs) and abnormalities in physical and laboratory tests, were performed until 30 days after the last administration. AEs were graded according to the National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE) version 4.03.

Statistical analysis

In this study, the sample size was determined to be 48, based on a two-sided α of 0.1, power of 80%, 6-month PFS rate of a minimum of 25%, 6-month PFS rate increased to 45% after apatinib treatment, and a duration of 18 months (calculated using PASS 11.0; NCSS, LLC., Kaysville, UT, USA). Considering possible patient dropouts (estimated as 10%), the required number of participants was increased to 53.

The full analysis set (FAS) was according to the intention-to-treat (ITT) principle and included all enrolled patients. Only patients who received at least two cycles of the study drug and did not have any major protocol deviations were enrolled in the per-protocol set (PPS). The safety set (SS) included all patients who received at least one dose of study drug and had at least one safety evaluation. The ORR was calculated in participants who had at least one response evaluation.

Continuous data are presented as means ± standard

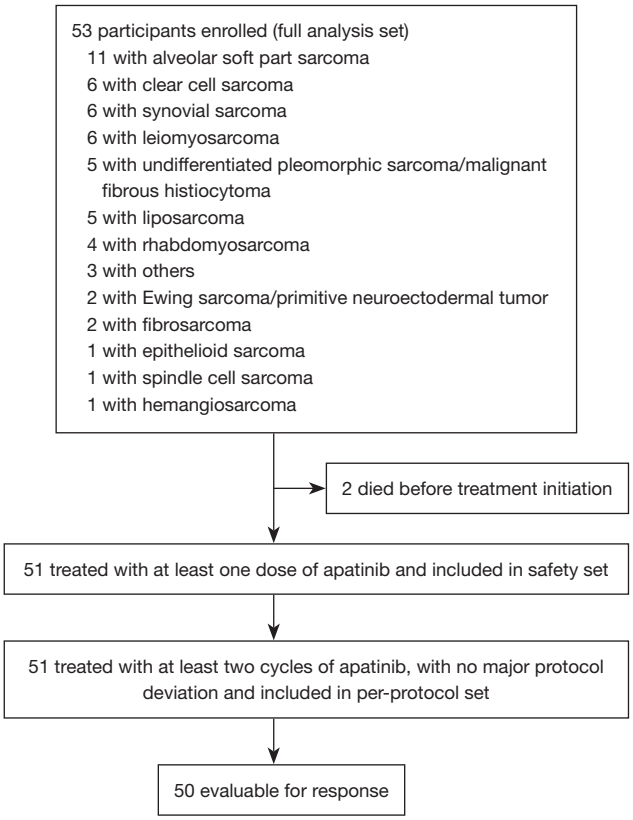

Figure 1 A flowchart showing the participant enrollment and follow-up process.

deviations, or medians and interquartile range (IQR), namely, quartile 1 (Q1) and quartile 3 (Q3). Categorical data and ranked data are presented as numbers, percentages, and confidence intervals (CI). The 6-month PFS rate, median PFS, and OS were estimated using the Kaplan-Meier method, and the survival curves were plotted. Only descriptive statistical analysis was used for safety evaluation. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Basic characteristics of the participants

A total of 53 participants were recruited from June 2017 to October 2018. All were included in the FAS. Two patients died before treatment initiation. The remaining patients (n=51) were all included in the PPS and SS. The enrollment and follow-up data are detailed in *Figure 1*. The median age of the participants was 38.0 years (IQR 28.0–49.0 years) and there were 28 (52.8%) males. The ECOG PS was 0 (n=18, 34.0%) or 1 (n=35, 66.0%). Most patients presented with 2 or fewer metastases (n=41, 77.4%). The most common histopathological subtypes were ASPS (n=11, 20.8%), CCS, synovial sarcoma, and leiomyosarcoma (n=6, 11.3%, for each subtype). Prior to apatinib, most participants (n=41, 77.4%) had received chemotherapy, 12 (22.6%) participants were chemotherapy-naïve, 19 (35.8%) had received radiotherapy, and 47 (88.7%) patients had undergone surgery (*Table 1*).

Course of treatment and follow-up

By September 3, 2020, the median follow-up was 13.3 months (IQR 6.8–27.4; data was missing for one patient due to loss to follow-up) and all 53 participants (100%) had discontinued treatment. The reasons for treatment discontinuation were PD (26 participants, 49.1%), AEs (10 patients, 18.9%), termination of treatment requested by participants (7, 13.2%), death (3, 5.7%), investigator's judgement (1, 1.9%), and other reasons (4, 7.5%).

Efficacy

In the FAS, the 6- and 12-month PFS rates were 46.8% [95% confidence interval (CI): 31.5–60.6%] and 25.2% (95% CI: 12.2–40.6%), respectively. The median PFS was 5.6 months (95% CI: 3.8–9.2 months). The median PFS within each cohort was 5.5 months (95% CI: 3.6–9.2 months) for chemotherapy-refractory patients, 9.1 months (95% CI: 3.7–13.9 months) for untreated patients, 13.9 months (95% CI: 9.1–14.5 months) for patients with ASPS, and 3.7 months [95% CI: 1.8–not estimated (NE)] for patients with CCS (*Figure 2*, Figure S1).

