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REVIEW

Combination of immune checkpoint inhibitors and anthracyclines as a potential first-line regimen for dedifferentiated liposarcoma: systematic review and meta-analysis

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Abstract

Introduction Dedifferentiated liposarcoma (DDLPS) is a rare and aggressive subtype of soft tissue sarcoma, characterized by limited treatment options and poor prognosis. Despite surgical resection being the only potentially curative treatment for localized DDLPS, the recurrence rate remains high, and systemic chemotherapy, typically anthracycline-based, shows limited efficacy in advanced stages. While immune checkpoint inhibitors (ICIs) have shown promise in various sarcoma subtypes, including DDLPS, their role as a first-line treatment remains unclear.

Methods We conducted a systematic meta-analysis to evaluate the efficacy of ICIs in treating patients with DDLPS. A total of 25 studies encompassing 245 patients were included. Data on overall response rate (ORR), progression-free survival, and grade III–V treatment-related adverse events were analyzed. We assessed treatment efficacy based on the line of therapy and treatment regimens, including ICI monotherapy, dual ICI therapy, and ICI combinations with other modalities.

Results The pooled ORR for all ICI-based treatments was 7%. First-line ICI therapy yielded a significantly higher ORR of 22%, compared to 4% in later-line treatment. The combination of ICI with anthracyclines demonstrated the highest ORR of 52%. In contrast, ICI regimens combined with trabectedin or other agents showed limited efficacy. Sensitivity analysis confirmed the stability of results, and publication bias was not detected.

Conclusion This meta-analysis supports the potential role of ICIs, particularly in combination with anthracyclines, as a first-line therapeutic strategy for DDLPS. These results provide a foundation for future prospective studies aimed at optimizing immunotherapy approaches for this rare and challenging malignancy.

Keywords Dedifferentiated liposarcoma · Immune checkpoint inhibitors · Meta-analysis immunotherapy

Abbreviations

ASPS	Alveolar soft part sarcoma
CI	Confidence intervals
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
DDLPS	Dedifferentiated liposarcoma
ICB	Immune checkpoint blockade
ICI	Immune checkpoint inhibitor
LPS	Liposarcoma
MINORS	Methodological index for non-randomized studies

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MLPS	Myxoid liposarcoma
MPLPS	Myxoid pleomorphic liposarcoma
MSI	Microsatellite instability
NSCLC	Non-small-cell lung cancer
OR	Odds ratios
ORR	Overall response rate
OS	Overall survival
PD-1	Programmed cell death protein 1
PFS	Progression-free survival
PLPS	Pleomorphic liposarcoma
RFS	Recurrence-free survival
STS	Soft tissue sarcoma
TLS	Tertiary lymphoid structures
TMB	Tumor mutational burden
TRAE	Treatment-related adverse events
WDLPS	Well-differentiated liposarcoma
WHO	World Health Organization

Introduction

Soft tissue sarcomas (STSs) represent a heterogeneous group of malignancies arising from mesenchymal tissues, including muscle, fat, blood vessels, nerves, and tendons [1]. According to the 2020 World Health Organization (WHO) classification, bone tumors and STSs comprise over 100 distinct pathological entities, many of which are ultrarare with incidences of less than 1 per million [2].

Liposarcoma (LPS) is a rare and heterogeneous malignancy of adipocytic origin. It remains the most prevalent histologic subtype of soft tissue sarcoma (STS), accounting for approximately 20% of all cases [3]. Based on the 2020 WHO Classification of Soft Tissue Tumours, LPS is categorized into five subtypes: well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma (MLPS), pleomorphic liposarcoma (PLPS), and myxoid pleomorphic liposarcoma (MPLPS) [4]. DDLPS, which accounts for the majority of liposarcomas, most often occurs in the retroperitoneum. Both WDLPS and DDLPS are nontranslocation-associated sarcomas characterized by the amplification of genes on chromosome 12q13–15, particularly MDM2 and CDK4 [5, 6].

For patients with localized DDLPS—whether arising in the retroperitoneum or the extremities—surgical resection remains the only potentially curative treatment option [7]. However, even after complete macroscopic resection, the disease is marked by a local recurrence rate of up to 70% at 5 years [8] and a metastatic rate ranging from 15 to 30% [9]. Comprehensive analyses further indicate that patients with DDLPS experience the poorest long-term outcomes among liposarcoma subtypes, with 5- and 10-year survival rates of approximately 50% and 35%, respectively [10, 11].

For advanced or metastatic disease, systemic chemotherapy, typically an anthracycline-based regimen, remains the standard first-line treatment, despite its limited efficacy [12]. For example, a randomized controlled trial in STS demonstrated a response rate of 14% for doxorubicin monotherapy compared to 26% for a combination of doxorubicin and ifosfamide, though without a corresponding improvement in overall survival [13–15]. Second-line treatment options, including regimens such as gemcitabine plus docetaxel, trabectedin, and eribulin, have yielded only modest benefits. Moreover, multi-tyrosine kinase inhibitors have repeatedly failed to show clinical benefit in DDLPS across multiple trials [16–18].

The role of radiotherapy in managing DDLPS, particularly for retroperitoneal tumors, remains controversial. The recent EORTC-STRASS trial, which randomized 266 patients with primary resectable retroperitoneal sarcoma to receive either preoperative radiotherapy (50.4 Gy) followed by surgery or surgery alone, found no significant improvement in abdominal recurrence-free survival with the addition of radiotherapy [19]. Although post hoc analyses suggested a potential benefit for low-grade LPS, high-grade DDLPS did not show a similar advantage, reaffirming that complete surgical resection remains the cornerstone of treatment for retroperitoneal sarcomas [20]. These challenges underscore the pressing need for more effective therapeutic strategies for DDLPS.

Over the past decade, immune checkpoint blockade (ICB) has revolutionized cancer therapy [21]. Certain sarcomas, such as alveolar soft part sarcoma (ASPS), have shown exceptional responses to ICB, leading to the US Food and Drug Administration approving first-line PD-L1 inhibitors for ASPS [22]. Emerging evidence also suggests that ICB agents targeting programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) may be active in metastatic DDLPS. In the multicenter, prospective SARC028 trial investigating pembrolizumab in advanced soft tissue and bone sarcomas—including DDLPS, leiomyosarcoma, undifferentiated pleomorphic sarcoma, synovial sarcoma, Ewing sarcoma, osteosarcoma, and chondrosarcoma—objective responses were observed only in patients with DDLPS and undifferentiated pleomorphic sarcoma [23]. In addition, some studies have shown that ICBs have no obvious adverse effects [24]. Despite these promising signals, the intrinsic heterogeneity of STS has meant that most clinical trials to date have enrolled mixed histologies, and dedicated prospective studies exclusively focusing on ICB in DDLPS remain lacking [25, 26].

