THERAPEUTIC ADVANCES in
Medical Oncology

Original Research

Advancing treatment efficacy: combined therapy of eribulin, anlotinib, and camrelizumab in advanced or metastatic retroperitoneal liposarcoma

Ther Adv Med Oncol

2024, Vol. 16: 1–14

DOI: 10.1177/17588359241276968

Weiwei Jia*, **Jianhui Wu***, **Hongtao Zhang**, **Yan Wu**, **Daoning Liu**, **Zhen Wang**, **Xiaopeng Wang**, **Chengpeng Li** and **Chunyi Hao**

Abstract

Background: Retroperitoneal liposarcoma (RLPS) typically shows limited response to standard chemotherapy, presenting a challenge in treating advanced or metastatic RLPS.

Objective: This study aimed to evaluate the potential advantages of a combined therapeutic strategy utilizing eribulin, anlotinib, and camrelizumab.

Design: Between December 2020 and March 2023, this retrospective study enrolled patients with advanced or metastatic RLPS who received treatment at Peking University Cancer Hospital Sarcoma Center. The treatment regimen involved eribulin plus anlotinib and camrelizumab administered every 3 weeks (Q3W).

Methods: Efficacy was assessed following the Response Evaluation Criteria in Solid Tumors version 1.1, while safety was evaluated using the Common Terminology Criteria for Adverse Events version 5.0.

Results: The study included 47 patients with RLPS with a median age of 55.5 years. Patients received a median of 4.5 (range, 2–21) cycles of treatment. Notably, partial response was observed in 8 patients (18.2%), while 25 (56.8%) exhibited stable disease. The objective response rate (ORR) and disease control rate were 18.2% and 75%, respectively. Significant differences in ORR were observed among histological subtypes (well-differentiated vs de-differentiated vs myxoid: 0 vs 17.9% vs 50%; $p = 0.039$). Six patients underwent surgery before disease progression, and one patient with myxoid liposarcoma (MLPS) had a pathological complete response. With a median follow-up of 21.8 (range, 2.7–30.7) months, the median progression-free survival (mPFS) was 6.9 (95% confidence interval (CI), 4.7–9.1) months, and the 6-month PFS rate was 60.5%. Based on various histological subtypes, the mPFS was 8.4 (95% CI, 4.1–12.7) months with well-differentiated liposarcoma, 5.8 (95% CI, 3.3–8.3) months with de-differentiated liposarcoma and not reached with MLPS, respectively. Treatment-related adverse events (TRAEs) of any grade occurred in 36 (76.6%) patients, with grade 3 or higher TRAEs in 21 (44.7%) patients. The most common TRAEs were neutropenia (53.2%), proteinuria (21.3%), and anorexia (21.3%).

Conclusion: The combined treatment strategy involving eribulin, anlotinib, and camrelizumab showed promising efficacy and manageable safety in patients with advanced or metastatic RLPS, particularly in those with MLPS.

Keywords: anlotinib, camrelizumab, combined therapy, eribulin, retroperitoneal liposarcoma

Received: 11 February 2024; revised manuscript accepted: 6 August 2024.

Correspondence to:
Chengpeng Li
Chunyi Hao
Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Sarcoma Center, Peking University Cancer Hospital & Institute, 52 Fucheng Road, Haidian District, Beijing 100142, China
chengpengli@bjmu.edu.cn
haochunyi@bjmu.edu.cn

Weiwei Jia
Jianhui Wu
Daoning Liu
Zhen Wang
Xiaopeng Wang
Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Sarcoma Center, Peking University Cancer Hospital & Institute, Beijing, China

Hongtao Zhang
Jilin Guowen Hospital, Changchun, Jilin Province, China

Yan Wu
Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Pathology, Peking University Cancer Hospital & Institute, Beijing, China

*These authors contributed equally as co-first authors.

Introduction

Retroperitoneal soft tissue sarcomas (RSTs) encompass a rare and diverse array of tumors originating from mesenchymal cells, constituting approximately 10% of all soft tissue sarcomas (STSs).[1,2] Within the retroperitoneum, over 50 histologic subtypes have been identified. Among these, retroperitoneal liposarcomas (RLPSs) are the most prevalent, accounting for 45%–63% of cases.[2–6] Liposarcomas (LPSs) are classified into five histologic subtypes, each with distinct characteristics: well-differentiated liposarcoma (WDLPS) or atypical lipomatous tumor, de-differentiated liposarcoma (DDLPS), myxoid liposarcoma (MLPS), pleomorphic liposarcoma (PLPS), and myxoid pleomorphic liposarcoma (MPLPS).[1] Each subtype demonstrates distinct biological traits, recurrence patterns, metastatic risks, therapeutic effects, and prognoses.

WDLPS is a low-grade, locally aggressive neoplasm composed of proliferating mature adipocytes.[7] It has a favorable outcome when complete resection is performed. Although WDLPS rarely metastasizes, there is a higher risk of local recurrence.[8] DDLPS is a more aggressive, high-grade sarcoma with a higher risk of recurrence and metastasis. As a result, patients with DDLPS have a poor prognosis.[9,10] Primary retroperitoneal MLPS is rare, accounting for about 5% of all MLPS cases.[11] It is considerably more sensitive to chemotherapy and radiotherapy than WD/DDLPS.[12] PLPS is a high-grade sarcoma characterized by high invasion, metastasis, and recurrence. It is often insensitive to chemotherapy or radiotherapy.[1,12,13] MPLPS is an extremely rare adipocytic malignancy that preferentially involves the mediastinum of young patients.[1,14]

Treatment options for LPS remain limited, with first-line therapies typically involving chemotherapy using doxorubicin, ifosfamide, or a combination of both. However, most LPS subtypes exhibit resistance to conventional treatment. As a result, more new effective treatment options are urgently needed for LPS patients.

Recent clinical trials have explored novel treatments for LPS, including innovative chemotherapies, targeted therapies, and immunotherapies. Eribulin (eribulin mesylate), derived from the marine natural product halichondrin B, is a microtubule-targeting agent. It exerts its action by binding strongly to microtubule plus ends, thereby suppressing dynamic instability. Currently, eribulin has gained approval for managing unresectable or metastatic LPS in patients who have previously received anthracycline-containing chemotherapy.