The 6-, 12-, and 24-month OS rates were 80.8% (95% CI: NE–NE), 58.6% (95% CI: 43.7–70.7%), and 44.9% (95% CI: NE–NE), respectively, and the median OS was 20.0 months (95% CI: 9.2–31.1 months) in the FAS. The median OS within each cohort was 10.7 months (95% CI: 7.5–23.4 months) for chemotherapy-refractory patients, and NE for untreated patients, patients with ASPS, nor patients with CCS (*Figure 2*, Figure S2). The PFS and OS in the PPS were similar to those in the FAS (Figure S3).

Fifty participants had at least one response evaluation in both the FAS and the PPS. The ORR was 18.0%, and the disease control rate (DCR) was 86.0%. The ORR of

Table 1 Basic characteristics of the patients

Characteristics	All (n=53)	Chemotherapy-refractory (n=41)	Untreated (n=12)	Alveolar soft part sarcoma (n=11)	Clear cell sarcoma (n=6)
Age (years)					
Mean ± SD	39.5±13.0	41.6±12.9	32.4±11.2	31.7±10.6	39.2±10.5
Median	38.0	43.0	27.0	26.0	41.5
IQR	28.0–49.0	30.0–50.0	25.0–42.0	23.0–43.0	28.0–47.0
Sex, n (%)					
Male	28 (52.8)	19 (46.3)	9 (75.0)	6 (54.6)	4 (66.7)
Female	25 (47.2)	22 (53.7)	3 (25.0)	5 (45.5)	2 (33.3)
Pathological grade, n (%)					
G2	8 (15.1)	6 (14.6)	2 (16.7)	0	2 (33.3)
G3	28 (52.8)	22 (53.7)	6 (50.0)	5 (45.5)	2 (33.3)
Gx	9 (17.0)	8 (19.5)	1 (8.3)	2 (18.2)	0
Unknown	7 (13.2)	4 (9.8)	3 (25.0)	3 (27.3)	2 (33.3)
Missing	1 (1.9)	1 (2.4)	0	1 (9.1)	0
Clinical stage, n (%)					
IIB	1 (1.9)	1 (2.4)	0	0	0
III	3 (5.7)	3 (7.3)	0	0	0
IV	49 (92.5)	37 (90.2)	12 (100.0)	11 (100.0)	6 (100.0)
Metastasis site, n (%)					
≤2	41 (77.4)	31 (75.6)	10 (83.3)	10 (90.9)	5 (83.3)
>2	10 (18.9)	8 (19.5)	2 (16.7)	1 (9.1)	1 (16.7)
Unknown	2 (3.8)	2 (4.9)	0	0	0
ECOG PS score[a], n (%)					
0	18 (34.0)	13 (31.7)	5 (41.7)	6 (54.6)	1 (16.7)
1	35 (66.0)	28 (68.3)	7 (58.3)	5 (45.5)	5 (83.3)
Pathologic diagnosis, n (%)					
Alveolar soft part sarcoma	11 (20.8)	4 (9.8)	7 (58.3)	–	–
Clear cell sarcoma	6 (11.3)	1 (2.4)	5 (41.7)	–	–
Synovial sarcoma	6 (11.3)	6 (14.6)	0	–	–
Leiomyosarcoma	6 (11.3)	6 (14.6)	0	–	–
UPS/malignant fibrous histiocytoma	5 (9.4)	5 (12.2)	0	–	–
Liposarcoma	5 (9.4)	5 (12.2)	0	–	–
Rhabdomyosarcoma	4 (7.6)	4 (9.8)	0	–	–
Ewing sarcoma/primitive neuroectodermal tumor	2 (3.8)	2 (4.9)	0	–	–

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	All (n=53)	Chemotherapy-refractory (n=41)	Untreated (n=12)	Alveolar soft part sarcoma (n=11)	Clear cell sarcoma (n=6)
Fibrosarcoma	2 (3.8)	2 (4.9)	0	–	–
Epithelioid sarcoma	1 (1.9)	1 (2.4)	0	–	–
Spindle cell sarcoma	1 (1.9)	1 (2.4)	0	–	–
Hemangiosarcoma	1 (1.9)	1 (2.4)	0	–	–
Others	3 (5.7)	3 (7.3)	0	–	–
Chemotherapy history, n (%)					
Yes[b]	41 (77.4)	–	–	–	–
No	12 (22.6)	–	–	–	–
Radiotherapy history, n (%)					
Yes	19 (35.8)	–	–	–	–
No	34 (64.2)	–	–	–	–
Tumor surgery history, n (%)					
Yes	47 (88.7)	–	–	–	–
No	6 (11.3)	–	–	–	–

[a], no patient was of PS 2; [b], in the last 6 months, patients who failed at least one chemotherapy regimen (anthracycline included) or could not tolerate treatments. SD, standard deviation; IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group performance status; UPS, undifferentiated pleomorphic sarcoma.

chemotherapy-refractory and -naïve patients was 15.8% and 25.0%, respectively, and the DCR was 84.2% and 91.7%, respectively. For each subtype, the ORR of Ewing sarcoma (50.0%), fibrosarcoma (50.0%), CCS (33.3%), ASPS (27.3%), and rhabdomyosarcoma (25.0%) were relatively high (i.e., ≥25%; *Table 2*). The Waterfall plot of tumor response, swim lane, and spider plot are shown in *Figure 3*.

