



# Efficacy of PD-1 inhibitors combined with pegylated liposomal doxorubicin and dacarbazine compared with liposomal doxorubicin and dacarbazine in advanced leiomyosarcoma patients: a retrospective, single-institutional cohort study

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**Background:** PD-1 inhibitor monotherapy is ineffective for metastatic leiomyosarcoma (LMS), but it remains unclear whether PD-1 inhibitors demonstrate any efficacy when combined with chemotherapy. This study retrospectively evaluated pegylated liposomal doxorubicin (PLD) and dacarbazine (DTIC) with/without PD-1 inhibitors for advanced/metastatic LMS patients treated in our single institution.

**Methods:** The inclusion criteria were a confirmed histological diagnosis of LMS, treatment between January 2020 and March 2022, measurable disease (evaluated by CT or MRI), an Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ , and age  $\geq 18$  years. The endpoints were progression-free survival (PFS), overall survival (OS), and overall response rate (ORR).

**Results:** A total of 41 patients were included in this study, among whom 21 received PLD and DTIC alone while 20 received PLD and DTIC with PD-1 inhibitors. There were no differences of clinical characteristics between the two groups. Although the chemo plus PD-1 group had a better ORR (30% *vs.* 4.8%,  $P=0.04$ ), there were no benefits in terms of disease control rate (DCR) (80% *vs.* 66.7%,  $P=0.29$ ), PFS (8.8 months, 95% CI: 4.57–13.0 *vs.* 6.1 months, 95% CI: 3.03–9.14,  $P=0.54$ ), and OS (not reached in both groups,  $P=0.84$ ) when compared to chemo alone. Multiple treatment lines and previous use of tyrosine kinase inhibitors (TKIs) seemed to be negative factors for PFS in the univariate analysis, but failed to be significant in the multivariate analysis.

**Conclusions:** This retrospective, single-institutional study showed that PD-1 inhibitors combined with standard PLD and DTIC chemotherapy failed to exert benefits on survival for LMS patients. Considering the small sample size and retrospective clinical research design, further explorations are needed to verify the conclusion.

**Keywords:** Leiomyosarcoma (LMS); PD-1; chemotherapy; immunotherapy

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## Introduction

Leiomyosarcoma (LMS) is one of the most common histotypes in the heterogeneous soft tissue sarcoma (STS) family, which accounts for approximately 10% to 20% of all STS cases (1). This tumor may arise from any location of the body, including the extremities, abdomen, retroperitoneum, blood vessels, and the uterus. It is a clinically aggressive neoplasm with a metastatic rate of 40–45% (2). For unresectable metastatic LMS, chemotherapy is still the first-line treatment. Despite discrepant clinical responses being observed among different primary tumor origins in some clinical trials (3-5), current available data do not support preferential selection of specific conventional substances based on the primary location (6).

Doxorubicin-based and gemcitabine-based regimens are considered the preferred regimens for metastatic LMS. Dacarbazine (DTIC) has been shown to be an effective compound for combination therapy, as a European Organization for Research and Treatment of Cancer (EORTC)-conducted retrospective analysis showed that doxorubicin plus DTIC had favorable activity over doxorubicin monotherapy and doxorubicin plus ifosfamide in untreated advanced or metastatic LMS (7). However, combination therapy is not necessarily superior to monotherapy. The randomized phase III GeDDiS trial compared the efficacy of doxorubicin monotherapy with gemcitabine/docetaxel combination therapy and reported no superiority of combination therapy either in the whole group or the LMS subgroup (8). Another randomized phase II study also demonstrated that trabectedin was unable to act as an effective combination compound with doxorubicin for untreated metastatic LMS patients (9). The LMS03 study, which was designed to assess the efficacy and tolerance of gemcitabine plus pazopanib, also failed to show that the addition of pazopanib was beneficial for advanced LMS patients as a second-line therapy (10).

Since the attempts to explore an effective combination compound for doxorubicin have failed for most cytotoxic agents and angiogenesis inhibitors, attention has been paid to immune checkpoint inhibitors (ICIs). Although the phase II trial SARC028 found that LMS patients did not benefit from pembrolizumab monotherapy (11), a phase I/II trial combining avelumab and trabectedin for advanced liposarcoma and LMS revealed that better progression-free survival (PFS) was observed compared to prior studies of trabectedin alone (12). There is also a previous case reporting successful treatment of a refractory LMS patient

with nivolumab (13).

Because of the uncertainty in this field and the lack of prospective controlled studies, we collected a retrospective series of patients with advanced/metastatic LMS who were treated with pegylated liposomal doxorubicin (PLD)/DTIC plus PD-1 inhibitors in our single institution. This study aims to evaluate the efficacy of PD-1 inhibitors when added to the PLD/DTIC regimen in LMS. We present the following article in accordance with the STROBE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3963/rc>).