In a randomized phase III trial comparing eribulin to dacarbazine in patients with advanced LPS and leiomyosarcoma, eribulin notably improved overall survival (OS) among LPS patients. Despite a low objective response rate (ORR) of 4%,[15] subgroup analyses of eribulin's activity in advanced LPS indicated significant improvements in both OS and progression-free survival (PFS) compared to dacarbazine.[16] The LEADER study demonstrated promising results for the combination of lenvatinib and eribulin in a limited patient cohort.[17] Nevertheless, further research is essential to comprehensively evaluate the efficacy and safety of this treatment in a larger patient population.

Anlotinib, an orally administered tyrosine kinase inhibitor (TKI), targets vascular endothelial growth factor receptor, fibroblast growth factor receptor, platelet-derived growth factor receptor, and c-kit, thereby inhibiting both tumor angiogenesis and tumor cell proliferation.[18,19] Clinical trials have shown its efficacy in improving PFS and OS among patients with refractory metastatic STSs. Within the spectrum of STSs, anlotinib achieved an ORR of 13%, with a specific ORR of 7.7% in LPS subtypes.[20] In addition, in a phase II trial, anlotinib displayed promising efficacy as a maintenance treatment post-initial anthracycline-based chemotherapy, showing an ORR of 12% in LPS patients.[21]

Despite the revolutionary impact of immune checkpoint inhibitors (ICIs) in cancer treatment, their application in advanced STSs has been limited due to poor immune cell infiltrates.[22–24] Pembrolizumab had an ORR of 18% in advanced STSs in the SARC028 trial.[25] Combining ICIs with TKIs has shown the potential to improve the effectiveness of immunotherapy while reducing the risk of immune-related adverse events (irAEs).[26,27] A single-center retrospective analysis combining ICIs with TKIs in advanced STSs revealed an ORR of 36.3% in patients with DDLPS, with one patient achieving a pathological complete response (pCR).[28] Similarly, a study from our department investigating anlotinib and

camrelizumab in treating RSTs showed an ORR of 13.3% among LPS patients.[29]

Building upon these findings, this study was initiated at our center to assess the efficacy and safety of eribulin in combination with anlotinib and camrelizumab for treating patients with advanced or metastatic RLPS.[30] The study sought to evaluate the potential benefits of this combination therapy.

Methods

Study design and patients

Between December 2020 and March 2023, this single-center retrospective study reviewed patients with advanced or metastatic RLPS who received treatment with eribulin, anlotinib, and camrelizumab at the Sarcoma Center of Peking University Cancer Hospital. We included patients 18 years of age and older with histologically confirmed locally advanced, locally recurrent, or metastatic RLPS; with adequate bone marrow, renal, and hepatic function; regardless of prior treatment history. Patients with histologically proven subtypes of retroperitoneal sarcoma other than RLPS were excluded.

All patients provided written informed consent, and the study followed the Declaration of Helsinki, guidelines for Good Clinical Practice, and local regulations on clinical trials. The study was approved by the Institutional Review Board of Peking University Cancer Hospital medical ethics committee (2022KT84).

Treatments

Before treatment initiation, all patients underwent baseline assessments including chest imaging evaluated by chest computed tomography (CT) or positron emission tomography-CT, contrast-enhanced CT or magnetic resonance imaging (MRI) of the abdomen and pelvis within 30 days. In addition, a complete blood count (CBC), hepatic and renal function tests, as well as endocrine function assessments within 2 weeks, were required.

Eribulin was administered intravenously at a dose ranging from 0.7 to 1.4 mg/m^2 on both day 1 and day 8 of a 3-week cycle. In some cases, the dosage of eribulin was reduced by 25% for certain patients experiencing treatment-related adverse events (TRAEs) in the previous cycle, in accordance with the Common Terminology Criteria for Adverse Events (CTCAE v5.0). Anlotinib was orally administered at a daily dose of 12 mg with a schedule of 2 weeks on and 1 week off. Camrelizumab was administered intravenously at a dose of 200 mg on day 1 of each treatment cycle.

Outcomes and follow-up

Tumor response, according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), was assessed using contrast-enhanced CT or MRI every three cycles.[31] Patients who underwent at least one response evaluation were included in the efficacy analysis.

The safety analysis set included these treated patients who had at least one post-baseline safety assessment. CBCs and biochemical tests were conducted before each treatment cycle. TRAEs were assessed and graded based on CTCAE v5.0.

Patients were recommended to undergo follow-up visits every three cycles (approximately 9 weeks) to assess clinical outcomes, including symptoms, physical examinations, and imaging assessments. Follow-up was maintained as long as the patient remained alive. PFS was defined as the duration from the baseline examination to the first documented disease progression, last follow-up, or death from any cause. OS was defined as the time from the baseline examination to the date of death, regardless of the cause.

Statistical analysis

The statistical cutoff date for all data analyses was October 13, 2023. Subtype differences were analyzed using Fisher's exact or Pearson's chi-squared test. Kaplan–Meier survival tests were used to assess OS and PFS, while the log-rank test assessed correlations between prognosis and tumor grade. The data processing and statistical analyses were conducted using SPSS version 26 (SPSS Inc., Chicago, IL, USA). Univariate and multivariate Cox proportional hazards models were utilized to analyze the relationship between clinicopathological parameters and PFS, using R Version 4.3.2. A two-sided p value <0.05 was considered significant, and a 95% confidence interval (CI) was calculated. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[32] (Supplemental Material).

Results

Patient characteristics

The study collected data from a cohort of 47 RLPS patients who received combination therapy involving eribulin, anlotinib, and camrelizumab at our center. The study population included 24 (51.1%) males and 23 (48.9%) females, with a median age of 55.5 (range, 25–74) years. All participants had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2. The histologic subtypes consisted of WDLPS ($n=11$), DDLPS ($n=30$), and MLPS ($n=6$). As per the Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) grading system,[33] G1, G2, and G3 accounted for 19.1%, 34.0%, and 46.8% of RLPS cases, respectively. Among them, 40 (85.1%) patients presented with locally advanced disease, while 7 (14.9%) patients had distant metastases in the peritoneum ($n=2$), liver ($n=1$), lungs ($n=1$), and bone ($n=3$). Initially, unresectable RLPSs were observed in 2 (4.3%) patients, whereas the remaining 45 (95.7%) patients experienced recurrence or metastasis following prior surgery. Of these, 37 (78.7%) patients received the combination therapy as first-line treatment, while 10 (21.3%) patients received it as second-line treatment due to disease progression after doxorubicin-based chemotherapy. Detailed baseline characteristics are presented in Table 1.