Safety

The median duration of exposure to apatinib was 128.0 days (range, 28.0 to 763.0 days). The relative dose intensity was 86.7%±16.0%.

All participants experienced treatment-related adverse events (TRAEs). Forty-three patients (84.3%) had grade 3 or above TRAEs. The most common TRAEs of any grade were hypertension (n=45, 88.2%), proteinuria (n=39, 76.5%), and hand-foot syndrome (n=33, 64.7%). The most common grade 3–4 TRAEs were hypertension (n=30, 58.8%), proteinuria (n=8, 15.7%), and hypertriglyceridemia (n=6, 11.8%; *Table 3*).

Ten patients (19.6%) experienced dose reduction due to TRAEs and the most common reason was hand-foot syndrome (n=2). Eight patients discontinued study treatment due to TRAEs, with pneumothorax (n=3) being the most common reason for discontinuation. One patient died of unknown cause after receiving 3 cycles of apatinib.

Discussion

For most STSs, standard treatment after disease progression is limited. In addition, since ASPS and CCS are not sensitive to chemotherapy, an appropriate systemic therapy remains to be elucidated (7,10). The present trial was designed in 2016. At that time, immune checkpoint inhibitors and most TKIs against sarcomas were not available in China. Thus, new treatment options for these patients were in urgent need. Apatinib has been shown to be effective and safe in various solid tumors (15-18), but data related to apatinib use in patients with STS is limited. Therefore, this study evaluated the efficacy and safety of apatinib in patients with chemotherapy-refractory STS. This phase 2 trial suggested that apatinib is effective and tolerable in patients with STS.

The acting site of apatinib is the ATP binding site of

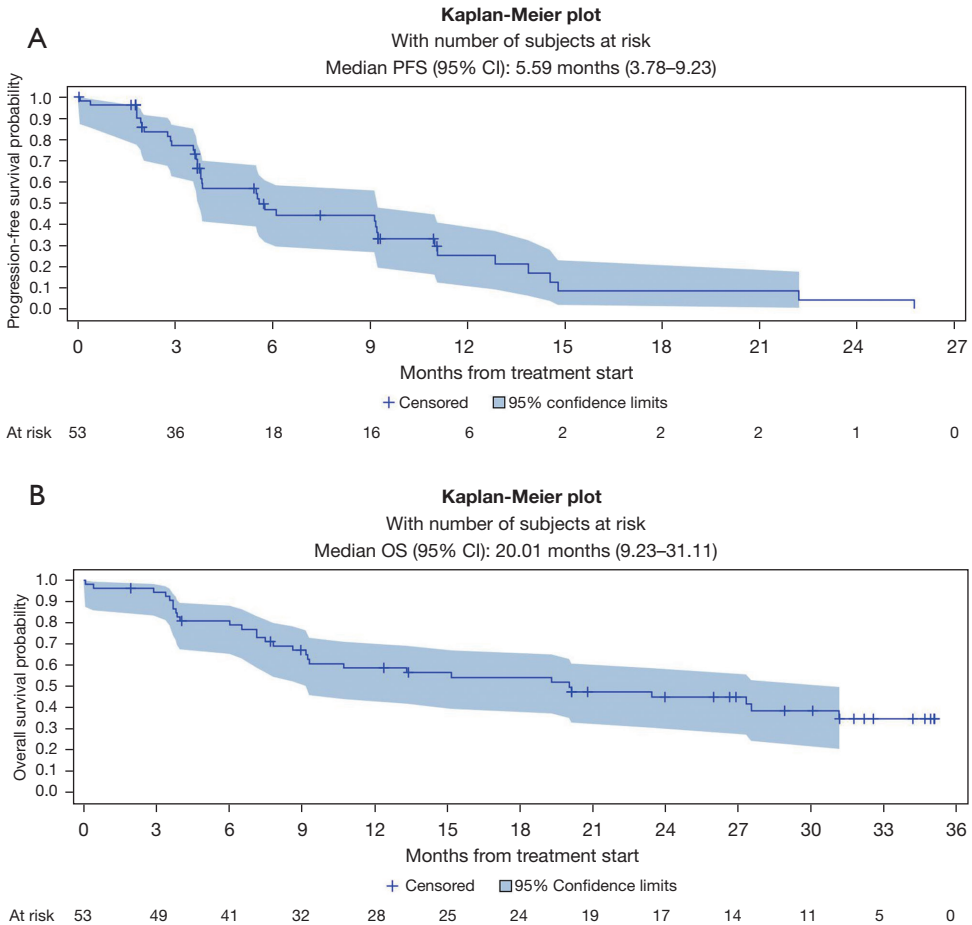

Figure 2 Kaplan-Meier curve of (A) PFS and (B) OS in the full analysis set. PFS, progression-free survival; CI, confidence interval; OS, overall survival.

the tyrosine kinase receptor and activity assays have shown that it has a high binding affinity to the VEGFR (21). Pharmacodynamic studies showed that apatinib could reduce the VEGFR tyrosine kinase activity, inactivate VEGF-binding signal transduction, and strongly inhibit tumor angiogenesis. Apatinib can also inhibit the platelet-derived growth factor receptor (PDGFR), C-Kit, and C-SRC kinases (22,23). The expression of VEGFR (24), PDGFR (25), C-Kit (26), and C-SRC (27) can promote the proliferation of STS, and the expression of these molecules is clinically associated with the poor prognosis of STS. In the transplanted sarcoma S180 mouse model, apatinib showed tumor inhibitory rate of 60.3–69.9% (28).

