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CLINICAL TRIAL REPORT

Camrelizumab Plus Apatinib in Advanced Unresectable Alveolar Soft Part Sarcoma and Undifferentiated Pleomorphic Sarcoma Patients: A Single-Center, Exploratory Case Series

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Background: Certain histologic subtypes of advanced soft tissue sarcomas, including alveolar soft part sarcoma (ASPS) and undifferentiated pleomorphic sarcoma (UPS), lack standardized therapeutic options following anthracycline-based first-line therapy. This study was to investigate the efficacy and safety of camrelizumab plus apatinib in advanced unresectable ASPS or UPS.

Methods: In this single-center, exploratory case series, patients with ASPS or UPS received a combination of camrelizumab and apatinib. The primary endpoint was the objective response rate (ORR), while the exploratory endpoints included progression-free survival (PFS), overall survival (OS), and safety.

Results: The median follow-up period was 24.0 months, with an ORR of 88.9% (8/9). In the ASPS subgroup (n=7), neither the median PFS (mPFS) nor median OS (mOS) was reached, while the ORR was 100.0% (7/7). In the UPS subgroup (n=2), the mPFS was 7.5 months and the mOS was 9.5 months, with the ORR of 50.0% (1/2). One patient with ASPS died from immune-mediated myocarditis; all other adverse events (AEs) were grade 1–2 and manageable with symptomatic treatment.

Conclusion: The combination therapy of camrelizumab and apatinib may provide benefits in clinical outcomes for ASPS, while the outcomes in UPS appears more variable, warranting further study. Close monitoring for AEs, especially fatal complications such as immune-mediated myocarditis, is essential.

Registration: ClinicalTrials.gov (identifier: NCT04447274), registration date: 23-Jun-2020.

Keywords: alveolar soft part sarcoma, ASPS, camrelizumab, apatinib, undifferentiated pleomorphic sarcoma, UPS

Introduction

Soft tissue sarcomas (STSs) are a rare and highly heterogeneous group of malignancies of mesenchymal origin. Among these, alveolar soft-part sarcoma (ASPS) is a distinct subtype of STS, first described in 1952 for its unique clinico-pathological features, including tumor cells arranged in "alveolar" or "acinar" patterns.[1,2] ASPS is characterized by a pathognomonic chromosomal translocation, t (X;17) (p11;q25), which is present in approximately 90% of cases. This translocation results in the fusion of the ASPS chromosome region, candidate 1 (*ASPSCR1*) and transcription factor E3

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(*TFE3*) genes—detectable via fluorescence in-situ hybridization, reverse transcription–polymerase chain reaction, or next-generation sequencing. Additionally, nuclear expression of TFE3, observed in over 95% of cases, serves as a highly sensitive immunohistochemical diagnostic marker.[3] This fusion drives constitutive TFE3 activation, upregulating proangiogenic pathways [eg, mesenchymal epithelial transition and vascular endothelial growth factor (VEGF)] and promoting tumor vasculogenesis and metastasis.[3] With a global incidence of <1 per million, ASPS accounts for 0.5–1.0% of STS cases. While it can occur at any age, the peak incidence is between 15–35 years (median: 25 years). Primary sites include deep soft tissues of the extremities (61%), particularly the thigh/buttock and lower limbs (51%), as well as the trunk (20%), head/neck (9%), and viscera (8%).[4] ASPS typically presents as a slow-growing, painless mass, with diagnosis often delayed until metastasis occurs. Symptoms such as pain, paresthesia, or motor deficits may arise from nerve or vascular compression. Common metastatic sites include the lungs, bones, and brain. Histologically, ASPS exhibits as peritumoral vascular hyperplasia with frequent venous dilatation and tumor thrombi, facilitating early hematogenous spread. The prognosis varies markedly by the disease stage: the 5-year overall survival (OS) ranges from 60–100% for localized disease but drops to 20–46% for metastatic cases.[4] A study of 293 ASPS patients reported post-resection 1-, 2-, and 5-year OS rates of 95%, 86%, and 73%, respectively, compared to 89%, 76%, and 46% for metastatic disease. Multivariate analysis confirmed metastasis, but not sex or tumor location, as the sole independent predictor of a poor survival.[5]

Wide local excision remains the cornerstone of early-stage ASPS management. Adjuvant radiotherapy may be used postoperatively or for inoperable tumors, though ASPS exhibits inherent radioresistance. Conventional chemotherapy (eg, anthracyclines and ifosfamide) is largely ineffective for ASPS due to its unique low proliferative activity (typically Ki-67 <10%) and slow cell division. Additionally, its aberrant vasculature impedes drug penetration, prompting exploration of antiangiogenic agents combined with immunotherapy, which may offer a strategic advantage. For advanced ASPS, targeted therapies with tyrosine kinase inhibitors (TKIs, such as sunitinib and pazopanib) and immune checkpoint inhibitors (eg, atezolizumab and pembrolizumab) have shown promise.[6,7] Other TKIs, including anlotinib, axitinib, bevacizumab, and apatinib [the latter showing a 100% objective response rate (ORR) in a small cohort (5/5)],[8,9] also have demonstrated efficacy. Notably, the limitations of monotherapy have spurred interest in TKI-immunotherapy combinations, which outperform single-agent regimens in preliminary studies (albeit with limited sample sizes). Antiangiogenic drugs not only normalize the tumor vasculature and ameliorate hypoxia, but they also remodel the immunosuppressive microenvironment by modulating immune cell infiltration and cytokine profiles, thereby synergizing with immunotherapies. These findings position combination strategies as a pivotal direction for future ASPS treatment.[10]

UPS is one of the most common STS subtypes, accounting for 25–35% of all STSs and 14–20% of annual STS diagnoses, with China reporting over 4000 new cases yearly.[11,12] It predominantly affects middle-aged and elderly patients, typically presenting as a painless, progressively enlarging mass. UPS is highly aggressive, with frequent postoperative recurrence, distant metastases, and a notable rate of regional lymph node metastasis- where nodal involvement carries prognostic significance equivalent to visceral metastases.[11,13] For localized UPS, the mainstay treatment is wide excision with R0 margins combined with adjuvant radiotherapy. However, advanced UPS commonly metastasizes to the lungs, bones, and other sites.[14] The prognosis is highly variable: the 5-year survival reaches 65–70% for nonmetastatic cases, compared to a median OS (mOS) of approximately one year for metastatic disease.[15] UPS exhibits relative chemosensitivity, with the doxorubicin plus ifosfamide regimen remaining the first-line therapy for unresectable cases. Nevertheless, there is no consensus on second-line therapy for nonspecific STSs. Anlotinib may serve as a second-line targeted therapeutic option for advanced or unresectable STSs including UPS. Meanwhile, immunotherapy may offer promising therapeutic potential for advanced UPS patients, with potential predictive biomarkers including programmed death-ligand 1 (PD-L1) expression, high tumor mutational burden, and microsatellite stable status. The presence of tumor-infiltrating lymphocytes and tertiary lymphoid structures further suggests immunotherapeutic potential, though large-scale clinical validation remains necessary.