Treatment and safety

All patients received the combined treatment of anlotinib plus camrelizumab and eribulin. Eribulin was administered at different doses based on variations in the ECOG PS and drug tolerance, with 19 (40.4%) patients receiving a dose of 0.7–1.1 mg/m^2 and 28 (59.6%) patients receiving a dose of 1.1–1.4 mg/m^2. Nineteen (40.4%) patients discontinued treatment due to severe TRAEs. In addition, 8 (17.0%) patients had their eribulin dosage reduced, while 6 (12.8%) experienced dose interruptions. Among these, one patient required prednisone hormone therapy and discontinued camrelizumab due to grade 3 immune-related colitis. Another patient chose to discontinue treatment independently for over 3 months, leading to disease progression. The remaining four patients experienced dose interruptions with eribulin.

According to CTCAE v5.0, TRAEs of any grade occurred in 36 (76.6%) patients. The most common TRAEs included neutropenia ($n=25$, 53.2%), proteinuria ($n=10$, 21.3%), and anorexia ($n=10$, 21.3%). Twenty-one (44.7%) patients experienced grade 3 or higher TRAEs, including 10 (21.3%) with neutropenia, 4 (8.5%) with fatigue, 2 (4.3%) with anorexia, 2 (4.3%) with oral mucositis, and 1 (2.1%) each with drug-induced liver injury, hypertension, palmar-plantar erythrodysesthesia syndrome, immune-related diarrhea/colitis, and thrombocytopenia. Neutropenia ($n=3$, 6.4%) was the only grade 4 adverse event reported, and there were no TRAE-related fatalities. Table 2 provides a summary of the TRAEs.

Efficacy

Three patients with RLPS (one with WDLPS and two with DDLPS) out of the total 47 were excluded from the efficacy analysis as they only underwent one treatment cycle due to drug intolerance ($n=2$) and the impact of the COVID-19 pandemic ($n=1$). Among the 44 patients eligible for efficacy analysis, there were 10 (22.7%) with WDLPS, 28 (63.7%) with DDLPS, and 6 (13.6%) with MLPS. The median number of cycles per patient was 4.5 (range, 2–21), and none achieved complete response (CR). Outcomes were distributed as partial response (PR) in 8 (18.2%) patients, stable disease (SD) in 25 (56.8%), and progressive disease (PD) in 11 (25.0%) as per RECIST v1.1 criteria. The ORR and disease control rate (DCR) were 18.2% and 75.0%, respectively.

In the WDLPS subgroup, there were no PR cases, 8 (80.0%) SD cases, and 2 (20.0%) PD cases. Five (17.9%) patients with DDLPS and 3 (50.0%) with MLPS had PR. Meanwhile, 15 (53.6%) with DDLPS and 2 (33.3%) with MLPS showed SD, and 8 (28.6%) with DDLPS and 1 (16.7%) with MLPS had PD. The ORRs for patients with WDLPS, DDLPS, and MLPS were 0, 17.9%, and 50.0%, respectively, displaying a significant difference between the subgroups ($p=0.039$). However, the DCRs among patients with WDLPS, DDLPS, and MLPS were 80.0%, 71.4%, and 83.3%, respectively, indicating no statistically significant difference ($p=0.889$). Further detailed data are available in Table 3 and Figure 1.

In the subgroup analysis based on the FNCLCC grade system, the ORRs among patients with G1, G2, and G3 were 0, 20%, and 25%, respectively

Table 1. Patient characteristics.

Variable	*N* = 47 (100%)
Median age (years), median(range)	55.5 (25–74)
Gender, *n* (%)	
Male	24 (51.1)
Female	23 (48.9)
ECOG PS, *n* (%)	
0	15 (31.9)
1	28 (59.6)
2	4 (8.5)
Histologic subtype, *n* (%)	
Well-differentiated	11 (23.4)
De-differentiated	30 (63.8)
Myxoid	6 (12.8)
FNCLCC grade, *n* (%)	
G1	9 (19.1)
G2	16 (34.0)
G3	22 (46.8)
Stage, *n* (%)	
Locally advanced	40 (85.1)
Metastatic	7 (14.9)
Prior surgery, *n* (%)	
Yes	45 (95.7)
No	2 (4.3)
Treatment, *n* (%)	
First line	37 (78.7)
Second line	10 (21.3)

Data presented as *n* (%) unless otherwise noted; due to rounding, percentages might not total 100.
ECOG PS, Eastern Cooperative Oncology Group performance status; FNCLCC, Fédération Nationale des Centers de Lutte Contre le Cancer.

($p = 0.32$). The DCRs among patients with G1, G2, and G3 were 77.8%, 60.0%, and 85.0%, respectively ($p = 0.257$). No significant difference was observed in ORR and DCR among these subgroups. Additional detailed data are presented in Table 4.

Follow-up and survival

Six out of the 44 cases included in the efficacy analysis underwent surgery before experiencing disease progression. Among the remaining 38 patients, after a median follow-up of 21.8 months (range, 2.7–30.7 months), the median progression-free survival (mPFS) was 6.9 months (95% CI, 4.7–9.1 months), and the 6-month PFS rate stood at 60.5%. Analysis based on the histologic subgroups of RLPS revealed comparable mPFS values (WDLPS vs DDLPS vs MLPS: 8.4 months vs 5.8 months vs not reached, respectively; $p = 0.126$; Figure 2(a)). In addition, the mPFS among FNCLCC grade subgroups was 6.9 months (95% CI, 4.6–9.2 months) with G1, 7.4 months (95% CI, 0–15.3 months) with G2, and 5.8 months (95% CI, 3.5–8.1 months) with G3 ($p = 0.086$; Figure 2(b)).

One among the eight patients who showed a PR underwent surgery before experiencing disease progression. The remaining seven patients had a mPFS of 9.2 months (95% CI, 7.0–11.3 months). Six of these patients exhibited tumor progression, with PFS durations ranging from 7.4 to 21.9 months. After completing 21 cycles of combination therapy, 1 patient maintaining a PR status discontinued eribulin treatment due to TRAEs but continued maintenance therapy with anlotinib and camrelizumab (Figure 3).

Before disease progression, six patients underwent surgery, resulting in complete resection (R0/R1) for five of them. Pathological analysis revealed a pCR in one patient with MLPS and an 80% response rate in another with DDLPS. The patient achieving pCR underwent 7.5 cycles of combination therapy and attained PR according to RECIST v1.1. Furthermore, 10 patients underwent surgery post-disease progression due to severe symptoms or emergency conditions. Among them, seven had R0/R1 resections. However, locoregional recurrence occurred in 6 out of 12 patients with R0/R1 resection.