In light of these challenges and the emerging role of immunotherapy, the objective of our study is to systematically evaluate the efficacy of ICIs in patients with DDLPS. By comprehensively reviewing the available literature—including 25 studies encompassing 245 patients—we aim

to elucidate the overall response rate (ORR) and the differential efficacy observed among various ICI regimens (e.g., ICI monotherapy, dual ICI therapy, ICI combined with anthracyclines, ICI plus trabectedin, and ICI with other agents) as well as the impact of treatment line. We hope that our findings will provide critical insights into the role of ICIs in DDLPS and guide future clinical research in this understudied malignancy.

Methods

Data sources and search strategy

We obtained all relevant data for this study from the PubMed, EMBASE, and Cochrane Library databases. In addition, we incorporated the latest unpublished clinical trial data on ICI treatment for LPS presented at international conferences such as the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO). A comprehensive search was conducted across these databases, covering all records published up to February 8, 2025. The search strategy utilized keywords related to "liposarcoma" and "checkpoint inhibitors" (for a detailed description of the search strategy, please refer to the Supplementary Data). This meta-analysis was registered in INPLASY (registration no. INPLASY202520047).

Inclusion and exclusion criteria

Inclusion criteria

Full-text articles were screened according to the following criteria to identify studies for inclusion in the meta-analysis:

i. Articles must be published in English.
ii. The primary study subjects must be patients with histologically confirmed LPS, excluding those with MLPS, PLPS, and MPLPS.
iii. Clinical trials evaluating ICIs that provided ORR were included, regardless of randomization status. ICIs could be administered as monotherapy or in combination with other therapeutic modalities (e.g., radiotherapy, chemotherapy, surgery, or targeted therapy).

Exclusion criteria

The exclusion criteria were as follows:

i. Studies that did not address the key outcomes relevant to this meta-analysis.
ii. Non-original research articles, including case reports, reviews, letters, or editorials.
iii. Studies with overlapping or repeating data.
iv. Retrospective studies or cohort studies.
v. Studies that, at the design phase, exclusively enroll patients based on a specific biomarker positivity (e.g., only high TMB or PD-L1 positive patients).

Data extraction and quality assessment

Three researchers (ABZ, XZ, and WGL) individually examined the eligible studies and evaluated their risk of bias. Any differences in opinion were settled either through discussion or, if needed, by involving a designated arbitrator (WGL). The data were directly obtained from the included articles and conference abstracts. In addition, the parameters were extracted in a uniform format, including first author, year of publication, sample size, ClinicalTrials.gov identifier, accepted line of therapy, medications of intervention, primary endpoint, and outcome. Since the majority of the relevant studies were single-arm clinical studies, the methodological index for non-randomized studies (MINORS) checklist was used to assess the quality of the included studies. Each item was scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate), with the global ideal score being 16 for non-comparative studies and 24 for comparative studies [27].

The primary outcome was the efficacy of ICIs in the treatment of LPS, as measured by the ORR. The secondary outcomes included progression-free survival (PFS), and the incidence of grade III–V treatment-related adverse events (TRAE).

Statistical analysis

All statistical analyses were performed using STATA version 15.1 (STATA, College Station, TX, USA). The meta-analysis of the non-comparative binary outcomes was suitable for the included studies, which were single-arm clinical trials [28]. The metaprop command was used to perform the meta-analysis, pooling data to calculate odds ratios (OR) and 95% confidence intervals (CI), and generating a forest plot for visualization. A Q test with $P > 0.05$ or $I^2 < 50\%$ indicated that there was no significant heterogeneity among the studies, so a fixed-effect model was adopted; otherwise, a random-effects model was used [29, 30]. Subgroup analyses were conducted based on accepted line of therapy (0 or ≥ 1), medications of intervention (ICI monotherapy, dual ICI therapy, ICI combined with anthracyclines, ICI combined with trabectedin, and ICI combined with other treatments), and grade III–V TRAE (%). Sensitivity analysis was performed using the metainf command to assess the reliability of the data. Publication bias was assessed by Begg's and Egger's linear regression test, and visualization by funnel plot [31, 32]. $P < 0.05$ was considered statistically significant.

Result

Study selection

This review included 25 articles, corresponding to 23 clinical trials shown in Table 1. The selection process is shown in the PRISMA flow diagram (Fig. 1). Of these, three articles reported phase I studies [33–35]. Additionally, three studies were phase I/II trials [36–38], and 19 articles were phase II studies, which included three randomized controlled trials with two treatment arms [39–41] and 16 single-arm studies [23, 42–56]. Four of the records were abstracts from conferences [44, 45, 49, 52]. Among the 25 studies, 11 were multicenter trials [23, 34, 35, 37–39, 41, 47, 49, 52, 53]. All studies were rated as moderate-to-high quality based on the MINORS criteria (Table 1).

Characteristics of included studies

A comprehensive summary of the 25 studies included in the review, involving 245 patients (median 7, interquartile range 3–11), is provided in Table 1. The overall pooled ORR for all treatment regimens was 0.07 (95% CI 0.03–0.12) (Fig. 2). Of the studies, only four provided data on the safety outcomes specific to the DDLPS group, with the incidence of grade III–V toxicities reported as 0.14 (95% CI 0.05–0.24) (Supplementary Fig. 3). The median PFS across studies ranged from 3.9 to 6.2 months. In all the pooled results, heterogeneity was 0, which represents high confidence in the results.

Subgroup analysis: treatment line

A subgroup analysis was conducted to evaluate the efficacy of treatment based on the line of therapy. The analysis included 245 patients: 33 in the first-line treatment group and 212 in the later-line treatment group. First-line treatment was assessed in five studies, yielding an ORR of 0.22 (95% CI 0.12–0.35) (Supplementary Fig. 4A). The role of ICIs in later-line treatment was investigated in 20 studies, with a pooled ORR of 0.04 (95% CI 0.00–0.09) (Supplementary Fig. 4B).