We conducted this single-center, exploratory case series, aiming to evaluate the efficacy and safety of camrelizumab [an antiprogrammed cell death protein 1 (PD-1) immune checkpoint inhibitor] plus apatinib (a VEGF receptor 2 TKI) in patients with advanced unresectable ASPS or UPS. The findings may provide evidence supporting this combination

regimen as a potential therapeutic strategy to improve the outcomes of patients with either of these two aggressive subtypes of STS.

Materials and Methods

Patients

In this single-center, exploratory case series (identifier: NCT04447274 on ClinicalTrials.gov, registration date: 23-Jun -2020), patients with advanced unresectable ASPS or UPS were screened for eligibility and enrolled at the Cancer Hospital, Chinese Academy of Medical Sciences (Beijing, China), spanning from the initiation date in March 2021 and continued until April 2024. Eligible patients met the following inclusion criteria: histopathologically confirmed advanced UPS who had failed prior standard therapy, or histopathologically confirmed advanced ASPS who were either untreated or had failed prior antiangiogenic therapy or other treatments. Eligible patients had radiologically evaluable lesions, including at least one unidimensionally measurable lesion (longest diameter ≥10 mm as measured by spiral computed tomography) according to the RECIST 1.1. criteria. Additionally, the eligible patients had an Eastern Cooperative Oncology Group performance status score ≤1, were aged ≥16 years, and had an estimated survival exceeding 3.0 months. All acute toxicities caused by prior antitumor therapies had to resolve to Grade 0–1 (NCI CTCAE version 5.0) or to levels specified in the enrollment/exclusion criteria (excluding toxicities such as alopecia that the investigator deemed to pose no safety risk to the subject) prior to enrollment.

During enrollment, patients with the following conditions were excluded from participation: (1) Known active central nervous system metastases and/or carcinomatous meningitis. Subjects who had undergone prior treatment for brain metastases may participate provided they are in stable condition and meet the following criteria: no evidence of radiographic progression for at least four weeks prior to the first dose of study treatment; any neurological symptoms have returned to baseline; no evidence of new or enlarging brain metastases; and no steroid use for at least seven days before study treatment. This exception does not apply to carcinomatous meningitis, which is excluded regardless of clinical stability. (2) Use of immunosuppressive medications within 14 days prior to the first administration of camrelizumab, excluding intranasal and inhaled corticosteroids or physiological doses of systemic steroids (ie, no more than 10 mg/day of prednisolone or an equivalent dose of other corticosteroids). (3) Prior treatment with therapies, including anti-PD-1, anti-PD-L1, or anti-PD-L2 agents, or drugs targeting another stimulatory or co-inhibitory T-cell receptor [eg, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), OX-40, and CD137].

This study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (approval number: 20/165-2361). Written informed consent was obtained from each patient prior to their participation in this study. This study adhered to good clinical practices and the Declaration of Helsinki. All data were anonymized to maintain patient confidentiality.

Treatment

Camrelizumab (an anti-PD-1 antibody) was administered intravenously at a fixed dose of 200 mg per infusion over 30 min (including line flushing, with the total infusion duration strictly maintained between 20 min and 60 min) every 2 weeks until progressive disease (PD), unacceptable toxicity, or a maximum of 2 years or 53 cycles of immunotherapy. Concurrently, apatinib was given orally at a dose of 500 mg once daily, approximately 30 min after meals, with warm water at a consistent daily time for 5 consecutive days, followed by a 2-day break. The combination regimen of camrelizumab plus apatinib was administered in 2-week cycles until PD or intolerable toxicity. The specific dose was adjusted for each patient according to their adverse events (AEs).

Evaluation of Efficacy and Safety

Imaging assessments were performed every four treatment cycles prior to dosing, with each treatment cycle lasting two weeks and with an allowable window of ±7 days, to monitor the efficacy and safety of the biweekly regimen combining targeted therapy and immunotherapy. For patients who achieved a partial response (PR) or maintained long-term stable disease (SD), the follow-up assessment interval could be extended to 3.0–6.0 months. Unscheduled imaging was conducted if

disease progression was suspected (eg, worsening symptoms). Responses were categorized as complete response (CR), PR, SD, or PD. PD was defined as a minimum 20% increase in the sum of the diameters of target lesions compared to the smallest recorded sum, with an absolute increase of ≥5 mm, and/or progression of nontarget lesions, and/or the appearance of one or more new lesions. The ORR was defined as the sum of CR and PR, and the disease control rate (DCR) was defined as the sum of CR, PR, and SD. Progression-free survival (PFS) was defined as the time from the initiation of treatment to PD or death from any cause, and OS was defined as the time from treatment initiation to death from any cause.

If the investigator confirmed a CR or PR based on RECIST 1.1, the patient underwent a repeat assessment for confirmation four weeks after the initial evaluation. Patients were expected to continue study treatment until radiologically confirmed PD, unless one of the following occurred: withdrawal of informed consent, intolerable drug toxicity, or investigator-determined ineligibility for further study participation. If a patient discontinued the study prior to PD, tumor progression was monitored via imaging assessments every eight weeks. No other antitumor therapies were permitted before study discontinuation.

For safety assessment, AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, NCI-CTCAE version 5.0. All AEs and serious AEs observed during this study were recorded, including abnormal laboratory results, clinical symptoms, and vital sign abnormalities. For each event, we documented the following: characteristics and severity grade, onset and duration, management approach, and clinical outcomes, along with causality assessment relative to the investigational treatment.

The primary endpoint was ORR, while PFS, OS, and safety profiles characterized by AEs were exploratory endpoints.