Currently, four patients continue to receive combination therapy. A total of 20 patients have passed away, with 3 of them due to COVID-19 infection. The median survival (mOS) has not yet been reached.

Table 2. Summary of treatment-related adverse events (*N* = 47).

TRAEs	Total, *N* (%)	Grade 1–2, *N* (%)	Grade 3–4, *N* (%)
Any adverse events	36 (76.6)	33 (70.2)	21 (44.7)
Neutropenia	25 (53.2)	15 (31.9)	10 (21.3)
Proteinuria	10 (21.3)	10 (21.3)	0
Anorexia	10 (21.3)	8 (17.0)	2 (4.3)
Fatigue	9 (19.1)	5 (10.6)	4 (8.5)
Drug-induced liver injury	6 (12.8)	5 (10.6)	1 (2.1)
Hypothyroidism	5 (10.6)	5 (10.6)	0
Telangiectasis	5 (10.6)	5 (10.6)	0
Vomiting	4 (8.5)	4 (8.5)	0
Palmar-plantar erythrodysesthesia syndrome	4 (8.5)	3 (6.4)	1 (2.1)
Thrombocytopenia	4 (8.5)	3 (6.4)	1 (2.1)
Hypertension	4 (8.5)	3 (6.4)	1 (2.1)
Immune-related diarrhea/colitis	3 (6.4)	2 (4.3)	1 (2.1)
Oral mucositis	3 (6.4)	1 (2.1)	2 (4.3)
Hyperthyroidism	1 (2.1)	1 (2.1)	0
Dysgeusia	1 (2.1)	1 (2.1)	0

Data presented as *n* (%) unless otherwise noted. Maximum grade per patient.
TRAEs, treatment-related adverse events.

Table 3. Efficacy results of the histologic subtypes according to RECIST v1.1 (*N* = 44).

	Total	WDLPS	DDLPS	MLPS	*p* value
Best overall response, *n* (%)					
PR	8 (18.2)	0	5 (17.9)	3 (50.0)	
SD	25 (56.8)	8 (80.0)	15 (53.6)	2 (33.3)	
PD	11 (25.0)	2 (20.0)	8 (28.6)	1 (16.7)	
ORR, %	18.2	0	17.9	50.0	0.039
DCR, %	75.0	80	71.4	83.3	0.889

Data presented as *n* (%) unless otherwise noted; due to rounding, percentages might not total 100.
DCR, disease control rate; DDLPS, de-differentiated liposarcoma; MLPS, myxoid liposarcoma; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; WDLPS, well-differentiated liposarcoma.

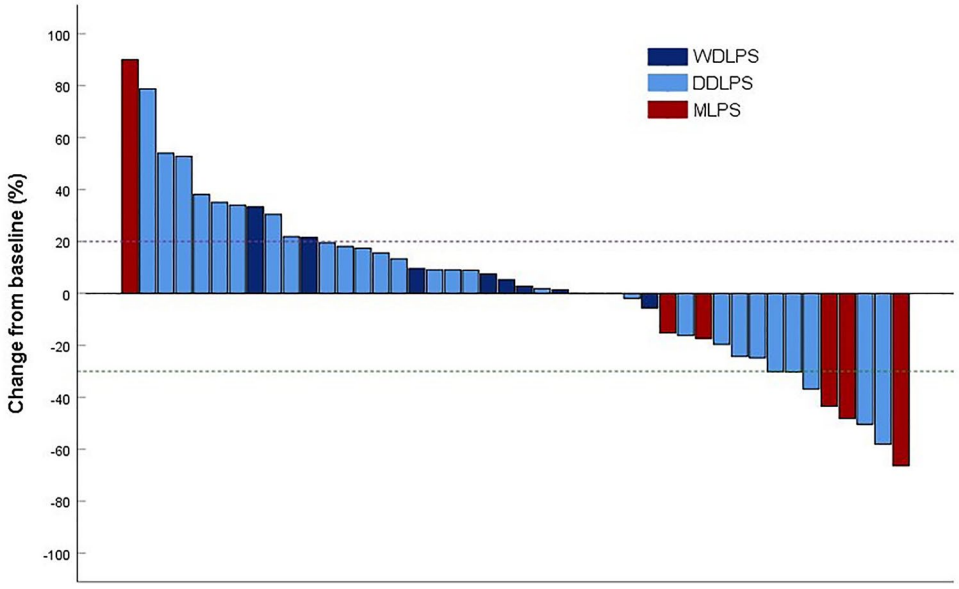

Figure 1. Waterfall plot for the response to eribulin plus anlotinib and camrelizumab in patients with retroperitoneal liposarcoma. The purple line represents the threshold for progressive disease. The green line represents the threshold for partial response. Red columns represent myxoid liposarcoma (MLPS), light blue columns represent de-differentiated liposarcoma (DDLPS), and dark blue columns represent well-differentiated liposarcoma (WDLPS).

Table 4. Efficacy results of the FNCLCC grade subgroups according to RECIST v1.1 (*N* = 44).

	Total	G1	G2	G3	*p* value
Best overall response, *n* (%)					
PR	8 (18.2)	0	3 (20.0)	5 (25.0)	
SD	25 (56.8)	7 (77.8)	6 (40.0)	12 (60.0)	
PD	11 (25.0)	2 (22.2)	6 (40.0)	3 (15.0)	
ORR, %	18.2	0	20.0	25.0	0.32
DCR, %	75.0	77.8	60.0	85.0	0.257

Data presented as *n* (%) unless otherwise noted; due to rounding, percentages might not total 100.
DCR, disease control rate; FNCLCC, Fédération Nationale des Centers de Lutte Contre le Cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Univariate and multivariate Cox regression analyses

Univariate and multivariate Cox regression analyses were conducted to explore the association between PFS and the patient's clinical characteristics in this study (Table 5). The results of the univariable analysis indicated that ECOG PS, stage, and TRAE grade significantly affected PFS as prognostic factors. In the multivariate analysis, ECOG PS emerged as an independent risk factor for PFS (HR = 3.66, 95% CI, 1.31–10.20, $p = 0.013$).