Subgroup analysis: per treatment group

The efficacy of different treatment regimens was analyzed based on treatment groups. The ICI monotherapy group included 72 patients, yielding an ORR of 0.09 (95% CI 0.02–0.18) (Supplementary Fig. 5A). The dual ICI therapy group consisted of 34 patients, showing an ORR of 0.02 (95% CI 0.00–0.13) (Supplementary Fig. 5B). In the ICI plus trabectedin group, 25 patients were treated, with an ORR of 0.03 (95% CI 0.00–0.18) (Supplementary Fig. 5C). The ICI plus anthracyclines group included 24 patients, yielding an ORR of 0.52 (95% CI 0.29–0.74) (Supplementary Fig. 5D). Finally, the ICI plus other modalities group comprised 90 patients, with an ORR of 0.03 (95% CI 0.00–0.11) (Supplementary Fig. 5E).

Sensitivity analysis and publication bias

Sensitivity analysis was performed by STATA. The sensitivity analysis of the group found that the results were stable (Supplementary Data). Besides, we used STATA to detect publication bias. The funnel plots are shown in Supplementary Data. Egger's test indicated no publication bias in the results ($P = 0.75$).

Discussion

This meta-analysis represents, to our knowledge, the first comprehensive synthesis of ICI therapy in DDLPS. By pooling data from 25 studies comprising 245 patients, we determined an ORR of 7% for ICI-based treatments in this rare malignancy. Our subgroup analyses revealed significant heterogeneity in treatment efficacy across different regimens. While ICI monotherapy and dual ICI therapy yielded modest ORRs of 9% and 2%, respectively, the combination of ICI with anthracyclines achieved a markedly higher ORR of 52%, suggesting a potential synergistic interaction. In contrast, regimens combining ICI with trabectedin or other agents resulted in limited efficacy, with ORRs of only 3% each. Our analysis also indicated that treatment line significantly influenced outcomes, with first-line ICI therapy associated with a substantially higher ORR of 22%, compared to just 4% in later-line settings. Collectively, these findings underscore the promise of specific ICI-based combination strategies—particularly when deployed as first-line treatments—in enhancing therapeutic outcomes for patients with DDLPS, while also highlighting the need for further investigation into optimizing treatment regimens and patient selection.

Our meta-analysis demonstrated a striking difference in the ORR between patients with DDLPS receiving first-line ICI therapy versus those treated in later lines. This finding is consistent with trends observed in other malignancies. For example, in non-small-cell lung cancer (NSCLC), the KEYNOTE-024 trial showed that first-line pembrolizumab significantly improved ORR, PFS, and OS compared to platinum-based chemotherapy in patients with high PD-L1 expression [57]. Similarly, in melanoma, studies such as CheckMate-067 have reported that the use of first-line combination immunotherapy (nivolumab plus ipilimumab) results in markedly higher response rates and more durable

Table 1 Overview of included studies

Author	Study name (NCT)	Pub year	N	Accepted line of therapy	Intervention	Primary endpoint	ORR (n/N, %)	OS	PFS	G3/4 TRAE (%)	MINORS scores
Wilky [33]	NCT03860272	2025	6	≥ 1	Botensilimab and balstilimab	Dose-limiting toxicities	2/4, (50%)	NA	NA	Crossover group: 0/1, (0%)	16
Seligson [39]	NCT02500797(expansion cohorts and correlative analyses)	2024	N: 12; N+I 12	≥ 1	Ipilimumab and nivolumab	Confirmed objective response rate (CRR)	N: 1/12, (8.33%); N+I 2/12 (16.67%)	N: 8.1 (95% CI 6.8–Inf)mo; N+I:14.6 (95% CI 9.1–Inf) mo	N:4.6 (95% CI 3.2–Inf)mo; N+I:5.5 (95% CI 2.8–Inf) mo	N: 4/15, (26.67%); N+I 2/14, (14.29%)	16
Roland [40]	NCT03307616	2024	17	0	Ipilimumab and nivolumab	Pathologic response	1/17, (5.88%)	2 year OS: 82% (IQR 55–94	NA	NA	16
Haddox [46]	NCT03899805	2024	20	≥ 1	Eribulin and pembrolizumab	12-week PFS	3/20, (15%)	1 year OS: 75.0% (90% CI 60.7–92.7); Median OS: 97.6 (65.4–not reached (NR)) week	12-week PFS rate, % (90% CI): 69.6 (54.5–89.0); median PFS: 31.7 [12.4-not reached (NR)] week	NA	16
Curigliano [34]	NCT03301896	2024	1	≥ 1	LHC165 and PDR001	Safety and tolerability	0/1, (0%)	NA	NA	NA	16
Rosenbaum [44]	NCT04438824	2024	28	0	Palbociclib and INCMGA00012 (retifanlimab)	Orr	4/28, (14.29%)	Median OS: 24.8 (24.8-not reached (NR)) mo	Median PFS: 2.2 (1.8-not reached (NR)) mo	17/28, (60.71%)	16
Liu [45]	NCT04356872	2024	10	0	Sintilimab, doxorubicin and ifosfamide	Orr	5/10, (50%)	NA	NA	NA	16
Subramanian [43]	NCT04118166	2024	5	≥ 1	Ipilimumab and nivolumab	Orr	0/5, (0%)	NA	NA	NA	16
Maud Toulmonde [42]	METROMAJX	2024	1	≥ 1	JX-594, cyclophosphamide and avelumab	6 months PFS	0/1, (0%)	NA	NA	NA	16
Cho [47]	NCT03798106	2024	3	≥ 1	Pazopanib and durvalumab	Orr	0/3, (0%)	NA	NA	NA	16

Table 1 (continued)

Author	Study name (NCT)	Pub year	N	Accepted line of therapy	Intervention	Primary endpoint	ORR (n/N, %)	OS	PFS	G3/4 TRAE (%)	MINORS scores
Gordon [36]	NCT03138161	2023	14	First stage: ≥1; second stage: 0	Trabectedin, ipilimumab, and nivolumab	Safety	0/14	NA	NA	NA	
Sch€offski [35]		2023	2	≥1	Pembrolizumab and olaratumab	AEs	0/2, (0%)	NA	NA	NA	16
Kelly [48]	NCT03414229	2023	2	≥1	Epacadostat and pembrolizumab	24 weeks orr	0/2, (0%)	NA	NA	NA	16
D'Angelo[53]	NCT03282344	2022	10	≥1	NKTR-214(Bempegaldesleukin) and nivolumab	Orr	0/10, (0%)	Median OS: 21.7mo	Median PFS: 3.9mo	NA	16
Tian [50]	ChiCTR1900027009	2022	3	≥1	Sintilimab and doxorubicin	Safety and orr	3/3, (100%)	NA	Compared with patients with other pathological subtypes: HR = 0.42 (95% CI 0.21–0.83; $P = 0.013$)	NA	14
Wagner [37]	NCT03074318	2022	9	≥1	Trabectedin and avelumab	Safety and orr	0/9, (0%)	NA	NA	NA	16
Somaiah [51]	NCT02815995	2022	6	≥1	Durvalumab and tremelimumab	12-week PFS	0/6, (0%)	NA	12-week PFS rate: 17% (95% CI 1–52)	NA	16
McKean [52]	NCT03611868	2022	17	≥1	Alrizomadlin and pembrolizumab	Orr	1/17, (5.88%)	NA	NA	NA	16
Toulmonde [49]	NCT03085225	2022	2	≥1	Trabectedin and durvalumab	The recommended phase II dose (RP2D) and orr	0/2, (0%)	NA	NA	NA	16
Livingston [54]	NCT03056001	2021	7	0	Pembrolizumab and doxorubicin	Safety	2/7, (28.57%)	NA	NA	NA	16