Statistical Analysis

Given the small sample size (n=9), categorical variables were shown, and analysis for time-to-event outcomes (PFS and OS) was performed using a Cox regression model, just intended for descriptive reference and exploratory attempts that were ultimately not interpretable Statistical analyses were conducted using SPSS (version 22.0), while GraphPad Prism (version 10.1.2) and R software (version 4.0.1) were utilized for graphical representation.

Results

Baseline Characteristics

Nine patients with histologically confirmed advanced sarcomas were enrolled in this study, including seven cases of ASPS (treatment-naive, or previously treated with failed antiangiogenic therapy or other treatments) and two cases of UPS (previous treatment-refractory).

The ASPS subgroup consisted of two females and five males, with a mean age of 23.4 years. The primary tumor locations included the shoulder/back (n=2), abdominal wall (n=2), psoas major muscle (n=1), and thigh (n=2). All ASPS patients exhibited bilateral lung metastases with additional metastases in the brain, occiput, and ischium. The tumor sizes ranged from 6.0 cm to 12.5 cm, with Ki67 proliferation indices of 2–20%. Prior therapies included chemotherapy regimens with epirubicin and ifosfamide, as well as targeted therapy agents such as apatinib, pazopanib, and anlotinib. Treatment lines involving camrelizumab combined with apatinib were distributed as follows: first line (n=4), second line (n=2), and fourth line (n=1).

The UPS subgroup comprised two males with a mean age of 56.5 years. The primary tumor locations were the lung (n=1) and mediastinum (n=1). Both patients in the UPS subgroup demonstrated bilateral lung metastases, along with additional metastases to the chest wall, sternum, sacrum, and ilium. The tumor sizes ranged from 8.0 cm to 11.1 cm, with a consistent Ki67 index of 50%. Prior treatments included epirubicin, ifosfamide, gemcitabine, and docetaxel chemotherapy, as well as anlotinib. Camrelizumab combined with apatinib was administered as a third-line therapy. The detailed demographic characteristics and clinical data at baseline for these nine patients are shown in Table 1.

Overall Treatment Response and Outcomes

The treatment response and outcomes of the nine patients are shown in Figure 1. As of the data cut-off (April 15, 2025), one patient achieved a pathological complete response, pCR following conversion surgery, one patient with confirmed

Table 1 Demographic and Clinical Characteristics of ASPS and UPS Patients at Baseline

Characteristic	ASPS (n=7)	UPS (n=2)
Gender		
Female	2 (22.2)	0 (0.0)
Male	5 (55.6)	2 (22.2)
Age (years)		
<20	3 (33.3)	0 (0.0)
≥20	4 (44.4)	2 (22.2)
Primary location		
Shoulder and back	2 (22.2)	0 (0.0)
Abdominal wall	2 (22.2)	0 (0.0)
Psoas major muscle	1 (11.1)	0 (0.0)
Thigh	2 (22.2)	0 (0.0)
Lung	0 (0.0)	1 (11.1)
Mediastinum	0 (0.0)	1 (11.1)
Lung metastasis		
No	0 (0.0)	0 (0.0)
Yes	7 (77.8)	2 (22.2)
Brain metastasis		
No	6 (66.7)	2 (22.2)
Yes	1 (11.1)	0 (0.0)
Bone metastasis		
No	6 (66.7)	1 (11.1)
Yes	1 (11.1)	1 (11.1)
Other metastatic sites		
No	6 (66.7)	0 (0.0)
Yes	1 (11.1)	2 (22.2)
Number of surgeries		
0	4 (44.4)	2 (22.2)
1	2 (22.2)	0 (0.0)
2	1 (11.1)	0 (0.0)
Tumor size		
≤10 cm	4 (44.4)	1 (11.1)
>10 cm	3 (33.3)	1 (11.1)
Ki67		
≤20%	4 (44.4)	0 (0.0)
20%<index≤50%	0 (0.0)	2 (22.2)
Absent	3 (33.3)	0 (0.0)
MMR status		
pMSS	1 (11.1)	1 (11.1)
Unknown	6 (66.7)	1 (11.1)
PD-L1 CPS		
15	1 (11.1)	0 (0.0)
70	0 (0.0)	1 (11.1)
Absent	6 (66.7)	1 (11.1)
TMB		
0	1 (11.1)	0 (0.0)
Absent	7 (77.8)	1 (11.1)
Prior treatment		
First-line	4 (44.4)	0 (0.0)
Non-first-line	3 (33.3)	2 (22.2)

Note: Data are presented as the number of patients and the percentage within the cohort.

Abbreviations: ASPS, alveolar soft part sarcoma; UPS, undifferentiated pleomorphic sarcoma; MMR, mismatch repair; pMSS, proficient mismatch repair/microsatellite stable; PD-L1 CPS, programmed death-ligand 1 combined positive score; TMB, tumor mutational burden.