Discussion

This retrospective study reported a cohort of 47 RLPS patients who received combination therapy of eribulin, anlotinib, and camrelizumab. This cohort study revealed the efficacy of this combination therapy for RLPS, with an ORR of 18.2%

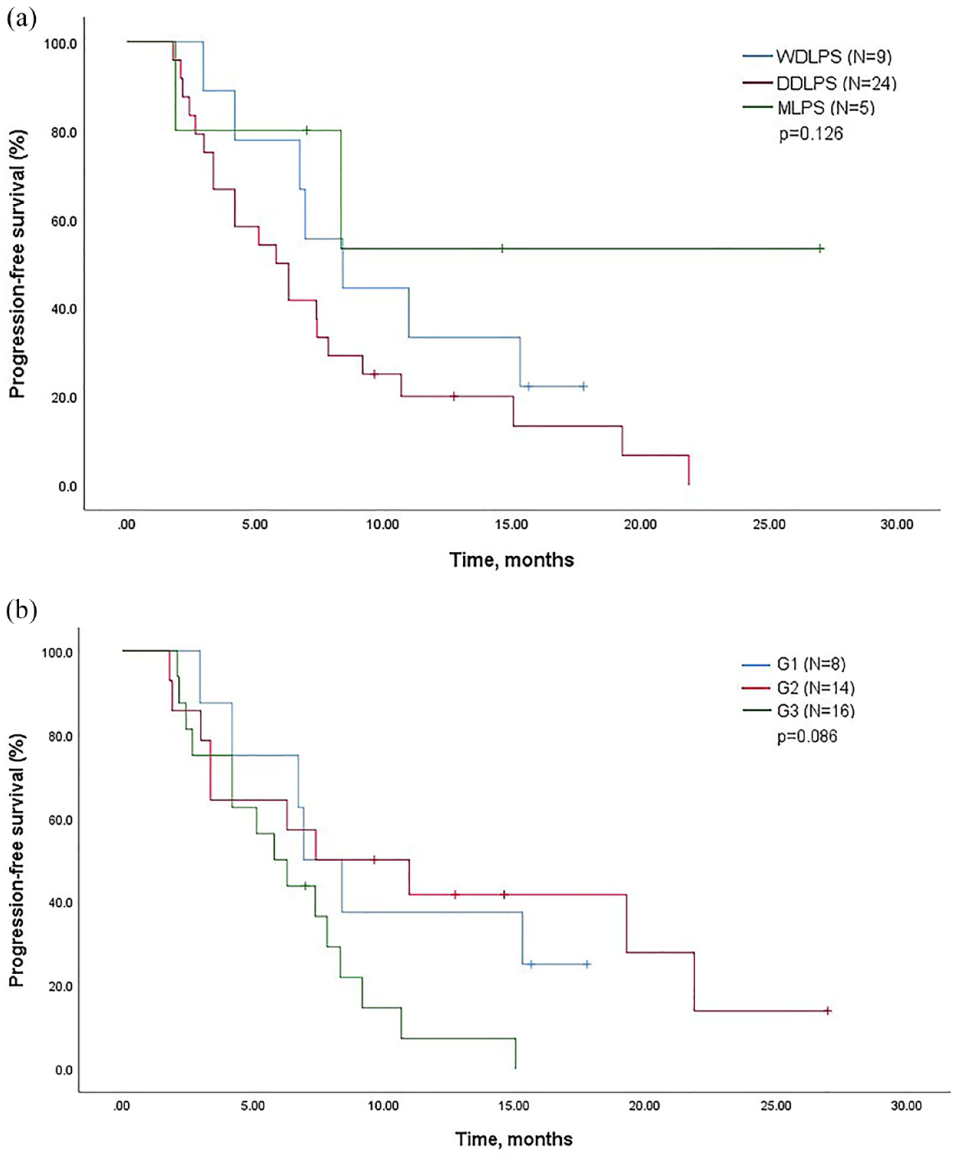

Figure 2. Kaplan–Meier curve of subgroup analysis of PFS in 38 RLPS patients who underwent combination therapy of eribulin plus anlotinib and camrelizumab. (a) PFS in subgroups of WDLPS (blue line), DDLPS (red line), and MLPS (green line) was compared, showing that the mPFS between the histologic subtypes of RLPS was no significant difference (WDLPS vs DDLPS vs MLPS: 8.4 months vs 5.8 months vs not reached, respectively; $p = 0.126$). (b) PFS in G1 (blue line), G2 (red line), and G3 (green line) RLPS were compared, and the mPFS between the different FNCLCC grade subgroups showed no significant differences (G1 vs G2 vs G3: 6.9 months vs 7.4 months vs 5.8 months, respectively; $p = 0.086$).
DDLPS, de-differentiated liposarcoma; FNCLCC, Fédération Nationale des Centres de Lutte Contre Le Cancer; MLPS, myxoid liposarcoma; mPFS, median progression-free survival; PFS, progression-free survival; RLPS, retroperitoneal liposarcoma; WDLPS, well-differentiated liposarcoma.

based on RECIST v1.1, a mPFS of 6.93 months, and a 6-month PFS rate of 60.5%. The ORR in patients with MLPS was higher than those with DDLPS and WDLPS (50% vs 17.9% vs 0%, respectively). In addition, the mPFS for the patients with WDLPS, DDLPS, and MLPS was 8.4 (95% CI, 4.1–12.7) months, 5.8 (95% CI, 3.3–8.3) months, and not reached, respectively. The study emphasized both the treatment safety profile and the patient's tolerance to TRAEs. Moreover, the minimal loss to follow-up validated the data's reliability.

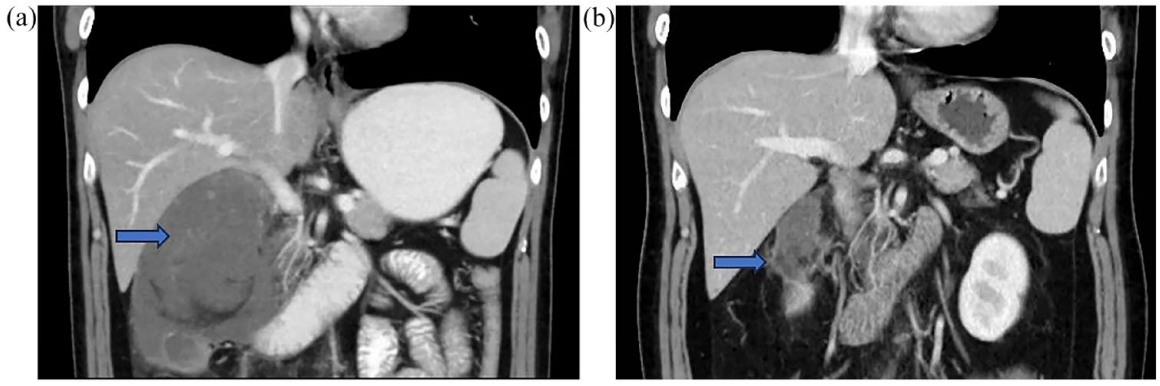

Figure 3. One patient with MLPS achieved partial response after a combination therapy of eribulin plus anlotinib and camrelizumab. (a) The baseline MLPS (blue arrow) in the retroperitoneal space, and (b) the patient maintained a partial response (blue arrow) after 21 cycles of combination treatment.
MLPS, myxoid liposarcoma.