Table 1 (continued)

Author	Study name (NCT)	Pub year	N	Accepted line of therapy	Intervention	Primary endpoint	ORR (n/N, %)	OS	PFS	G3/4 TRAE (%)	MINORS scores
Pollack [38]	NCT02888665	2020	4	0	Pembrolizumab and doxorubicin	Orr	2/4, (50%)	NA	NA	NA	16
Burgess [56]	NCT02301039	2019	39	≥ 1	Pembrolizumab	Orr	4/39, (10.26%)	Median OS: 13 [95% CI 8, NR] mo	Median PFS: 2 [95% CI 2, 4]mo; 12-week PFS rate: 44% [95% CI 28, 60]	0/34, (0%)	16
Wilky [55]	NCT02636725	2019	2	≥ 1	Pembrolizumab and axitinib	3 month PFS	0/2, (0%)	NA	NA	NA	16
D'Angelo [41]	NCT02500797	2018	N: 2; N+I: 3	≥ 1	Ipilimumab and nivolumab	Orr	N: 0/3, (0%), N+I: 0/2, (0%)	NA	NA	NA	16
Tawbi [23]	NCT02301039	2017	10	≥ 1	Pembrolizumab	Orr	2/10, (20%)	NA	Median PFS: 25 [95% CI 8–42] week	NA	16

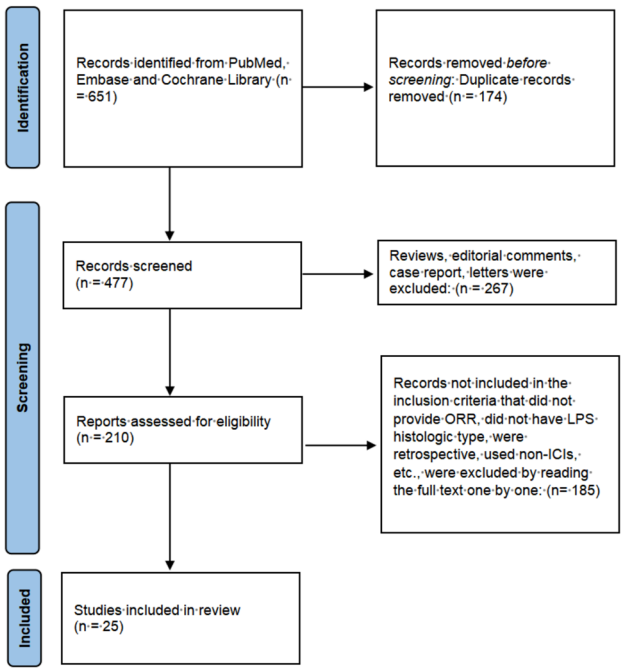

Fig. 1 Preferred Reporting Items for systematic reviews and meta-analyses (PRISMA) 2020 flow diagram illustrating the selection of studies included in meta-analysis. A total of 651 records were retrieved through the PubMed, EMBASE and Cochrane Library database, and there were 174 duplicate articles. After excluding literature types such as reviews, editorial comments, case report, letters, 477 literatures remained (including the latest unpublished clinical trials on ICIs for LPS from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO) and other international tumor congresses). According to the inclusion and exclusion criteria, the records that did not meet the requirements were excluded after reading the full text one by one, and finally 25 target articles were confirmed

survival outcomes than later-line applications [58]. These parallels suggest that the timing of immunotherapy is a critical determinant of its clinical success. Patients receiving first-line treatment generally have a more intact immune system and lower tumor burden, which may enhance the antitumor immune response elicited by ICIs. In contrast, heavily pretreated patients often have compromised immune function and a more immunosuppressive tumor microenvironment, factors that likely contribute to the lower efficacy observed in later-line settings [59].

In selecting an ICI-based regimen, the combination of ICI with anthracyclines has emerged as particularly promising. Our analysis incorporated four studies that evaluated this combination in patients with unresectable or metastatic STS, including cohorts of DDLPS. In the study by Pollack et al. (NCT02888665) [35], patients with unresectable or metastatic STS who had not previously received anthracycline therapy were treated with doxorubicin plus pembrolizumab. Among the four evaluable patients, two achieved an objective response. The safety profile in a broader cohort of 37 STS patients was favorable, with no grade 5 toxicities reported; the only grade 4 events were neutropenia ($n=6$), leukopenia ($n=1$), and febrile neutropenia ($n=1$), all of which resolved. Notably, two patients experienced grade 3 reductions in ejection fraction attributable to doxorubicin. Similarly, the study by Livingston et al. (NCT03056001) [51] evaluated this combination as a first-line treatment for unresectable STS, and within the subset of DDLPS patients ($n=7$), one patient achieved a complete response and another an objective response. Although 56.7% (17/30) of the overall cohort experienced at least one serious adverse event, the study met its primary safety endpoint, underscoring the regimen's feasibility even in this challenging patient population. In another investigation by Zhichao Tian (ChiCTR1900027009) [47], patients with unresectable or metastatic STS who had previously failed systemic therapy received up to six cycles of doxorubicin combined with sintilimab, a PD-1 inhibitor. Notably, all three DDLPS cases in this study achieved an objective response. The most recent data from Liuxin et al. (NCT04356872) [42], presented at the 2024 ASCO meeting, further support these findings. In this first-line setting for advanced STS, sintilimab combined with doxorubicin and ifosfamide was administered to 46 patients, including 10 with DDLPS, yielding an impressive ORR of 50% in the DDLPS subgroup. The most frequent grade 3 adverse events in the overall cohort were leucopenia (50.0%), neutropenia (45.7%), thrombocytopenia (21.7%), anemia (21.7%), and febrile neutropenia (21.7%). Collectively, although the current analysis of the ICI plus anthracycline regimen in DDLPS includes only 24 patients, the safety profile appears manageable and the therapeutic efficacy is notably superior compared to other ICI-based approaches. Pending the completion of ongoing studies, these encouraging results may provide robust evidence to support the incorporation of ICI plus anthracycline combinations as a first-line treatment option for patients with advanced, unresectable DDLPS.