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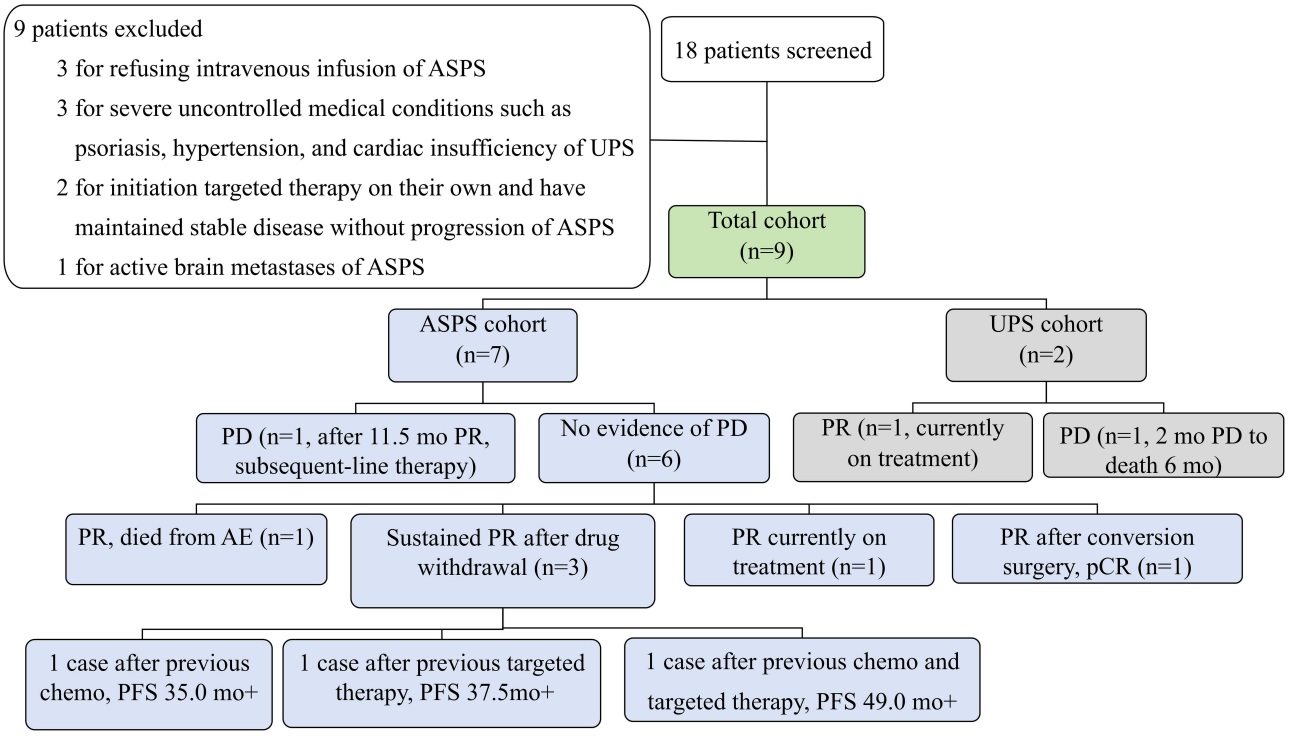

Figure 1 Flow chart of the treatment response and overall outcomes. "+" indicates that follow-up was conducted under close surveillance, as of the data cutoff on April 15, 2025.

Abbreviations: ASPS, alveolar soft part sarcoma; UPS, undifferentiated pleomorphic sarcoma; PFS, progression-free survival; PR, partial response; PD, progressive disease; pCR, pathological complete response.

PD started subsequent-line therapy, two patients remained on continued treatment, two patients died during follow-up, and three patients maintained a PR during follow-up after treatment discontinuation.

Efficacy

From the first patient enrollment (March 3, 2021) through the data cutoff (April 15, 2025), neither mPFS nor mOS had been reached in the cohort, with a median follow-up of 24.0 months. Both the overall ORR and DCR were 88.9% (8/9).

In the ASPS subgroup (n=7), neither the mPFS nor mOS had been reached, with a median follow-up of 23.8 months. Both the ORR and DCR were 100.0% (7/7), with all patients achieving PR after 3.5–8.5 months of treatment. One patient underwent successful conversion surgery and achieved a subsequent pCR. The mean maximum tumor shrinkage among the seven cases was 68.7%. Four patients (4/7, 57.1%) demonstrated clinically meaningful sustained PR, including three patients who had entered treatment-free follow-up (with treatment discontinuation durations of 7.5, 10.0, and 10.5 months, and ongoing PFS of 37.5, 35.0, and 49.0 months, respectively), while one patient continued ongoing therapy.

In the UPS subgroup (n=2), the mPFS was 7.5 months and the mOS was 9.5 months, with a median follow-up of 13.0 months. Both the ORR and DCR were 50.0% (1/2). One patient experienced PD and the other achieved PR after 2.5 months of treatment, with a maximum tumor shrinkage of 61.3%. The findings in the UPS subgroup are anecdotal and hypothesis-generating only.

Further short-term efficacy and long-term outcome data of individual patients are presented in Table 2 and Figures 2–4. Subgroup analysis of survival outcomes using Kaplan-Meier curves was performed, with the results presented in Figures 5 and 6 for the two histological subtypes (ASPS and UPS) and in Figures 7 and 8 for the treatment-line subgroups of ASPS (first-line and non-first-line therapies). The heterogeneous PFS and OS between the histologic subtypes were shown in Figures 5 and 6, and no statistical comparisons were performed between groups due to the small sample size. While no significant difference in PFS or OS was observed between prior first-line and non-first-line therapies in the ASPS subgroup (n=7) ($p>0.05$), patients who received prior first-line chemotherapy or targeted therapy

Table 2 Individual Patient Treatment Response, Tumor Reduction, and Survival Outcomes

Patient No.	Age/Sex	Tumor Location	Tumor Size	Treatment Line	Best Response	Tumor Shrinkage	PFS (Months)	OS (Months)
1	27/M	Shoulder and back	7.7	4	PR	−62.3%	49+	49+
2	18/F	Shoulder and back	6.0	1	PR	−68.5%	9	9
3	18/M	Abdominal wall	6.0	2	PR	−60.0%	37.5+	37.5+
4	28/M	Psoas major muscle	12.5	2	PR	−71.2%	35+	35+
5	19/M	Thigh	10.1	1	PR	−56.7%	12.5+	12.5+
6	24/F	Abdominal wall	9.0	1	pCR	−100.0%	12+	12+
7	30/M	Thigh	11.5	1	PR	−62.5%	11.5	12+
8	62/M	Lung	8.0	3	PD	+30.6%	2	6
9	51/M	Mediastinum	11.1	3	PR	−61.3%	13+	13+

Notes: Patients 1–7 have ASPS, while patients 8–9 have UPS. In the PFS column, "+" indicates ongoing treatment or follow-up under close surveillance as of as of April 15, 2025. In the OS column, "+" denotes patient survival as of April 15, 2025.
Abbreviations: M, male; F, female; PFS, progression-free survival; OS, overall survival; PR, partial response; PD, progressive disease; pCR, pathological complete response.

demonstrated improved disease control and survival benefit (PFS not reached vs. 12.0 months, p=0.1869; OS not reached in either group, p=0.3865) (Figures 7 and 8).

Safety

Among the nine treated patients, one death (1/9, 11.1%) occurred due to sudden immune-mediated myocarditis in the ASPS subgroup during the COVID-19 pandemic. Notably, the patient experienced rapid deterioration, with the time from the onset of discomfort to death being approximately 10 hours. The COVID-19 pandemic complicated the identification of causal factors, mainly owing to the pandemic and the associated public health measures. Prior to this event, the patient had achieved 9.0 months of sustained tumor remission.