## Methods

### *Participants*

The data of patients with advanced/metastatic LMS who presented to our institution between January 2020 and March 2022 were collected retrospectively. Clinicopathological characteristics including age, gender, primary tumor site, tumor grades, metastatic sites, number of previous treatment lines and regimens, and dose and cycles of regimens received in our institution were collected. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Peking University Cancer Hospital (approval No. 2019YZJ78-GZ01), and informed consent was obtained from all the patients.

### *Assessment*

The therapeutic decisions were made by their primary oncologist and the patients jointly. Patients who participated in other clinical trials were excluded. The inclusion criteria were as follows: patients over 18 years, Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ , pathologically proven LMS, patients who received at least 1 cycle of treatment, and those with a measurable disease at diagnosis. Screening examinations including physical examination, basic imaging, electrocardiography, and blood tests were performed before treatments started. The exclusion criteria were: insufficient bone marrow reserve, impairment of heart/liver/kidney function, brain metastasis, a second primary malignancy, and poor performance status. Chemotherapy was administered every 3 weeks. There were different types of PD-1 inhibitors available in our institution, including pembrolizumab, toripalimab, and sintilimab. Patients made their choice of PD-1 inhibitor

type based on their insurance status and consultation with their oncologist.

### Follow-up

The Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) were used to evaluate the treatment response. CT or MRI was performed every 2–3 cycles to determine the tumor status. Treatment was continued until disease progression, intolerable side effects, or refusal by the patient. Newer agents including anlotinib, eribulin, or gemcitabine were administered after progressive disease was observed.

### Statistical analysis

Statistical analysis was performed using SPSS software (version 25, SPSS, Inc., Chicago, USA). Continuous variables were reported as median and range. Qualitative variables were compared with chi-square and Fisher's exact tests. PFS was defined as the time from commencing

chemotherapy to either first disease progression or death due to any cause. Overall survival (OS) was defined as the time from commencing chemotherapy to death due to any cause. The Kaplan-Meier method was used to generate survival curves. When analyzing risk factors for PFS and OS, the Cox model was employed to obtain the odds ratio (OR). Tests were 2-sided. A P value <0.05 was accepted as statistically significant.

### Results

We identified 60 patients with metastatic or locally advanced LMS. A total of 19 patients were excluded from this study for receiving regimens including ifosfamide, gemcitabine, or tyrosine kinase inhibitors (TKIs). The remaining 41 patients received the same chemotherapy regimen including PLD and DTIC, with or without PD-1 inhibitors. The regimen consisted of PLD 30–40 mg/m<sup>2</sup> and DTIC 1 g/m<sup>2</sup> intravenously on day 1 every 3 weeks. The clinical and therapeutic characteristics are described in *Table 1*. There were no clinical differences between the two groups. There

**Table 1** Population characteristics

Characteristics	Full population	Chemotherapy alone (n=21)	Chemotherapy plus PD-1 (n=20)	P value
Age at diagnosis, years				0.64
Median	53	54	52.5	
Range	28–73	36–73	28–64	
Gender, N (%)				0.35
Male	7 (17.1)	3 (14.3)	4 (20.0)	
Female	34 (82.9)	18 (85.7)	16 (80.0)	
Site of primary tumor, N (%)				0.4
Uterus	19 (46.3)	10 (47.6)	9 (45.0)	
Extremities	2 (4.9)	2 (9.5)	0	
Trunk	5 (12.2)	3 (14.3)	2 (10.0)	
Retroperitoneal or intraperitoneal cavity	12 (29.3)	5 (23.8)	7 (35.0)	
Thoracic cavity	2 (4.9)	1 (4.8)	1 (5.0)	
NA	1 (2.4)	0	1 (5.6)	
Grade (FNCLCC), N (%)				0.43
2	6 (14.6)	3 (14.3)	3 (15.0)	
3	13 (31.7)	8 (38.1)	5 (25.0)	
NA	22 (53.7)	10 (47.6)	12 (60.0)	

**Table 1** (continued)

Table 1 (continued)