In the present study, the 6- and 12-month PFS rates were 46.8% and 25.2% respectively, the median PFS was 5.6 months, the ORR was 18.0%, and the DCR was 86.0%. The 6-month PFS was higher than the preplanned expected 45%, and the present trial satisfied its objective. These results were also supported by a previous phase 2 trial of apatinib for metastatic sarcoma that showed an ORR of 26.3% and a DCR of 86.7%, as well as a 12-week PFS rate of 70% (19,20). The median PFS of the two studies were similar, suggesting a possible similar antitumor effect of apatinib in STS irrespective of staging. In the chemotherapy-refractory cohort, most patients were in stage IV, and about two-thirds of patients had received a second-line or above chemotherapy. The median OS of all participants reached 20.0 months. The PFS and OS of the chemotherapy-refractory cohort after apatinib therapy were similar to those of trials involving pazopanib (12) or anlotinib (13). In addition, the ORR and DCR of apatinib in chemotherapy-refractory patients (15.8% and 84.2%, respectively) were numerically higher than those of pazopanib (6% and 72%, respectively) and

Table 2 Best overall response in the full analysis set (which was comparable to the per-protocol set)

Tumor types	n	PR, n (%)	SD, n (%)	PD, n (%)	ORR, %	DCR, %
Total	50	9 (18.0)	34 (68.0)	6 (12.0)	18.0	86.0
Chemotherapy-refractory	38	6 (15.8)	26 (68.4)	5 (13.2)	15.8	84.2
Chemotherapy-naïve	12	3 (25.0)	8 (66.7)	1 (8.3)	25.0	91.7
Alveolar soft part sarcoma	11	3 (27.3)	8 (72.7)	0	27.3	100.0
Clear cell sarcoma	6	2 (33.3)	3 (50.0)	1 (16.7)	33.3	83.3
Synovial sarcoma	6	1 (16.7)	4 (66.7)	1 (16.7)	16.7	83.3
Leiomyosarcoma	6	0	6 (100.0)	0	0.0	100.0
UPS/malignant fibrous histiocytoma	5	0	4 (80.0)	1 (20.0)	0.0	33.3
Liposarcoma	3	0	1 (33.3)	2 (66.7)	0.0	33.3
Rhabdomyosarcoma	4	1 (25.0)	2 (50.0)	0	25.0	75.0
Fibrosarcoma	2	1 (50.0)	1 (50.0)	0	50.0	100.0
Ewing sarcoma/primitive neuroectodermal tumor	2	1 (50.0)	0	1 (50.0)	50.0	50.0
Epithelioid sarcoma	1	0	1 (100.0)	0	0.0	100.0
Spindle cell sarcoma	1	0	1 (100.0)	0	0.0	100.0
Others	3	0	3 (100.0)	0	0.0	100.0

No complete response was observed. PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; UPS, undifferentiated pleomorphic sarcoma.

anlotinib (13% and 74%, respectively). These results in chemotherapy-refractory cohort were also supported by case series of patients with advanced synovial sarcoma (29) or various types of sarcoma (30). Interestingly, a trial of apatinib combined with doxorubicin in metastatic STS suggested no efficacy of the regimen, except for tumor shrinkage (31). The selection of patients and the different regimens may partially explain the conflicting results.

The median PFS and OS after apatinib therapy were 5.5 and 10.7 months, respectively, for chemotherapy-refractory sarcoma, and 9.1 months and NE, respectively, for untreated sarcoma. The results indicated that patients with previously untreated sarcomas had a better survival than those with chemotherapy-refractory sarcoma. However, the mature OS data of each subtype warrants further follow-up.

This study also suggested that each STS subtypes might have different responses, but the number of patients in each subtype was too small to reach a definitive conclusion. Indeed, this study included more than 12 kinds of STS. Other trials of sarcomas also included about 10 subtypes (13,31-33). In the present study, the most common pathological types were ASPS, synovial sarcoma, leiomyosarcoma, and CCS, and their distributions were different from those of a worldwide study (12), but similar to those of a Chinese study (34). There may be two reasons for the distribution. First, ASPS and CCS were not sensitive to chemotherapy (8,9), and patients with these two subtypes had strong requirements for treatment. Thus, in this study, chemotherapy-naïve ASPS or CCS patients were eligible. Since most patients were aware that they would suffer progression after chemotherapy in the short-term, they were more willing to participate in clinical trials. Second, the hospitals involved in the present trial have outstanding sarcoma treatment plans. If patients were diagnosed with chemotherapy-refractory sarcoma type elsewhere, they were more likely to seek better and more advanced treatment in the trial hospitals. That may explain why there were relatively higher portion of ASPS or CCS patients. The ORR and DCR of ASPS and CSC patients were relatively high. In the present study, the median PFS and OS after apatinib treatment were 13.9 months and NE, respectively, for ASPS, and 3.7 months and NE, respectively, for CCS. The median PFS of the ASPS cohort was similar to that of the whole cohort, but since ASPS represented the main