The most common AEs included hand-foot syndrome (6/9, 66.7%), capillary proliferation (5/9, 55.6%), proteinuria (5/9, 55.6%), hypertension (4/9, 44.4%), and mild liver enzyme elevation (2/9, 22.2%). These AEs were classified as Grade 1–2, generally tolerable, and primarily associated with apatinib. Symptoms were alleviated or resolved after symptomatic treatment or dose adjustment. Notably, the combination therapy significantly mitigated both the incidence and severity of camrelizumab-associated reactive cutaneous capillary endothelial proliferation while maintaining anti-tumor efficacy, potentially due to a synergistic effect of the two agents.

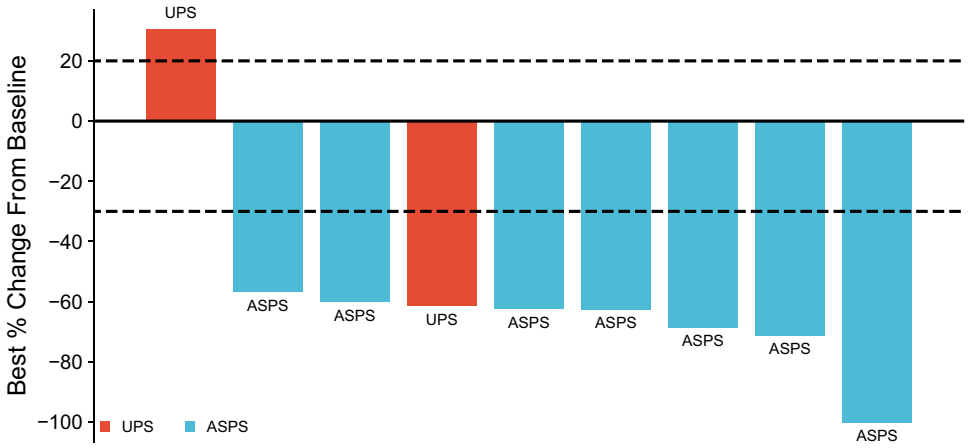

Figure 2 Waterfall plot of maximum tumor reduction outcomes in individual patients with ASPS or UPS. The waterfall plot was constructed, displaying the percentage change from the baseline tumor size, with the ASPS patients represented by blue bars and the UPS patients by red bars. Cases are arranged from left to right by a decreasing magnitude of tumor shrinkage. The upper black dotted horizontal line is set at +20%, indicating that tumor growth exceeding 20% corresponds to a PD assessment. The lower black dotted horizontal line is set at −30%, indicating that tumor shrinkage greater than 30% corresponds to an assessment of a PR or even a CR.
Abbreviations: ASPS, alveolar soft part sarcoma; UPS, undifferentiated pleomorphic sarcoma; PD, progressive disease; PR, partial response; CR, complete response.

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Discussion

Systemic treatment options for certain histologic subtypes of advanced and metastatic STSs, such as ASPS and UPS, remain limited. In our study, camrelizumab combined with apatinib suggested relatively better efficacy in patients with advanced unresectable ASPS, as indicated by the response data (Table 2 and Figure 2). Neither the mPFS nor mOS was reached, and both the ORR and DCR were 100.0% (7/7). Additionally, all ASPS patients achieved a PR within 3.5–8.5 months of treatment, and it was noted that achieving a PR may require patience, as tumor shrinkage can progress slowly over approximately six months.

No statistical comparisons between groups were performed in the differences of PFS and OS among histologic subtypes of STS due to the small sample size. In the ASPS subgroup, while differences in PFS and OS between first-line and non-first-line therapies were also not statistically significant (Figure 1 and Table 2), patients with prior therapy appeared to experience relatively improved disease control and potential survival benefits, which could potentially attributed to chemotherapy-induced elimination of fast-proliferating tumor cells that can lead to tumor antigen release and enhanced immunogenicity. For instance, anthracyclines can induce calreticulin exposure on tumor cells, facilitating the elimination of immunosuppressive cells via calreticulin-mediated mechanisms and enhancing the efficacy of PD-1 inhibitors. In addition, antiangiogenic targeted therapies may modify the tumor microenvironment to promote immune cell infiltration, creating favorable conditions for subsequent immunotherapy. These findings suggest that tumor rebound may occur after resistance to prior targeted monotherapy and that subsequent combination immunotherapy with targeted agents could potentially restore effective antitumor activity and reverse drug resistance.

Alternatively, the modest prognostic benefit observed may be attributed to an inadequate follow-up duration. Figures 3 and 4 depict the three patients with the longest ongoing PFS during treatment-free follow-up; these patients may have achieved a clinical complete response. However, comprehensive restaging using whole-body 18F positron emission tomography-computed tomography has not been conducted due to socioeconomic constraints. Our safety data highlighted the importance of close monitoring for AEs, particularly for fatal complications like immune-mediated myocarditis. Specifically, one patient in the ASPS subgroup died from immune-mediated myocarditis. This event occurred during the COVID-19 pandemic, and the patient had returned to his hometown, where medical resources were limited. Additionally, given the pandemic circumstances, including public health measures that complicated the