While the combination of ICI with anthracyclines has demonstrated an outstanding ORR, it is undeniable that the overall efficacy of ICI treatment remains modest at 7%. Consequently, accurately selecting patients who are most likely to benefit from ICI therapy is imperative. In this context, identifying robust predictive biomarkers becomes paramount. Below, we summarize and discuss several candidate biomarkers—including tertiary lymphoid structures (TLS), PD-L1 expression, immune infiltration, tumor mutational burden (TMB)/microsatellite instability (MSI), gene fusions, mutation subclonality, and other emerging markers—that may guide patient selection for ICI therapy in sarcomas, particularly in DDLPS.

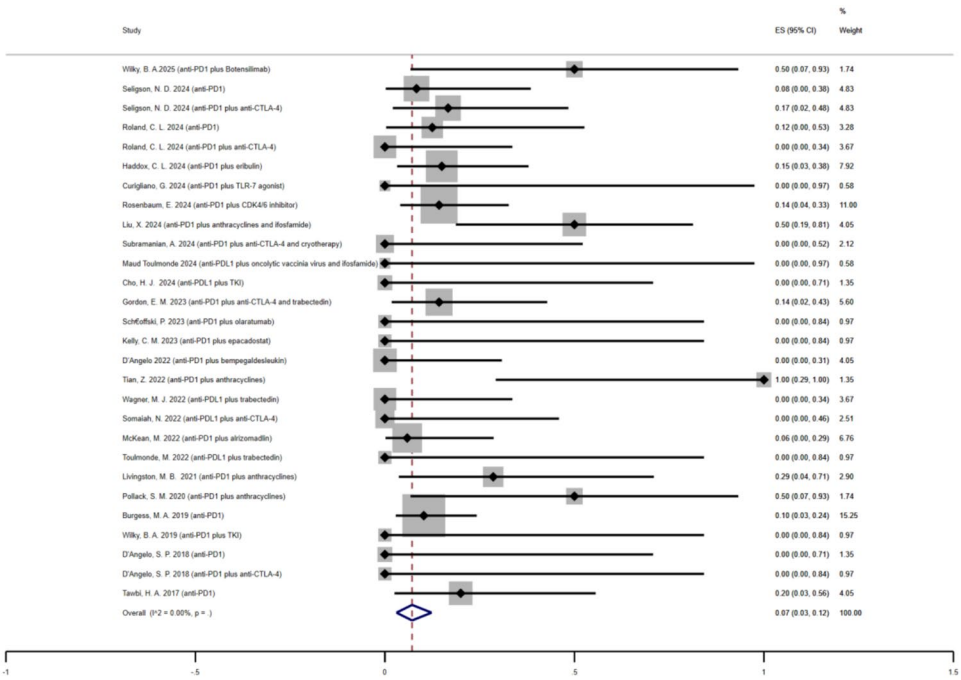

Fig. 2 Pooled objective response rates for all subjects. Objective response rate was defined as the number of responses (complete response (CR) + partial response (PR)) divided by the evaluable subjects in the study. ES, effect size; CI, confidence interval

Tertiary lymphoid structures (TLS)

Mature TLS are defined by the presence of a germinal center B cell zone containing follicular dendritic cells, with T cells predominantly localized at the periphery [60]. Several frameworks have been developed to describe the tumor microenvironment associated with immunotherapy response in sarcoma. For example, Petitprez and colleagues established an immune-based classification of sarcoma-immune classes and showed that the "immune-high" group—characterized by the presence of B cell-rich TLS—demonstrated a high response rate to PD-1 immunotherapy [61].

DDLPS, although baseline intratumoral B cells with TLS features (assessed by immunohistochemistry) were not associated with recurrence-free survival (RFS) or overall survival (OS), patients whose surgical specimens exhibited these features had significantly improved OS (median 29.1 months vs. no response; 5 of 8 vs. 0 of 8; log-rank $P = 0.045$) and a trend toward longer RFS (median 40 months vs. 13.4 months; 7 of 8 vs. 4 of 8; log-rank $P = 0.14$) [62]. Furthermore, additional clinical studies have confirmed that TLS-positive DDLPS patients achieved an ORR as high as 30% [63].

PD-L1 expression

PD-L1 expression as a predictive biomarker for ICB in sarcomas is controversial. For example, one study of DDLPS found that 80% (12 out of 15) of tumors exhibited PD-L1 expression > 1% at baseline, yet this was not associated with outcomes such as hyalinization at surgery, pathologic response (≥ 30% hyalinization), early relapse, ORR, or RFS [62]. Other studies report a wide range of PD-L1 expression (12–65%), depending on sarcoma histology, sample timing, and assay used. Moreover, clinical data suggest that patients may benefit from ICIs, regardless of tumor cell PD-L1 status. Notably, PD-L1 expression on immune cells such as dendritic cells and tumor-associated macrophages might better correlate with clinical response [64]. Overall, tumor cell PD-L1 expression alone may not serve as a reliable predictor of ICI response in DDLPS; however, PD-L1 expression on other cells within the tumor microenvironment might hold predictive potential [65].

Immune infiltration

Assessment of immune cell infiltration via multiplex IHC and deconvolution algorithms (e.g., CIBERSORTx) has provided insights into the tumor microenvironment. In DDLPS, a higher baseline proportion of cytotoxic T lymphocytes (CD3+CD8+cells) has been associated with improved RFS who received ICIs, whereas increased Treg (CD3+FoxP3+CD8–) infiltration correlates with shorter RFS [62]. Data from the SARC028 trial indicate that responders exhibit a higher density of various tumor-associated immune cell phenotypes, including PD-L1-expressing macrophages and cytotoxic T cells [65]. Yet, not all immune markers (e.g., CD4, CD68) show consistent associations across studies, suggesting that a composite evaluation of the immune contexture is necessary.