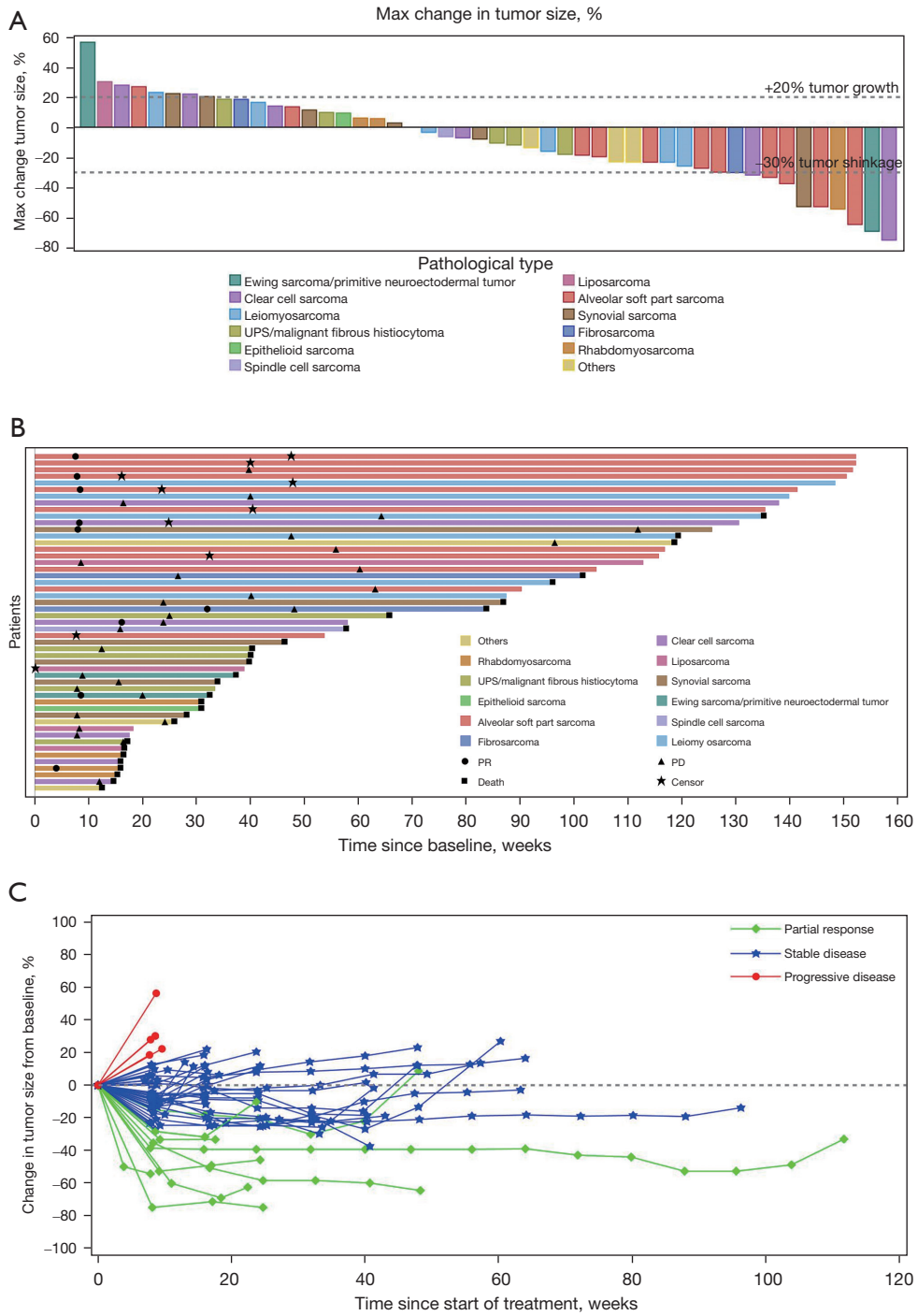

Figure 3 A Waterfall plot of tumor response (A), a swim lane plot (B), and a spider plot (C). UPS, undifferentiated pleomorphic sarcoma; PR, partial response; PD, progressive disease.