When compared to standard chemotherapy regimens such as anthracyclines, ifosfamide, and their combinations,[12,34] our observed ORR and PFS displayed substantial improvements. In addition, our findings outperformed the outcomes reported for single-agent eribulin in the advanced LPS study, where the ORR was notably lower, and the mPFS was at 2.9 months.[16] A previous retrospective study on anlotinib and camrelizumab combined therapy showed an ORR of 13.3% in RLPS cases,[29] notably lower than our study combining these with eribulin. However, the ORRs of different histological subtypes were similar between the two studies, with WDLPS and MLPS at 0 and 50%, and DDLPS at 17.9% and 21.4%, respectively.[29] In addition, our study's results may be more reliable due to a higher sample size.

One particularly notable case in our study involved a patient diagnosed with MLPS, achieving a PR status after completing 7.5 treatment cycles and subsequently undergoing complete resection with confirmed pCR upon pathological analysis. In our study, MLPS patients exhibited an ORR of 50%, and the mPFS remained undefined after a median follow-up of 21.8 months. These findings underscored the remarkable efficacy of our treatment regimen for MLPS, a subtype recognized for its chemotherapeutic responsiveness. Several retrospective single-center studies have reported ORRs ranging from 43.2% to 48% with doxorubicin-based conventional chemotherapy in MLPS patients based on RECIST criteria.[12,35,36] In addition, another retrospective study demonstrated an ORR of 51% with trabectedin,[37] a marine-derived alkaloid known for its multifaceted mechanisms affecting critical cellular processes within tumor cells and the tumor microenvironment.[38,39] Our study highlights the effectiveness of combination therapy for MLPS. Nonetheless, larger prospective studies with more patient cohorts are required to validate these findings, particularly to explore potential survival benefits.

In our study, we analyzed to assess efficacy and safety across different eribulin dose intensities. Patients were divided into two groups: high dose (1.1–1.4 mg/m^2) and low dose (0.7–1.1 mg/m^2). The ORRs were 24.0% for the high-dose group and 10.5% for the low-dose group. Despite the higher ORR in the high-dose group, no statistically significant difference was observed ($p = 0.433$). Similarly, the DCRs were 72.0% and 78.9% for high-dose and low-dose groups, respectively, without a statistically significant difference ($p = 0.731$). For the safety analysis, 22 (78.6%) patients experienced TRAEs, with 14 (50.0%) in the high-dose group encountering grade 3 or higher TRAEs, compared to 14 (73.7%) patients and 7 (36.8%) with TRAEs and grade 3 or higher TRAEs, respectively, in the low-dose group. No significant differences were observed in the incidence rates of any TRAEs or grade 3 and higher TRAEs between the two groups ($p = 0.737$ and $p = 0.551$, respectively). Univariant Cox regression analysis revealed a trend toward longer mPFS in the high-dose group compared to the low-dose group, but this difference was not statistically significant (HR = 0.81, 95% CI, 0.39–1.69, $p = 0.571$). These findings suggest that our study's

Table 5. Univariate and multivariate Cox regression analyses of the relationship between clinicopathological parameters and PFS.

Variable	*N* (%)	mPFS (months, 95% CI)	Univariable		Multivariable	
			HR (95% CI)	*p* value	HR (95% CI)	*p* value
Gender						
Female	21 (55.3)	8.33 (6.3–NA)	Reference			
Male	17 (44.7)	5.80 (4.2–NA)	1.41 (0.69–2.88)	0.348		
Age						
<60	28 (73.7)	7.38 (5.13–15)	Reference			
⩾60	10 (26.3)	6.52 (2.67–NA)	1.27 (0.56–2.85)	0.570		
ECOG PS						
0	13 (34.2)	19.27 (6.73–NA)	Reference		Reference	
1–2	25 (65.8)	5.80 (4.2–8.33)	4.5 (4.7–12)	0.003	3.66 (1.31–10.20)	0.013
Lines of treatment						
First	30 (78.9)	7.16 (5.80–15)	Reference			
Second	8 (21.1)	5.37 (2.97–NA)	1.36 (0.58–3.20)	0.480		
Eribulin dose						
<1.1	15 (39.5)	6.93 (4.20–NA)	Reference			
⩾1.1	23 (60.5)	7.83 (5.13–19.3)	0.81 (0.39–1.69)	0.571		
Stage						
Metastatic	7 (18.4)	5.13 (0.61–9.65)	Reference		Reference	
Locally advanced	31 (81.6)	8.33 (6.42–10.24)	0.28 (0.11–0.72)	0.008	0.40 (0.15–1.04)	0.060
Grades of TRAEs						
<3	22 (57.9)	6.30 (4.20–8.33)	Reference		Reference	
⩾3	16 (42.1)	9.17 (4.20–NA)	0.40 (0.18–0.89)	0.025	0.67 (0.28–1.56)	0.349

In univariable Cox regression analysis, those with ECOG PS of 0 had a significantly longer PFS compared to those with ECOG PS of 1–2 (HR = 4.5, 95% CI, 4.7–12, $p = 0.003$); those with 3 or higher grades of TRAEs had a significantly longer PFS than those with 1–2 grades of TRAEs (HR = 0.4, 95% CI, 0.18–0.89, $p = 0.025$); those with locally advanced RLPS had a longer PFS than those with metastatic RLPS (HR = 0.28, 95% CI, 0.11–0.72, $p = 0.008$). In multivariate Cox regression analysis, ECOG PS was the independent risk factor of PFS.
CI, conference interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mPFS, median progression-free survival; PFS, progression-free survival; RLPS, retroperitoneal liposarcoma; TRAEs, treatment-related adverse events.

high-dose group demonstrated a slightly higher ORR compared to the LEADER study (24% vs 22%),[17] implying that a moderate increase in eribulin dosage might enhance therapeutic efficacy.