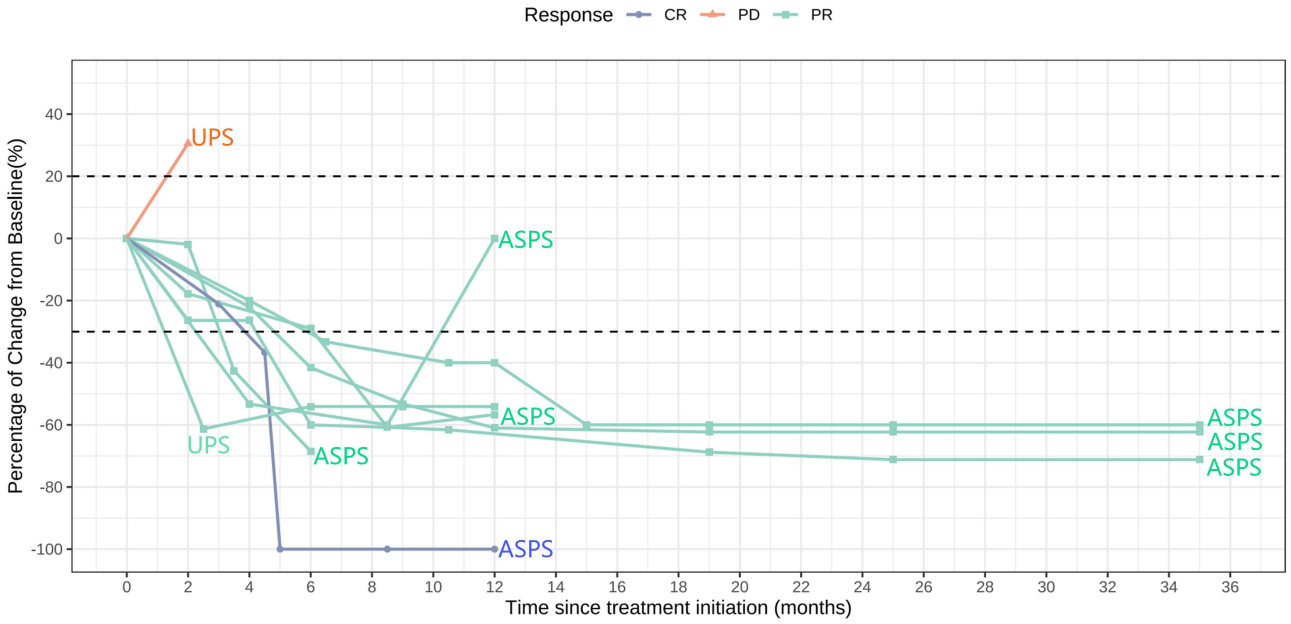

Figure 3 Spider plot of the percentage change of tumor size from baseline at each tumor response assessment. The spider plot was created, illustrating tumor reduction from baseline and variations in the treatment response.
Abbreviations: CR, complete response; PD, progressive disease; PR, partial response.

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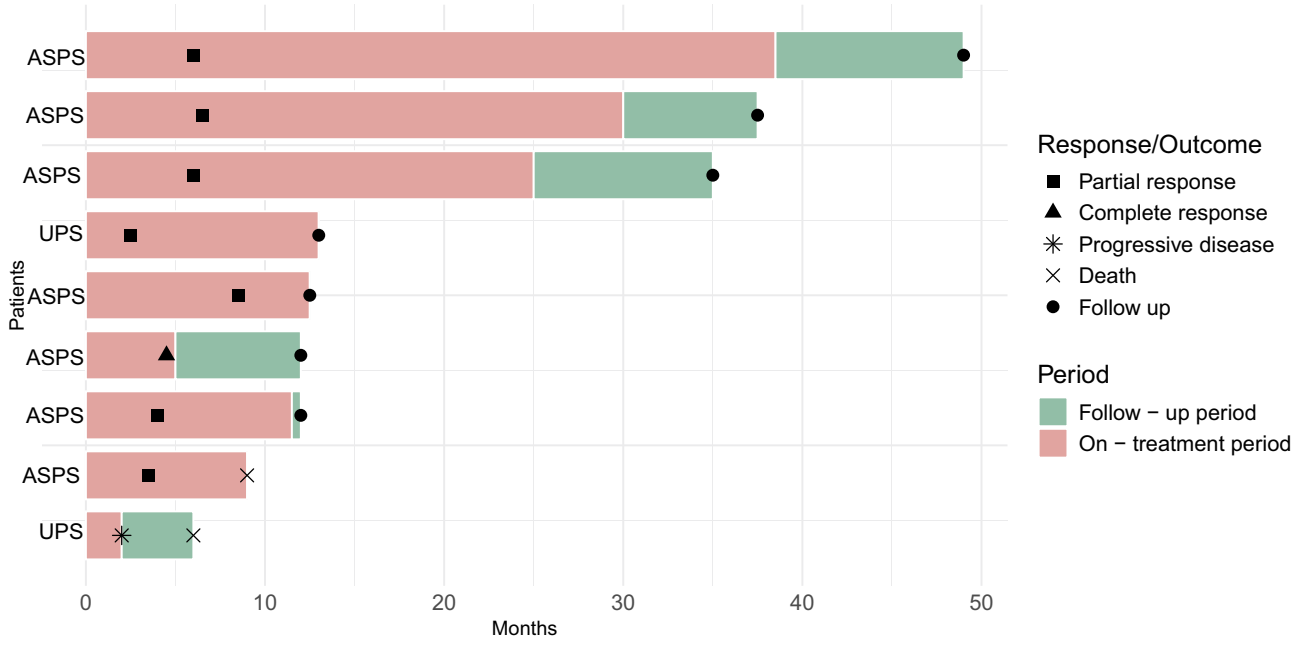

Figure 4 Swimmer plot depicting the treatment duration and follow-up for each patient. Horizontal bars represent individual patients, with colored segments denoting the treatment duration (light-red segments) and follow-up period (green segments).

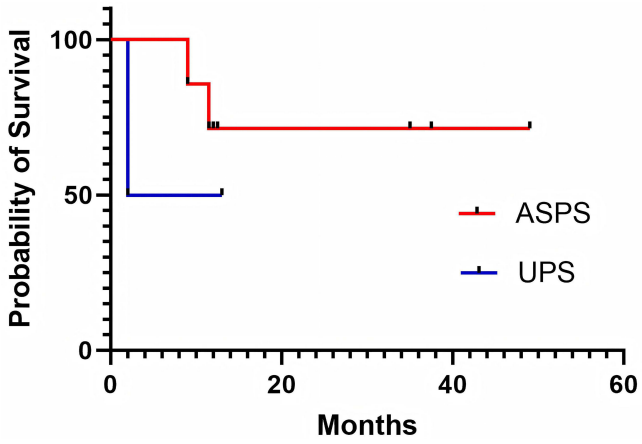

Figure 5 Kaplan–Meier curve of PFS by histologic subtypes (ASPS vs. UPS, not reached vs. 7.5 months). No statistical comparisons were performed between groups due to the small sample size.
Abbreviations: PFS, progression-free survival; ASPS, alveolar soft part sarcoma; UPS, undifferentiated pleomorphic sarcoma; m, months.

identification of causative factors, we cannot exclude the possibility that COVID-19 infection may have contributed to this case, nor can we disregard the potential for delayed treatment due to restricted access to medical care. Several previous studies have reported a range of severe immune-related AEs (Grade 3 and higher) in patients with ASPS receiving PD-1-based immunotherapy. These included serious cytokine release syndrome (CRS),[16] immune-related myocarditis and liver damage,[17] as well as immune-related pneumonitis, arthritis, pancreatitis, and colitis.[18]