Table 3 Treatment-related adverse events occurring in more than 10% of patients (n=51)

Adverse events	Any grade, n (%)	Grade 3 or 4, n (%)
Any adverse event	51 (100.0)	43 (84.3)
Hypertension	45 (88.2)	30 (58.8)
Proteinuria	39 (76.5)	8 (15.7)
Hand-foot syndrome	33 (64.7)	3 (5.9)
White blood cell count decreased	21 (41.2)	3 (5.9)
Hypertriglyceridemia	18 (35.3)	6 (11.8)
Aspartate aminotransferase increased	18 (35.3)	0
Neutrophil count decreased	18 (35.3)	3 (5.9)
Blood bilirubin increased	17 (33.3)	0
Platelet count decreased	17 (33.3)	5 (9.8)
Hypercholesterolemia	16 (31.4)	0
Headache	16 (31.4)	0
Alanine aminotransferase increased	14 (27.5)	0
Diarrhea	12 (23.5)	1 (2.0)
Vomiting	12 (23.5)	1 (2.0)
Weight decreased	11 (21.6)	4 (7.8)
Adynamia	10 (19.6)	0
Gamma-glutamyl transferase increased	9 (17.6)	2 (3.9)
Nausea	9 (17.6)	0
Anemia	9 (17.6)	1 (2.0)
Blood creatinine increased	8 (15.7)	0
Blood alkaline phosphatase increased	8 (15.7)	0
Hematuria	7 (13.7)	0
Bilirubin conjugated increased	6 (11.8)	0
Stomatitis	6 (11.8)	0
Pneumothorax	6 (11.8)	4 (7.8)
Occult blood positive	6 (11.8)	0
Decreased appetite	6 (11.8)	1 (2.0)

histological subtype, this probably affected the results. The efficacy of apatinib in various STS warrants further investigation in large-scale studies.

The relative dose intensity was 86.7%±16.0% in this trial. A study of pazopanib on STS (35) demonstrated that patients with relative dose intensity ≥80% had longer PFS. Thus, it is considered that most patients in the present study had a sufficient dose of apatinib. The general adverse event profile was similar to that of previous studies of apatinib (15-18), including studies specifically in STS (19,20,29-31). However, it was found that pneumothorax, which is a severe condition, occurred in 6 (11.8%) patients and 4 patients experienced lung metastases. Pneumothorax is not rare in sarcoma and other solid tumor patients receiving angiogenesis inhibitors [such as pazopanib (12), anlotinib (13), bevacizumab (combined with doxorubicin) (36), and sorafenib plus bevacizumab (37)].

This may be due to tumor invasion or necrosis of lesions during treatment (13). Thus, antiangiogenic agents should be prescribed to sarcoma patients with caution. One patient died of unknown cause, and the causality with apatinib could not be determined. The toxicity profile was tolerable and no other new safety signals were identified.

There were certain limitations to this study. This was an exploratory trial with a relatively small sample size which may limit the generalizability of the results. There were more than 12 different types of STS with specific natural history and distinct prognosis (1,3). Due to the lack of corresponding data, the sample sizes of each subtype have not been calculated. The follow-up time was short, thus the median OS of each subtype could not be observed. Additional studies are necessary to investigate the efficacy and safety of apatinib in patients with STS.

Conclusions

This study suggested that apatinib is effective and tolerable for patients with chemotherapy-refractory STS. The results also suggested that apatinib might be a treatment option for ASPS and further phase 3 trials are warranted.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4229/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4229/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4229/coif). All authors report that the study was supported by Jiangsu Hengrui Pharmaceuticals Co., Ltd. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Ethics Committee of the Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University (lead center, No. 2016-133). All participating centers were informed and agreed the study. All participants provided written informed consent before enrollment.

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Supplementary

Table S1 Participating centers, patients and principal investigators

Centers	Principal Investigator	Number of patients enrolled
Affiliated Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai	Yang Yao	15
Beijing Cancer Hospital	Zhengfu Fan	12
Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	Jing Chen	6
Xijing Hospital, The Fourth Military Medical University	Hongmei Zhang	6
Sun Yat-sen University Cancer Center	Xing Zhang	6
Fudan University Shanghai Cancer Center	Yong Chen	4
Harbin Medical University Cancer Hospital	Guofan Qu	2
Hunan Provincial Tumor Hospital	Gang Huang	1
Zhongshan Hospital, Fudan University	Yuhong Zhou	1