Tumor mutational burden (TMB) and microsatellite instability (MSI)

Liposarcomas generally exhibit low TMB (median ~ 1.7 Mut/Mb) [66], and high TMB (> 10 Mut/Mb) is exceedingly rare. Likewise, MSI is infrequent in these tumors, and MSI scores have not been associated with ICI response [39]. Despite FDA and EMA approvals of PD-L1, MSI/dMMR, and TMB as biomarkers in other cancers, their utility in sarcomas is limited by low overall mutation rates and poor stratification.

Gene fusions and mutation subclonality

Emerging genomic analyses suggest that the presence of gene fusions may correlate with improved clinical outcomes for who had ICIs across soft tissue sarcoma histologies. In an RNA-sequencing cohort, tumors harboring any gene fusion were more likely to achieve a PFS ≥ 12 weeks, and further analyses associated fusion presence with longer PFS and OS [39]. In addition, within DDLPS, a higher proportion of subclonal mutations (despite similar total mutation counts) has been independently associated with better PFS and OS, highlighting the potential role of intratumoral heterogeneity as a predictive marker [39].

Additional emerging biomarkers

Other potential biomarkers include circulating cytokines, angiogenic factors, and peripheral immune parameters. For instance, responders have been observed to exhibit higher levels of IFNα and IL4 at both pretreatment and on-treatment timepoints, along with increased posttreatment IFNγ and granzyme B expression in specific immune subsets. Furthermore, higher CD31+ vessel density ($P = 5.18 \times 10^{-3}$) and lower peripheral IL-6 levels have been linked to improved outcomes [33, 47]. Additionally, a baseline neutrophil-to-lymphocyte ratio greater than 5 has been associated with progressive disease [55].

Potential of this study and future directions

This study holds significant potential for advancing the treatment landscape of DDLPS, particularly by highlighting the promising role of immune checkpoint inhibitors ICIs, especially when combined with anthracyclines, as a first-line therapy. By synthesizing data from a variety of clinical trials, our findings suggest that ICIs may offer a valuable alternative to the traditional chemotherapy regimens that have shown limited efficacy in advanced stages of DDLPS. The demonstrated higher ORR in first-line treatment groups underscores the need to explore this therapeutic combination further in larger, more robust clinical trials. Despite these promising results, there are still notable knowledge gaps in the understanding of the full potential of ICIs in DDLPS. First, the variability in treatment outcomes based on different ICI combinations, such as the limited efficacy observed in combinations with trabectedin, points to the necessity for a deeper exploration of which specific combinations work best for different patient subgroups. Additionally, the lack of dedicated prospective studies on DDLPS and the frequent inclusion of mixed sarcoma histologies in clinical trials complicates our ability to draw definitive conclusions about the efficacy of ICIs for this specific malignancy. Furthermore, there remains an urgent need to identify predictive biomarkers that can help clinicians select the right patients for ICI therapy, ensuring optimal responses while minimizing unnecessary treatment exposure. Looking ahead, with ongoing clinical trials focused on DDLPS and other sarcoma subtypes, we anticipate more refined strategies that could optimize the timing and combination of ICIs with other modalities, like chemotherapy and targeted therapies. Moreover, advancements in biomarker discovery, including immune infiltration analysis and genetic profiling, are likely to revolutionize personalized treatment plans, enabling tailored immunotherapy approaches for DDLPS. As we gain a better understanding of the tumor microenvironment and immune evasion mechanisms, the integration of combination therapies that modulate both the immune system and tumor characteristics will likely emerge as a cornerstone of treatment. Overall, these developments could significantly improve outcomes for patients with this rare and aggressive cancer, making it a focal point for future research and clinical innovation.

Despite the promising findings of this meta-analysis, several limitations must be acknowledged. One key challenge is the small sample size and the heterogeneity of the selected trials. Many of the included studies had limited patient cohorts, which can affect the generalizability of the results. Additionally, the variability in treatment regimens and patient populations further complicates the ability to draw definitive conclusions about the optimal use of ICIs in DDLPS. Another notable limitation is the lack of translational endpoints in many studies, such as biomarkers or immune response data, which are critical for understanding the mechanisms of treatment efficacy and patient selection. Additionally, while our analysis demonstrated the potential of ICI combinations, the overall efficacy remains modest, with an ORR of just 7%. This highlights the need for more effective treatment strategies and underscores the importance of identifying patients who are more likely to respond to ICI therapy. The mixed histologic subtypes included in the trials further complicate the interpretation of the data, as treatment responses may differ significantly between different sarcoma subtypes. The inclusion of WDLPS patients in some trials, despite its generally poor response to treatments,

may have diluted the observed efficacy of ICIs in DDLPS specifically. Finally, the lack of long-term follow-up data in many studies is another limitation. Most of the studies included in our analysis did not provide sufficient information on long-term survival outcomes, such as overall survival and progression-free survival, particularly in the DDLPS cohort. These endpoints are crucial for determining the true potential of ICI therapies and assessing the durability of responses over time. Therefore, further studies with extended follow-up periods and more robust data on long-term outcomes are needed to fully evaluate the impact of ICIs in DDLPS treatment.

These limitations not only impact the current analysis but also reflect broader challenges in clinical research on DDLPS. The rarity of DDLPS and its frequent grouping with other soft tissue sarcomas have contributed to a scarcity of disease-specific data. Consequently, there is an urgent need for dedicated clinical studies that focus exclusively on DDLPS to better characterize both the safety and efficacy profiles of ICI therapies in this patient population.

Conclusion

This study represents the first meta-analysis evaluating the use of ICIs in DDLPS. Our findings highlight the promising potential of combining ICIs with anthracyclines, as this strategy achieved notably higher response rates. The data also indicate that ICI therapy is more effective when administered as a first-line treatment compared to later-line settings. Despite challenges posed by incomplete data, these results provide a valuable reference point and underscore the need for dedicated prospective clinical studies to further refine and optimize ICI-based treatment strategies for DDLPS.

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Declarations

Conflict of interests The authors declare no competing interests.