We further conducted a comparative analysis between two treatment regimens implemented at our center: TKI plus ICI and combination chemotherapy with TKI and ICI.[29] The observed TRAEs in our study markedly differed from those in the TKI plus ICI study. TRAEs, primarily attributed to chemotherapy, were more prevalent, including neutropenia (53.2%), anorexia (21.3%), and fatigue (19.1%), among others. Notably, chemotherapy-induced myelosuppression is a well-known and potentially fatal side effect of cancer treatment,[40] aligning with our

findings. Intriguingly, the combination therapy involving chemotherapy had a lower incidence of hypertension compared to the other group (8.5% vs 24.6%), indicating a significant statistical difference ($p = 0.031$).

Furthermore, TRAEs associated with the endocrine system were significantly lower in the chemotherapy combination, although statistical significance was not achieved (12.8% vs 26.3%, $p = 0.087$). Thus, our findings suggest that combining chemotherapy with ICI and TKI might provide a safer treatment approach for RLPS patients by mitigating the risk of adverse events from TKI or ICI. However, the limited number of relevant trials impeded a comprehensive understanding. A meta-analysis of randomized controlled trials evaluating first-line treatment options for advanced non-small-cell lung cancer revealed that most irAEs with a PD-1/PD-L1 inhibitor plus chemotherapy were less prevalent compared to a PD-1/PD-L1 inhibitor alone.[41] The immunosuppressive effects of chemotherapy might contribute to a reduced rate of irAEs,[41,42] although further elucidation of this mechanism requires additional data for validation.

In this study, several notable limitations merit consideration. First, it is essential to recognize that while ORR and PFS were explored as significant outcomes impacting treatment decisions, OS stands as the gold-standard endpoint in oncology studies. Unfortunately, our study did not reach OS. Second, this study was retrospective and sourced its patient data from a single-center cohort, potentially limiting the generalizability of the findings. Third, most of the RLPS patients in the study were locally advanced, and metastatic patients were in the minority. Thus, the result of prognoses, such as PFS and OS, might be overestimated. Fourth, the duration of follow-up was insufficient to adequately evaluate the long-term prognosis. Despite these limitations, the observed effectiveness of these drugs in treating advanced or metastatic RLPS, compared to conventional treatments, is noteworthy.

Conclusion

In conclusion, the combination therapy involving eribulin, anlotinib, and camrelizumab demonstrated promising efficacy in RLPS patients, particularly those with MLPS. Regarding safety, patients typically tolerated the combination therapy well, experiencing manageable TRAEs.

Declarations

Ethics approval and consent to participate

This study was designed following the Declaration of Helsinki, guidelines for Good Clinical Practice, and local regulations on clinical trials. Ethical approval was obtained from the Institutional Review Board of Peking University Cancer Hospital's medical ethics committee (2022KT84). All participants provided written informed consent prior to participating.

Consent for publication

Patients included in this study consented to have their study-related data published. Written informed consent was obtained from the patient or a legally authorized representative for anonymized patient information to be published in this article.

Author contributions

Weiwei Jia: Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Jianhui Wu: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Resources; Writing – original draft; Writing – review & editing.

Hongtao Zhang: Investigation; Writing – review & editing.

Yan Wu: Investigation; Validation; Writing – review & editing.

Daoning Liu: Investigation; Writing – review & editing.

Zhen Wang: Investigation; Writing – review & editing.

Xiaopeng Wang: Formal analysis; Investigation; Methodology; Writing – review & editing.

Chengpeng Li: Conceptualization; Formal analysis; Investigation; Methodology; Validation; Writing – review & editing.

Chunyi Hao: Conceptualization; Project administration; Resources; Validation; Writing – review & editing.

Acknowledgments

The authors thank all of the colleagues who contributed to this study.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or

publication of this article: This study was supported by Science Foundation of Peking University Cancer Hospital (approval No. XKFZ2421), Science Foundation of Peking University Cancer Hospital (Grant No. JC202407), Capital Health Research and Development of Special Funds (No. 2024-4-2159), Discipline Construction of Surgical Oncology (No. BMU2024XY038), Beijing Xisike Clinical Oncology Research Foundation (Grant No. Y-Young2020-0539, 2021-0111, 2022-0117), and Shandong Province Natural Science Foundation (ZR2021QH260).

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID iDs

Weiwei Jia https://orcid.org/0009-0009-7485-8679

Chunyi Hao https://orcid.org/0000-0002-1233-1689

Supplemental material

Supplemental material for this article is available online.

References

1. WHO Classification of Tumours. *Soft tissue and bone tumours*. 5th ed. Lyon (Franee): International Agency for Research on Cancer, 2020.
2. Gamboa AC, Gronchi A and Cardona K. Soft-tissue sarcoma in adults: an update on the current state of histiotype-specific management in an era of personalized medicine. *CA Cancer J Clin* 2020; 70(3): 200–229.
3. Wang J, Grignol VP, Gronchi A, et al. Surgical management of retroperitoneal sarcoma and opportunities for global collaboration. *Chin Clin Oncol* 2018; 7(4): 6.
4. Tseng WW, Seo HJ, Pollock RE, et al. Historical perspectives and future directions in the surgical management of retroperitoneal sarcoma. *J Surg Oncol* 2018; 117(1): 7–11.
5. Crago AM and Singer S. Clinical and molecular approaches to well differentiated and dedifferentiated liposarcoma. *Curr Opin Oncol* 2011; 23(4): 373–378.
6. Tan MC, Brennan MF, Kuk D, et al. Histology-based classification predicts pattern of recurrence and improves risk stratification in primary retroperitoneal sarcoma. *Ann Surg* 2016; 263(3): 593–600.
7. Thway K. Well-differentiated liposarcoma and dedifferentiated liposarcoma: an updated review. *Semin Diagn Pathol* 2019; 36(2): 112–121.
8. Gronchi A, Strauss DC, Miceli R, et al. Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS): a report on 1007 patients from the multi-institutional collaborative RPS working group. *Ann Surg* 2016; 263(5): 1002–1009.
9. Henricks WH, Chu YC, Goldblum JR, et al. Dedifferentiated liposarcoma: a clinicopathological analysis of 155 cases with a proposal for an expanded definition of dedifferentiation. *Am J Surg Pathol* 1997; 21(3): 271–281.
10. Singer S, Antonescu CR, Riedel E, et al. Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma. *Ann Surg* 2003; 238(3): 358–370; discussion 370–371.
11. Setsu N, Miyake M, Wakai S, et al. Primary retroperitoneal myxoid liposarcomas. *Am J Surg Pathol* 2016; 40(9): 1286–1290.
12. Jones RL, Fisher C, Al-Muderis O, et al. Differential sensitivity of liposarcoma subtypes to chemotherapy. *Eur J Cancer* 2005; 41(18): 2853–2860.
13. Gebhard S, Coindre JM, Michels JJ, et al. Pleomorphic liposarcoma: clinicopathologic, immunohistochemical, and follow-up analysis of 63 cases: a study from the French Federation of Cancer Centers Sarcoma Group. *Am J Surg Pathol* 2002; 26(5): 601–616.
14. Creytens D, Folpe AL, Koelsche C, et al. Myxoid pleomorphic liposarcoma-a clinicopathologic, immunohistochemical, molecular genetic and epigenetic study of 12 cases, suggesting a possible relationship with conventional pleomorphic liposarcoma. *Mod Pathol* 2021; 34(11): 2043–2049.
15. Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet* 2016; 387(10028): 1629–1637.
16. Demetri GD, Schöffski P, Grignani G, et al. Activity of eribulin in patients with advanced