Several previous studies investigated the efficacy of targeted therapies and immunotherapies in patients with ASPS. For instance, the ALTER-0203 study revealed that anlotinib monotherapy achieved an mPFS of 18.23 months in ASPS patients, which is a significant prolongation of 15.3 months compared to the mPFS of 3.0 months in the placebo group [hazard ratio (HR)=0.14, $p<0.0001$].[19] In the Phase III PALETTE clinical trial, pazopanib achieved an mPFS of 4.6 months, compared to 1.6 months for placebo in second-line or later-line therapy for STSs (HR=0.31, $p<0.0001$), though there was no significant difference in the mOS between the two groups.[20] A retrospective study of 30 ASPS patients

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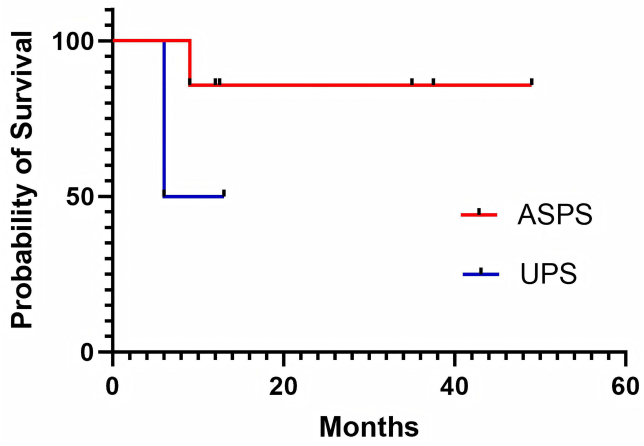

Figure 6 Kaplan–Meier curve of OS by histologic subtypes (ASPS vs. UPS, not reached vs. 9.5 months). No statistical comparisons were performed between groups due to the small sample size.
Abbreviations: OS, overall survival; ASPS, alveolar soft part sarcoma; UPS, undifferentiated pleomorphic sarcoma; m, months.

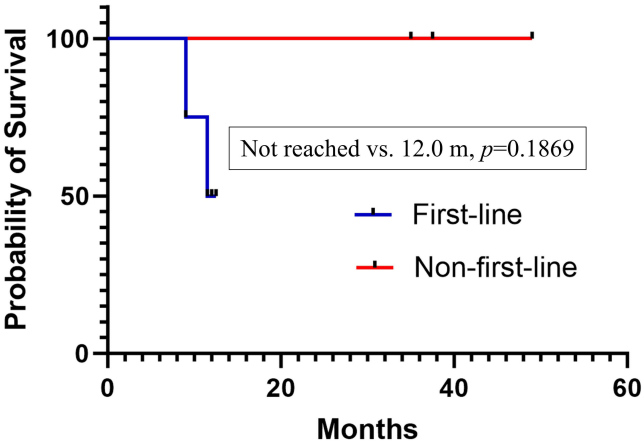

Figure 7 Kaplan–Meier curve analysis of the difference in PFS between prior first-line and non-first-line therapies in the ASPS subgroup.
Abbreviations: PFS, progression-free survival; ASPS, alveolar soft part sarcoma; m, months.

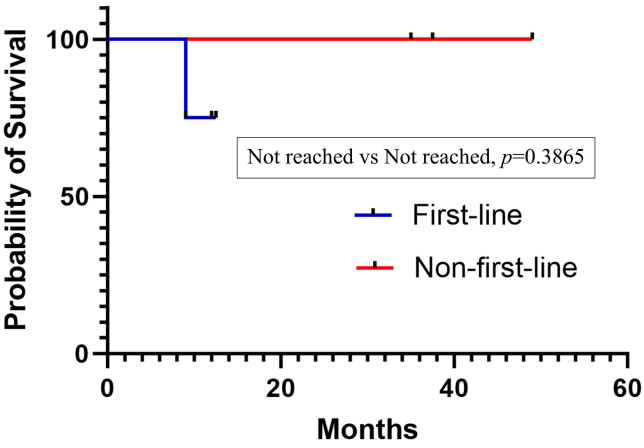

Figure 8 Kaplan–Meier curve analysis of the difference in OS between prior first-line and non-first-line therapies in the ASPS subgroup.
Abbreviations: OS, overall survival; ASPS, alveolar soft part sarcoma.

treated with pazopanib (including 13 who had prior antiangiogenic therapy) reported an ORR of 26.5%, an mPFS of 13.6 months, and a 1-year PFS rate of 59.0%.[21]

A basket trial of pembrolizumab enrolled 40 patients with STSs, including 4 cases of ASPS, of which 2 achieved PR and 2 had SD, with durations of response of 8 and 12 months, respectively.[22] In another efficacy study of atezolizumab involving 24 ASPS patients, interim analysis of 19 evaluable patients showed that 8 achieved PR and 9 had SD, yielding an ORR of 42.0%. Most responders maintained clinical benefit for over one year.[23] Additionally, a Phase II, multicenter, single-arm clinical study evaluating atezolizumab monotherapy in 52 patients with ASPS indicated a disease response in 19 patients, including 1 patient with a CR and 18 patients with a PR, yielding an ORR of 37%.[24] The trial results also revealed that the median time to response was 3.6 months, the mPFS was 20.8 months, and median duration of response was 24.7 months, inducing sustained responses in approximately one-third of advanced ASPS patients.[24]

The combination of immunotherapy and antiangiogenic therapy represents a promising therapeutic strategy to enhance treatment response and improve survival outcomes. A Phase II single-arm study evaluating pembrolizumab plus axitinib in 33 patients with advanced STSs reported a 3-month PFS rate, PFSR-3m of 65.6%, with the ASPS subgroup achieving a PFSR-3m of 72.7%. Among 12 ASPS patients, the regimen demonstrated an ORR of 54.5%, a DCR exceeding 80.0%, and an mPFS of 12.4 months, suggesting synergistic therapeutic potential.[25] An independent single-arm phase II clinical trial evaluating a PD-L1 inhibitor in combination with anlotinib in 30 patients with advanced STSs demonstrated tumor response in 9 out of 12 ASPS patients (75.0% ORR), with an mPFS of 23.1 months.[17] Furthermore, a phase II expansion study involving treatment-naive patients with locally advanced or metastatic ASPS who had not previously received antiangiogenic or immunotherapy agents (median age: 29 years) included 28 evaluable patients, of whom 6 (20.7%) had received prior chemotherapy. An objective response was achieved in 82.1% of patients, including 4 patients with a CR and 19 patients with a PR. The median time to response was 2.8 months, and the median duration of response was not reached, with an estimated mPFS of 35.2 months. Grade 3–4 treatment-related AEs occurred in 44.8% of patients, with no treatment-related deaths. Tumor microenvironment analysis of seven patients revealed significant differences in tertiary lymphoid structure formation between responders (three CR/near-CR cases) and nonresponders (four PD/no-response cases), with higher $CD20^{+}$ cell infiltration in responders (1.33% vs. 0.19%).[26]