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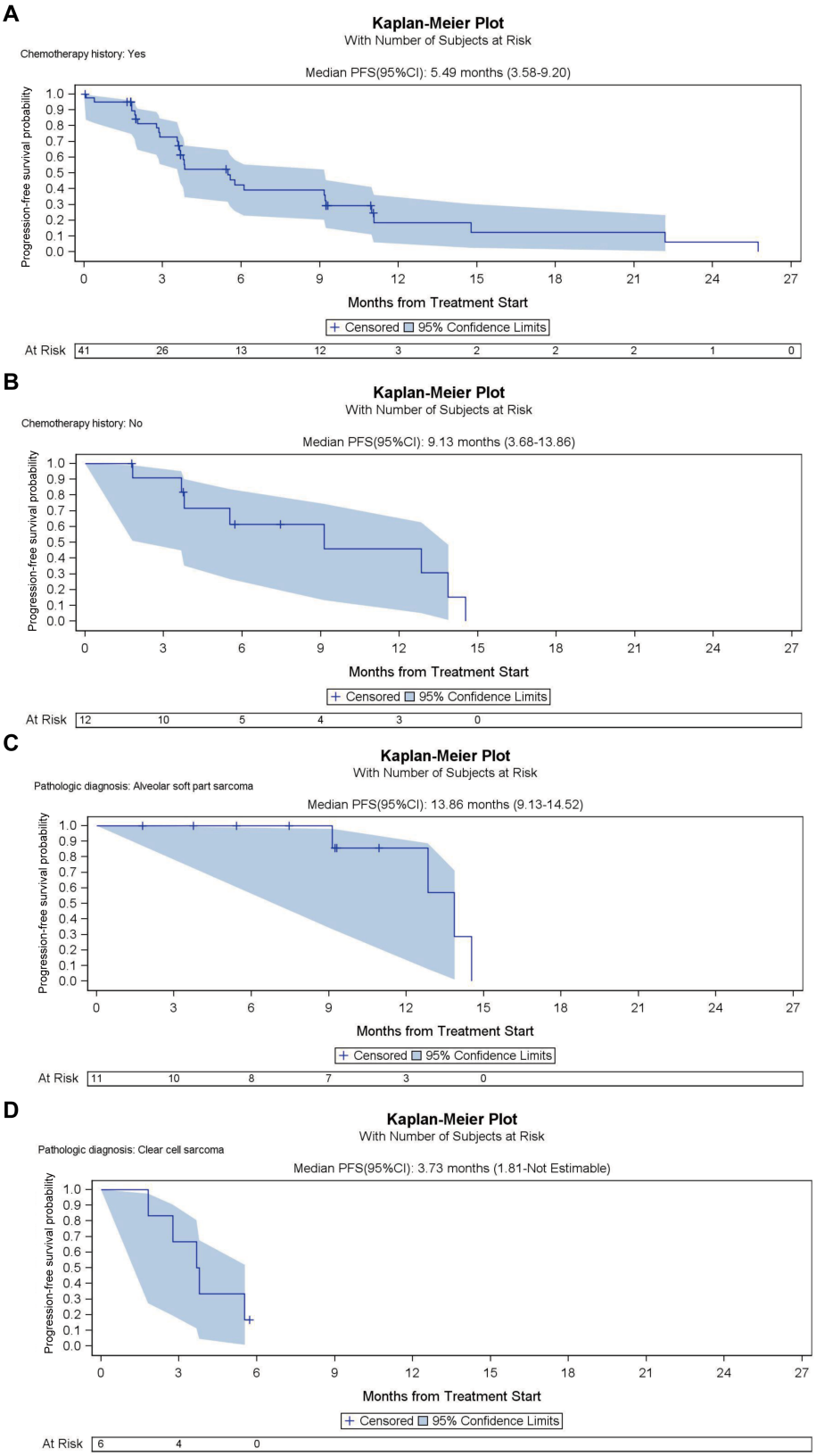

Figure S1 Kaplan-Meier curve of PFS in (A) chemo-refractory patients, (B) untreated patients, (C) alveolar soft part sarcoma, and (D) clear cell sarcoma. PFS, progression-free survival; CI, confidence interval; OS, overall survival.

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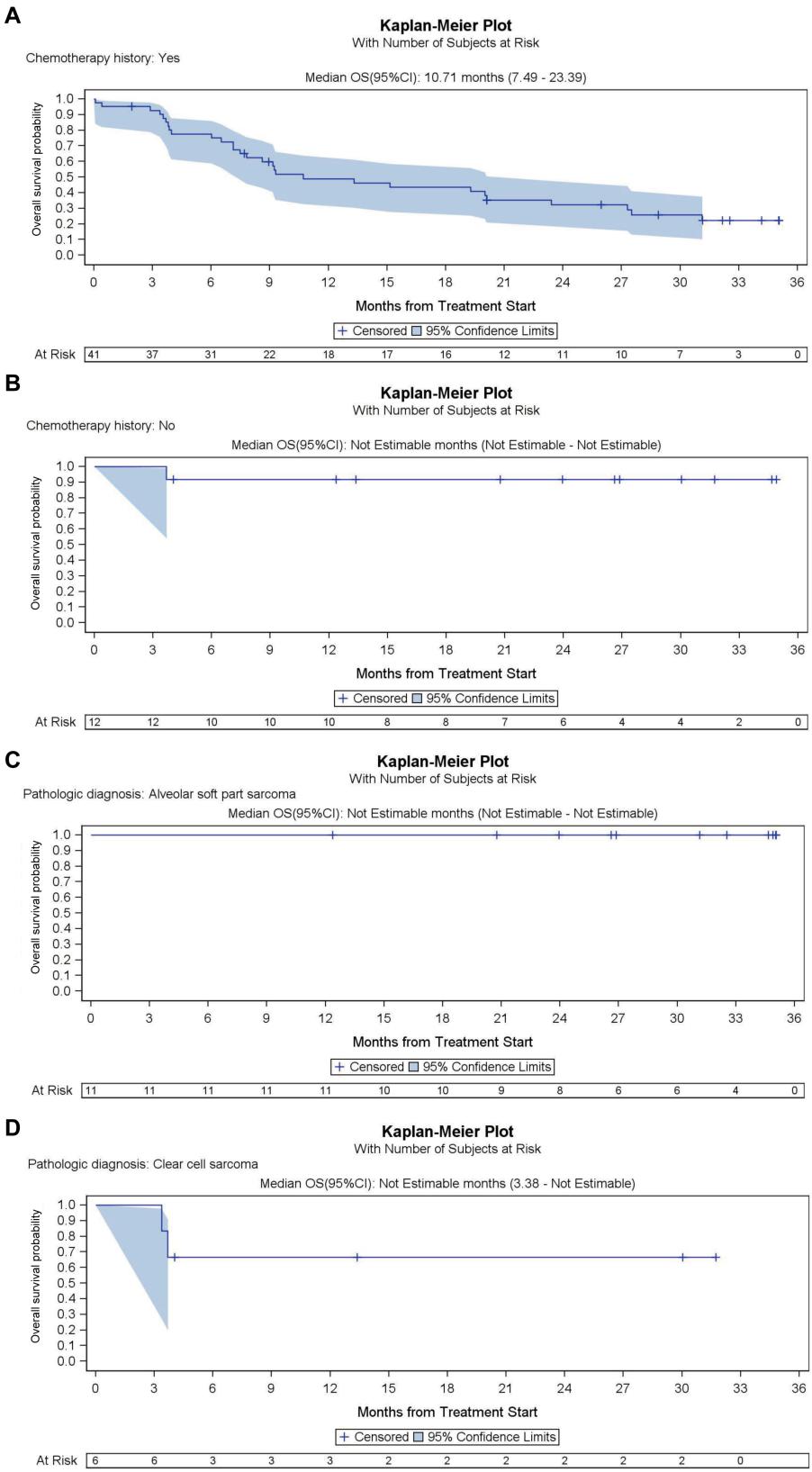