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References

1. Brennan MF, Antonescu CR, Moraco N, Singer S (2014) Lessons learned from the study of 10,000 patients with soft tissue sarcoma. Ann Surg 260(3):416–422
2. Anderson WJ, Doyle LA (2021) Updates from the 2020 World Health Organization classification of soft tissue and bone tumours. Histopathology 78:644–657
3. Bill KL, Casadei L, Prudner BC, Iwenofu H, Strohecker AM, Pollock RE (2016) Liposarcoma: molecular targets and therapeutic implications. Cell Mol Life Sci 73(19):3711–3718
4. Sbaraglia M, Bellan E, Dei Tos AP (2021) The 2020 WHO classification of soft tissue tumours: news and perspectives. Pathologica 113(2):70–84
5. Tyler R, Wanigasooriya K, Taniere P, Almond M, Ford S, Desai A, Beggs A (2020) A review of retroperitoneal liposarcoma genomics. Cancer Treat Rev 86:102013
6. Thway K, Jones RL, Noujaim J, Zaidi S, Miah AB, Fisher C (2016) Dedifferentiated liposarcoma: updates on morphology, genetics, and therapeutic strategies. Adv Anat Pathol 23(1):30–40
7. Haddox CL, Hornick JL, Roland CL, Baldini EH, Keedy VL, Riedel RF (2024) Diagnosis and management of dedifferentiated liposarcoma: a multidisciplinary position statement. Cancer Treat Rev 131:102846
8. Vos M, Koseła-Paterczyk H, Rutkowski P, van Leenders GJLH, Normantowicz M, Lecyk A, Sleijfer S, Verhoef C, Grünhagen DJ (2018) Differences in recurrence and survival of extremity liposarcoma subtypes. Eur J Surg Oncol 44(9):1391–1397

9. Nishio J, Nakayama S, Nabeshima K, Yamamoto T (2021) Biology and management of dedifferentiated liposarcoma: state of the art and perspectives. J Clin Med 10(15):3230
10. Amer KM, Congiusta DV, Thomson JE, Elsamna S, Chaudhry I, Bozzo A, Amer R, Siracuse B, Ghert M, Beebe KS (2020) Epidemiology and survival of liposarcoma and its subtypes: a dual database analysis. J Clin Orthop Trauma 11:S479–S484
11. Gootee JM, Curtin CE, Aurit SJ, Randhawa SE, Kang BY, Silberstein PT (2019) Treatment facility: an important prognostic factor for dedifferentiated liposarcoma survival. Fed Pract 36(Suppl 5):S34-s41
12. Italiano A, Toulmonde M, Cioffi A, Penel N, Isambert N, Bompas E, Duffaud F, Patrikidou A, Lortal B, Le Cesne A et al (2012) Advanced well-differentiated/dedifferentiated liposarcomas: role of chemotherapy and survival. Ann Oncol 23(6):1601–1607
13. Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay JY, Kerst JM, Sufliarsky J, Whelan J, Hohenberger P et al (2014) Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 15(4):415–423
14. Rizzo A, Nannini M, Astolfi A, Indio V, De Iaco P, Perrone AM, De Leo A, Incorvaia L, Di Scioscio V, Pantaleo MA (2020) Impact of chemotherapy in the adjuvant setting of early stage uterine leiomyosarcoma: a systematic review and updated meta-analysis. Cancers (Basel) 12(7):1899
15. Rizzo A, Pantaleo MA, Saponara M, Nannini M (2019) Current status of the adjuvant therapy in uterine sarcoma: a literature review. World J Clin Cases 7(14):1753–1763
16. Mir O, Brodowicz T, Italiano A, Wallet J, Blay JY, Bertucci F, Chevreau C, Piperno-Neumann S, Bompas E, Salas S et al (2016) Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 17(12):1732–1742
17. Riedel RF, Ballman KV, Lu Y, Attia S, Loggers ET, Ganjoo KN, Livingston MB, Chow W, Wright J, Ward JH et al (2020) A randomized, double-blind, placebo-controlled, phase II study of regorafenib versus placebo in advanced/metastatic, treatment-refractory liposarcoma: results from the SARC024 study. Oncologist 25(11):e1655–e1662
18. Sleijfer S, Ray-Coquard I, Papai Z, Le Cesne A, Scurr M, Schöffski P, Collin F, Pandite L, Marreaud S, De Brauwer A et al (2009) Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol 27(19):3126–3132
19. Bonvalot S, Gronchi A, Le Péchoux C, Swallow CJ, Strauss D, Meeus P, van Coevorden F, Stoldt S, Stoeckle E, Rutkowski P et al (2020) Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 21(10):1366–1377
20. Callegaro D, Raut CP, Ajayi T, Strauss D, Bonvalot S, Ng D, Stoeckle E, Fairweather M, Rutkowski P, van Houdt WJ et al (2023) Preoperative radiotherapy in patients with primary retroperitoneal sarcoma: EORTC-62092 trial (STRASS) versus off-trial (STREXIT) results. Ann Surg 278(1):127–134
21. Holder AM, Dedeilia A, Sierra-Davidson K, Cohen S, Liu D, Parikh AR, Boland GM (2024) Defining clinically useful biomarkers of immune checkpoint inhibitors in solid tumours. Nat Rev Cancer 24:498–512
22. Chen AP, Sharon E, O'Sullivan-Coyne G, Moore N, Foster JC, Hu JS, Van Tine BA, Conley AP, Read WL, Riedel RF et al (2023) Atezolizumab for advanced alveolar soft part sarcoma. N Engl J Med 389(10):911–921
23. Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, D'Angelo S, Attia S, Riedel RF, Priebat DA et al (2017) Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol 18(11):1493–1501
24. Guven DC, Erul E, Kaygusuz Y, Akagunduz B, Kilickap S, De Luca R, Rizzo A (2023) Immune checkpoint inhibitor-related hearing loss: a systematic review and analysis of individual patient data. Support Care Cancer 31(12):624
25. Braik D, Lemieux C, Wilson BE, Salawu A, Abdul Razak AR (2025) Clinical benefit and fragility evaluation of systemic therapy trials for advanced soft tissue sarcoma. Cancer 131(1):e35564
26. Schöffski P, Jones RL, Agulnik M, Blay JY, Chalmers A, Italiano A, Pink D, Stacchiotti S, Valverde C, Vincenzi B et al (2024) Current unmet needs in locally advanced (unresectable) or metastatic dedifferentiated liposarcoma, the relevance of progression-free survival as clinical endpoint, and expectations for future clinical trial design: an international Delphi consensus report. ESMO Open 9(7):103487
27. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J (2003) Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 73(9):712–716
28. Pei-xin W, Hong-tian LI, Jian-meng LIU (2012) Meta-analysis of non-comparative binary outcomes and its solution by stata. J Evid Based Med 12(1):52–55
29. Sun J, Freeman BD, Natanson C (2018) Chapter 22—meta-analysis of clinical trials. In: Gallin JI, Ognibene FP, Johnson LL (eds) Principles and practice of clinical research (Fourth edition). Academic Press, Boston, pp 317–327
30. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22(4):719–748
31. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50(4):1088–1101
32. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629
33. Wilky BA, Schwartz GK, Gordon MS, El-Khoueiry AB, Bullock AJ, Henick B, Agulnik M, Singh A, Mahadevan D, Stebbing J et al (2025) Botensilimab (Fc-enhanced anti–cytotoxic lymphocyte-association protein-4 antibody) plus balstilimab (anti–PD-1 antibody) in patients with relapsed/refractory metastatic sarcomas. J Clin Oncol. https://doi.org/10.1200/JCO-24-02524
34. Curigliano G, Jimenez MM, Shimizu T, Keam B, Meric-Bernstam F, Rutten A, Glaspy J, Schuler PJ, Parikh NS, Ising M et al (2024) A phase I trial of LHC165 single agent and in combination with spartalizumab in patients with advanced solid malignancies. ESMO Open 9(8):103643
35. Schöffski P, Bahleda R, Wagner AJ, Burgess MA, Junker N, Chisamore M, Peterson P, Szpurka AM, Ceccarelli M, Tap WD (2023) Results of an open-label, phase Ia/b study of pembrolizumab plus olaratumab in patients with unresectable, locally advanced, or metastatic soft-tissue sarcoma. Clin Cancer Res 29(17):3220–3228
36. Gordon EM, Chawla SP, Tellez WA, Younesi E, Thomas S, Chua-Alcala VS, Chomoyan H, Valencia C, Brigham DA, Moradkhani A et al (2023) SAINT: a phase I/expanded phase II study using safe amounts of Ipilimumab, Nivolumab and Trabectedin as first-line treatment of advanced soft tissue sarcoma. Cancers (Basel) 15(3):906
37. Wagner MJ, Zhang Y, Cranmer LD, Loggers ET, Black G, McDonnell S, Maxwell S, Johnson R, Moore R, De Viveiros PH et al (2022) A phase 1/2 trial combining avelumab and trabectedin for advanced liposarcoma and leiomyosarcoma. Clin Cancer Res 28(11):2306–2312