The findings in the UPS subgroup of our study are anecdotal and hypothesis- generating only. UPS is more chemotherapy-sensitive STS subtypes compared with ASPS. A European multicenter phase III randomized clinical trial (ISG-STS 1001) enrolled 287 STS patients, including 97 UPS cases (one of the largest UPS cohorts to date), and evaluated histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy.[27] Notably, the treatment paradigms for neoadjuvant and advanced-stage STSs overlapped, particularly in terms of the chemosensitivity profiles and recommended regimens (eg, anthracycline- and ifosfamide-based protocols). This study demonstrated that doxorubicin plus ifosfamide outperformed docetaxel plus gemcitabine, achieving an ORR of 26.4%, a DCR of 76.6%, and 1- and 2-year OS rates of 60.0% and 31.0%, respectively, further supporting doxorubicin-based regimens as the first-line standard for advanced STSs.[27] For later-line targeted therapies, targeted agents have shown mixed results. A study of sorafenib in 15 UPS patients reported 5 achieving SD as the best response, while 7 showed no benefit.[28] In addition, anlotinib was assessed in a phase II trial (second-line or later), and it yielded a response rate of 12.6%, a 12-week PFS rate of 68.4%, an mPFS of 5.6 months, and an mOS of 12.3 months.[29]

In immunotherapy for UPS, the SARC028 trial demonstrated its potential benefit, with 4 of 10 UPS patients (40.0%) achieving objective responses, an mPFS of 30 weeks, and the mOS not reached at the time of analysis.[30] Subsequent expansion trial results reported an ORR of 23.0% (9/40) in UPS patients. The Alliance A091401 randomized multicenter phase II trial compared PD-1 inhibitor nivolumab monotherapy to nivolumab plus the CTLA-4 inhibitor ipilimumab.[31] The monotherapy arm showed a modest 5.0% response rate, while the combination arm reached 16.0% (6/38), with the UPS subgroup exhibiting a striking 40.0% response rate, indicating markedly enhanced efficacy with the combination of nivolumab and ipilimumab for this specific STS subtype.[31] Collectively, these findings suggest that pembrolizumab exhibits limited activity as a monotherapy, nivolumab alone appears less effective, but combining PD-1 and CTLA-4 inhibitors may offer superior outcomes in UPS patients.

In the therapeutic landscape of UPS, emerging exploration of immunotherapy-chemotherapy combinations shows promise for enhancing treatment response rates and improving clinical outcomes in some cases. Cytotoxic chemotherapy

induces DNA damage, triggering cell death and the release of damage-associated molecular patterns, which may amplify T-cell responses by promoting immune activation and PD-L1 upregulation. For instance, a phase I/II study evaluating pembrolizumab plus doxorubicin as the first-line therapy for unresectable/metastatic STSs reported an ORR of 22% and a DCR of 81% (59% SD), with a 6-month PFS rate of 73.0%, surpassing the historical benchmark of 40.0%. These results suggest that doxorubicin may potentiate immune checkpoint inhibition, positioning this combination as a promising strategy for advanced STSs.[32] Another trial investigating eribulin plus pembrolizumab in 57 advanced STS patients reported a 12-week PFS rate of 52.6% in a cohort of patients with UPS or other sarcomas.[33] The single-arm phase II SAIS study, combining sintilimab, doxorubicin, and ifosfamide as the first-line treatment for advanced STSs, achieved an overall ORR of 68.3% among 41 evaluable patients, including 87.5% in UPS subgroup, which had an mPFS of 8.9 months and an mOS of 19.5 months.[34] These results suggest the potential synergy of immunochemotherapy, warranting further investigation.[34]

Given the small sample size and heterogeneous patient population, cross-trial comparisons are speculative. Therefore, multicenter clinical trials specifically investigating the combination of camrelizumab and apatinib in patients with ASPS and UPS should be conducted. Future research should focus on optimizing the combination of immune checkpoint inhibitors and anti-angiogenic agents, identifying responsive subtypes, and exploring factors associated with treatment efficacy to enhance patient selection for targeted-immunotherapy combination regimens. Further large-scale clinical trials are needed to validate the long-term effectiveness of this combined strategy, refine treatment protocols, and elucidate the mechanisms underlying tumor microenvironment interactions and drug resistance.

This single-center, exploratory case series has several limitations. First, the small sample size, particularly in the UPS subgroup, limits the statistical power and reliability of the outcomes. Second, the design may introduce potential bias in the assessment of AEs and treatment responses. Additionally, comprehensive reporting poses practical challenges due to the extremely low event frequency and relatively short and uneven follow-up durations. Third, the absence of a control group hinders the ability to draw definitive conclusions regarding the efficacy of the treatment.

Conclusions

In conclusion, this single center, exploratory case series suggests that the combination therapy of camrelizumab (an anti-PD-1 antibody) and apatinib (a VEGF receptor 2 TKI) may improve clinical outcomes in advanced unresectable ASPS patients, while the outcomes in UPS patients appear more variable, necessitating further research in this area. The occurrence of rare but fatal immune-mediated myocarditis in one patient underscores the need for vigilant monitoring. These findings warrant further investigation in larger trials to validate the efficacy and safety profile of this combination therapy, with the goal of assessing its potential as a systemic therapeutic option for patients with advanced ASPS or UPS.

Data Sharing Statement

The datasets generated and analyzed in the present study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (approval number: 20/165-2361). Written informed consent was obtained from each patient prior to their participation in this study. This study adhered to good clinical practices and the Declaration of Helsinki. All data were anonymized to maintain patient confidentiality.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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