Figure S2 Kaplan-Meier curve of OS in (A) chemo-refractory patients, (B) untreated patients, (C) alveolar soft part sarcoma, and (D) clear cell sarcoma. OS, overall survival; CI, confidence interval.

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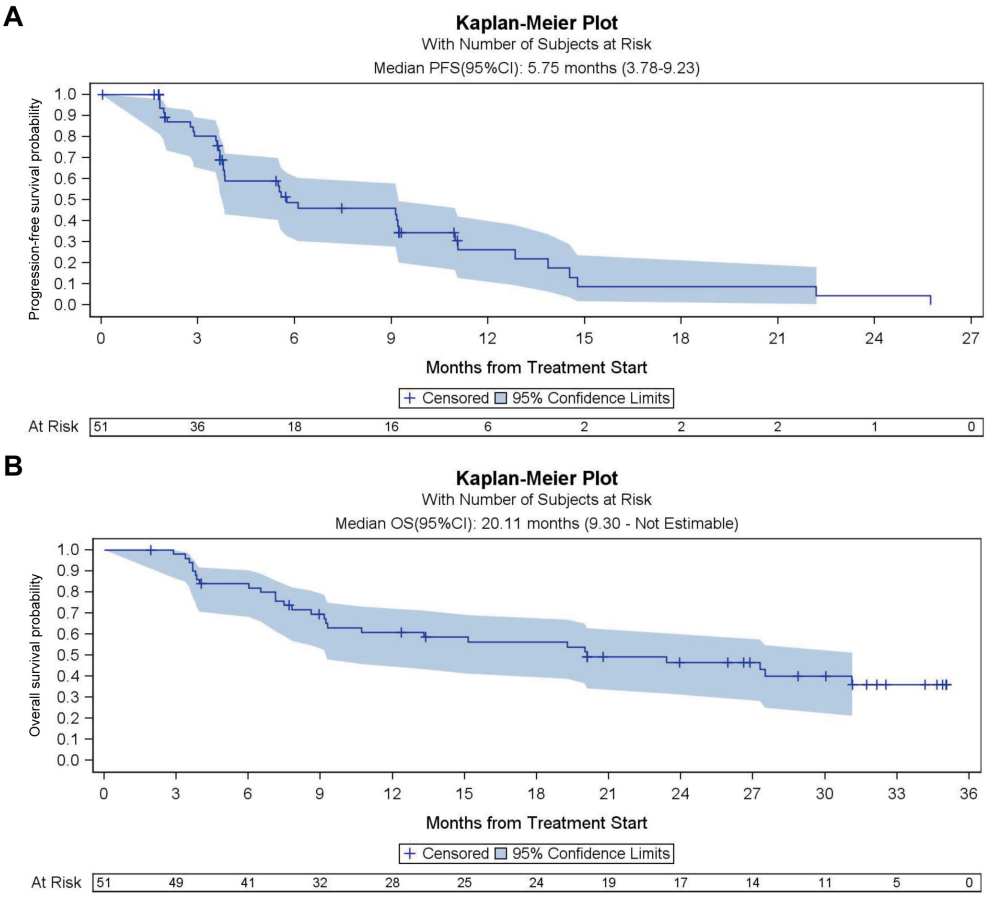

Figure S3 Kaplan-Meier curve of (A) PFS and (B) OS in per-protocol set. PFS, progression-free survival; CI, confidence interval; OS, overall survival.

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