liposarcoma demonstrated in a subgroup analysis from a randomized phase III study of eribulin versus dacarbazine. *J Clin Oncol* 2017; 35(30): 3433–3439.

17. Chen TW, Hsu CL, Hong RL, et al. A single-arm phase Ib/II study of lenvatinib plus eribulin in advanced liposarcoma and leiomyosarcoma. *Clin Cancer Res* 2022; 28(23): 5058–5065.
18. Xie C, Wan X, Quan H, et al. Preclinical characterization of anlotinib, a highly potent and selective vascular endothelial growth factor receptor-2 inhibitor. *Cancer Sci* 2018; 109(4): 1207–1219.
19. Shen G, Zheng F, Ren D, et al. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. *J Hematol Oncol* 2018; 11(1): 120.
20. Chi Y, Fang Z, Hong X, et al. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft-tissue sarcoma. *Clin Cancer Res* 2018; 24(21): 5233–5238.
21. Xu B, Pan Q, Pan H, et al. Anlotinib as a maintenance treatment for advanced soft tissue sarcoma after first-line chemotherapy (ALTER-S006): a multicentre, open-label, single-arm, phase 2 trial. *EClinicalMedicine* 2023; 64: 102240.
22. D'Angelo SP, Shoushtari AN, Agaram NP, et al. Prevalence of tumor-infiltrating lymphocytes and PD-L1 expression in the soft tissue sarcoma microenvironment. *Hum Pathol* 2015; 46(3): 357–365.
23. Pollack SM, He Q, Yearley JH, et al. T-cell infiltration and clonality correlate with programmed cell death protein 1 and programmed death-ligand 1 expression in patients with soft tissue sarcomas. *Cancer* 2017; 123(17): 3291–3304.
24. Petitprez F, de Reyniès A, Keung EZ, et al. B cells are associated with survival and immunotherapy response in sarcoma. *Nature* 2020; 577(7791): 556–560.
25. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol* 2017; 18(11): 1493–1501.
26. Fukumura D, Kloepper J, Amoozgar Z, et al. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol* 2018; 15(5): 325–340.
27. Khan KA and Kerbel RS. Improving immunotherapy outcomes with anti-angiogenic treatments and vice versa. *Nat Rev Clin Oncol* 2018; 15(5): 310–324.
28. You Y, Guo X, Zhuang R, et al. Activity of PD-1 inhibitor combined with anti-angiogenic therapy in advanced sarcoma: a single-center retrospective analysis. *Front Mol Biosci* 2021; 8: 747650.
29. Wu J, Li C, Liu B, et al. Efficacy and safety of anlotinib plus camrelizumab in treating retroperitoneal soft tissue sarcomas: a single-center retrospective cohort study. *Ann Transl Med* 2023; 11(5): 212.
30. Wu J, Hao C, Jia W, et al. Efficacy and safety of eribulin plus anlotinib and camrelizumab in advanced or metastatic retroperitoneal liposarcoma (RLPS) or leiomyosarcoma (RLMS): a singlecenter retrospective cohort study. *Ann Oncol* 2023; 34: S1043.
31. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45(2): 228–247.
32. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg* 2014; 12(12): 1495–1499.
33. Stoeckle E, Coindre JM, Bonvalot S, et al. Prognostic factors in retroperitoneal sarcoma: a multivariate analysis of a series of 165 patients of the French Cancer Center Federation Sarcoma Group. *Cancer* 2001; 92(2): 359–368.
34. Italiano A, Toulmonde M, Cioffi A, et al. Advanced well-differentiated/dedifferentiated liposarcomas: role of chemotherapy and survival. *Ann Oncol* 2012; 23(6): 1601–1607.
35. Katz D, Boonsirikamchai P, Choi H, et al. Efficacy of first-line doxorubicin and ifosfamide in myxoid liposarcoma. *Clin Sarcoma Res* 2012; 2(1): 2.
36. Patel SR, Burgess MA, Plager C, et al. Myxoid liposarcoma. Experience with chemotherapy. *Cancer* 1994; 74(4): 1265–1269.
37. Grosso F, Jones RL, Demetri GD, et al. Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study. *Lancet Oncol* 2007; 8(7): 595–602.
38. Larsen AK, Galmarini CM and D'Incalci M. Unique features of trabectedin mechanism of action. *Cancer Chemother Pharmacol* 2016; 77(4): 663–671.
39. Cuevas C and Francesch A. Development of Yondelis (trabectedin, ET-743). A semisynthetic

process solves the supply problem. *Nat Prod Rep* 2009; 26(3): 322–337.

40. Maxwell MB and Maher KE. Chemotherapy-induced myelosuppression. *Semin Oncol Nurs* 1992; 8(2): 113–123.

41. Wang M, Liang H, Wang W, et al. Immune-related adverse events of a PD-L1 inhibitor plus chemotherapy versus a PD-L1 inhibitor alone in first-line treatment for advanced non-small cell lung cancer: a meta-analysis of randomized control trials. *Cancer* 2021; 127(5): 777–786.

42. Mackall CL, Fleisher TA, Brown MR, et al. Distinctions between CD8+ and CD4+ T-cell regenerative pathways result in prolonged T-cell subset imbalance after intensive chemotherapy. *Blood* 1997; 89(10): 3700–3707.