Characteristics	Full population	Chemotherapy alone (n=21)	Chemotherapy plus PD-1 (n=20)	P value
Tumor extent, N (%)				0.48
Locally advanced	2 (4.9)	2 (9.5)	0	
Metastatic	39 (95.1)	19 (90.5)	20 (100.0)	
Metastatic site, N (%)				0.91
Lung	28 (68.3)	14 (66.7)	14 (70.0)	
Liver	10 (24.4)	4 (19.0)	6 (30.0)	
Bone	7 (17.1)	3 (14.3)	4 (20.0)	
Trunk or extremities	5 (12.2)	2 (9.5)	3 (15.0)	
Intraperitoneal organs or peritoneum	5 (12.2)	3 (14.3)	2 (10.0)	
Lymph node	1 (2.4)	1 (4.8)	0	
Treatment line, N (%)				0.26
1	30 (73.2)	17 (81.0)	13 (65.0)	
≥2	11 (26.8)	4 (19.0)	7 (35.0)	
Previous use of TKIs, N (%)				0.61
Yes	5 (12.2)	2 (9.5)	3 (15.0)	
No	36 (87.8)	19 (90.5)	17 (85.0)	
Dose of PLD per cycle (mg)				0.73
Median	60	60	60	
Range	40–80	40–80	60–80	
Dose of DTIC per cycle (g)				0.12
Median	1.6	1.4	1.6	
Range	1.0–2.0	1.0–2.0	1.0–2.0	
Total No. of cycles				0.22
Median	4	3	5.5	
Range	1–12	1–12	2–9	
Dose reduction, N (%)				0.59
Yes	3 (7.3)	2 (9.5)	1 (5.0)	
No	38 (92.7)	19 (90.5)	19 (95.0)	

NA, not available; FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; TKI, tyrosine kinase inhibitor; PLD, pegylated liposomal doxorubicin; DTIC, dacarbazine.

were 21 patients who received chemo alone versus 20 patients who received chemo + PD-1. Characteristics were similar among the 2 groups. At the time of analysis, the overall median follow-up was 5.4 months. The median numbers of administered cycles were 4, 3, and 5.5 for the whole population, the chemo group, and the chemo plus PD-1

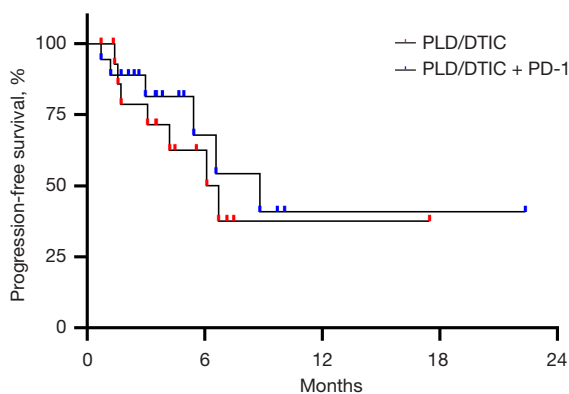
group, respectively.

Although no complete response (CR) was observed, the partial response (PR) and stable disease (SD) rates were 17.1% and 56.1%, respectively. The overall response rate (ORR) and disease control rate (DCR) were 17.1% and 73.2%, respectively. The chemo plus PD-1 group had a

**Table 2** Response analysis

	Chemo alone (n=21)	Chemo + PD-1 (n=20)
CR	0	0
PR	1 (4.8)	6 (30.0)
SD	13 (61.9)	10 (50.0)
PD	6 (28.6)	3 (15.0)
NA	1 (4.8)	1 (5.0)

Data were shown as N (%). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, evaluation not available.



**Figure 1** Progression-free survival. PLD, pegylated liposomal doxorubicin; DTIC, dacarbazine.

higher ORR and DCR compared to the chemo alone group, and the difference demonstrated statistical significance in ORR (30% *vs.* 4.8%,  $P=0.04$ ) but not in DCR (80% *vs.* 66.7%,  $P=0.29$ ), as shown in *Table 2*.

As for survival, the median PFS rates for the whole, the chemo alone, and the chemo plus PD-1 group were 6.7 (95% CI: 3.93–9.4) months, 6.1 (95% CI: 3.03–9.14) months, and 8.8 (95% CI: 4.57–13.0) months, respectively. No difference in PFS ( $P=0.54$ ) was observed between the 2 subgroups (*Figure 1*). Only 2 deaths were observed during the follow-up, with 1 in the chemo group and the other in the chemo plus PD-1 group. The median OS was not reached for either the whole population or the subgroups. No difference in OS ( $P=0.84$ ) was observed.

None of the factors including age, gender, primary tumor site, tumor grade, tumor extent, metastatic site, and previous use of doxorubicin-based regimens appeared no predictive value for neither PFS or OS. However, in the univariate

analysis, second or later line treatment and previous use of TKIs showed a poorer prognosis in PFS compared with first-line treatment (median PFS: 3.0 months *vs.* not reached, HR 0.30, 95% CI: 0.10–0.89) and no previous use of TKIs (median PFS: 8.8 *vs.* 1.73 months, HR 0.14, 95% CI: 0.03–0.64; *Figure S1A,S1B*). However, the 2 factors failed to show further predictive value in the multivariate analysis.

## Discussion

To our knowledge, there has been no published study reporting the viability of combining standard chemotherapy and PD-1 inhibitors in LMS patients. Despite the limitations of this retrospective study, we observed that although a higher ORR could be achieved (chemo + PD-1 30% *vs.* 4.8% chemo alone), the addition of PD-1 inhibitors did not prolong PFS. PD-1 monotherapy for LMS was proven to be ineffective in the phase II trial conducted by Ben-Ami *et al.*, which was stopped early for futility (14), and this was further confirmed by the SARC028 trial as LMS was found to be one of the least sensitive histologic subtypes (11). The combination of PD-1 inhibitors and TKIs was also investigated previously. In a phase 2 trial assessing the efficacy of axitinib plus pembrolizumab in patients with advanced sarcomas, 4 uterine LMS and 2 non-uterine LMS patients were enrolled. Only 1 PR and 1 minor response (decrease in the size of the target lesion of less than 30%) were observed in these 6 patients (15). A retrospective study, which included 20 LMS patients among 61 who received PD-1 and TKIs, suggested that LMS patients had the lowest response rate compared with other subtypes, and rapid progression could occur if PD-1 monotherapy was administered (16). As for PD-1 combination chemotherapy, a phase II study recruiting 15 LMS patients among 57 patients who received intravenous pembrolizumab and oral cyclophosphamide reported that the 6-month non-progression rate was 0% for LMS, but we considered the efficacy of this result limited as oral cyclophosphamide is not a standard regimen for LMS (17).

Several cases reported satisfying outcomes of LMS after PD-1 treatment, all of which had positive PD-1/PD-L1 expression (13,18). However, PD-1/PD-L1 expression may not serve as a sole predictor for PD-1 therapy in LMS. Pollack *et al.* selected 81 STS samples, in which 19 LMS samples were included. Analysis of PD-1 and PD-L1 expression was conducted, and the results showed that the PD-1 and PD-L1 positive rates were 88% and 59%, respectively, in LMS (19). Another study on PD-

L1 expression in uterine smooth muscle tumors enrolled 23 LMS patients, of whom 70% were PD-L1 positive and 65% had a PD-L1 combined positive score (CPS)  $\geq 1$  (20). This controversy in laboratory results and clinical responses remains to be clearly explained. One possible explanation is the high frequency of PTEN loss in LMS (21,22). PTEN is a tumor suppressor gene, and its loss correlates with decreased T-cell infiltration in tumor sites, reduced T-cell expansion, and negative outcomes for ICI responses in multiple tumors (23-25). A study collected tumor samples from a treatment-naïve metastatic LMS patients who had experienced complete tumor regression for >2 years on pembrolizumab monotherapy. The primary tumor and the treatment-resistant metastasis both stained diffusely for PD-L2 and sparsely for PD-L1, but the treatment-resistant metastasis harbored biallelic PTEN loss uniquely (26). These results might be evidence that PTEN loss results in the resistance to ICIs in LMS.

In the univariate analysis, only multiple treatment lines and previous use of TKIs were found to be predictive factors of PFS, and the latter showed worse prognosis (HR: 0.30 vs. 0.14). In contrast, previous use of doxorubicin-based regimens was not a significant factor ( $P=0.37$ ). Multiple mechanisms of TKI resistance have been intensely investigated in lung cancer, including the activation of the c-MET signaling pathway, MET amplification, and MET overexpression, which upregulate PD-L1 expression and promote the immune escape of tumor cells (27). Chemotherapy and immunotherapy were thought to be promising alternatives when TKI resistance occurred in non-small cell lung cancer (28,29). However, in sarcoma, evidence for further therapy choice was limited if TKI resistance occurred. A small-sample, retrospective study investigated the efficacy of rechallenge with multi-targeted TKIs in advanced sarcoma patients who progressed after initial TKI treatment. The benefit was not promising as the response rate was 0% and the PFS was only 3.3 months (30). Despite failing to show predictive value in the multivariate analysis in our study, this result reminds us of the potential risk for survival and the lack of evidence for selectable regimens after TKI resistance in sarcoma.

We have to acknowledge several limitations in this study. First, as a retrospective, single-institution study, selection bias was inevitable. Second, the study population was heterogeneous: the upfront treatment lines and regimens were not uniform, and imbalances might exist between the 2 subgroups. Furthermore, the small sample size and relatively short follow-up restricted the validity of our

results.

In conclusion, our study shows that PD-1 inhibitors combined with standard PLD and DTIC chemotherapy failed to exert benefits on survival for LMS patients.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3963/rc>

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*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). The study was approved by the ethics committee of Peking University Cancer Hospital (approval No. 2019YZJ78-GZ01), and informed consent was obtained from all the patients.

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