38. Pollack SM, Redman MW, Baker KK, Wagner MJ, Schroeder BA, Loggers ET, Trieselmann K, Copeland VC, Zhang S, Black G et al (2020) Assessment of doxorubicin and pembrolizumab in patients with advanced anthracycline-naive sarcoma: a phase 1/2 nonrandomized clinical trial. JAMA Oncol 6(11):1778–1782
39. Seligson ND, Chen JL, Goodrich AC, Van Tine BA, Campbell JD, Richards AL, Antonescu CR, Liebner DA, Milhem MM, Streicher H et al (2024) A multicenter, randomized, non-comparative, phase II study of nivolumab ± ipilimumab for patients with metastatic sarcoma (Alliance A091401): expansion cohorts and correlative analyses. J Immunother Cancer 12(9):e009472
40. Roland CL, Nassif Haddad EF, Keung EZ, Wang WL, Lazar AJ, Lin H, Chelvanambi M, Parra ER, Wani K, Guadagnolo BA et al (2024) A randomized, non-comparative phase 2 study of neoadjuvant immune-checkpoint blockade in retroperitoneal dedifferentiated liposarcoma and extremity/truncal undifferentiated pleomorphic sarcoma. Nature Cancer 5(4):625–641
41. D'Angelo SP, Mahoney MR, Van Tine BA, Atkins J, Milhem MM, Jahagirdar BN, Antonescu CR, Horvath E, Tap WD, Schwartz GK et al (2018) Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol 19(3):416–426
42. Toulmonde M, Guegan J-P, Spalato-Ceruso M, Peyraud F, Kind M, Vanhersecke L, Le Loarer F, Perret R, Cantarel C, Bellera C et al (2024) Reshaping the tumor microenvironment of cold soft-tissue sarcomas with oncolytic viral therapy: a phase 2 trial of intratumoral JX-594 combined with avelumab and low-dose cyclophosphamide. Mol Cancer 23(1):38
43. Subramanian A, Nemat-Gorgani N, Ellis-Caleo TJ, van Ijzendoorn DGP, Sears TJ, Somani A, Luca BA, Zhou MY, Bradic M, Torres IA et al (2024) Sarcoma microenvironment cell states and ecosystems are associated with prognosis and predict response to immunotherapy. Nat Cancer 5(4):642–658
44. Rosenbaum E, Qin LX, Dickson M, Movva S, Kelly CM, Chan J, Chi P, Banks L, Keohan ML, Gounder M et al (2024) 1720MO a phase II study of palbociclib combined with the PD-1 inhibitor retifanlimab in patients with advanced dedifferentiated liposarcoma. Ann Oncol 35:S1031
45. Liu X, Guo Y, Yan W, Chen Y, Xu Y, Wang CM, Yao W, Wang J, Yu L, Jiang S et al (2024) Sintilimab, doxorubicin and ifosfamide (AI) as first-line treatment in patients with advanced undifferentiated pleomorphic sarcoma (UPS), synovial sarcoma (SS), myxoid liposarcoma (MLPS) and de-differentiated liposarcoma (DDLPS): a singlearm phase 2 trial. J Clin Oncol 42(16):11505
46. Haddox CL, Nathenson MJ, Mazzola E, Lin JR, Baginska J, Nau A, Weirather JL, Choy E, Marino-Enriquez A, Morgan JA et al (2024) Phase II study of eribulin plus pembrolizumab in metastatic soft-tissue sarcomas: clinical outcomes and biological correlates. Clin Cancer Res 30(7):1281–1292
47. Cho HJ, Yun K-H, Shin S-J, Lee YH, Kim SH, Baek W, Han YD, Kim SK, Ryu HJ, Lee J et al (2024) Durvalumab plus pazopanib combination in patients with advanced soft tissue sarcomas: a phase II trial. Nat Commun 15(1):685
48. Kelly CM, Qin LX, Whiting KA, Richards AL, Avutu V, Chan JE, Chi P, Dickson MA, Gounder MM, Keohan ML et al (2023) A phase II study of epacadostat and pembrolizumab in patients with advanced sarcoma. Clin Cancer Res 29(11):2043–2051
49. Toulmonde M, Brahmi M, Giraud A, Chakiba C, Bessede A, Kind M, Toulza E, Pulido M, Albert S, Guégan JP et al (2022) Trabectedin plus durvalumab in patients with advanced pretreated soft tissue sarcoma and ovarian carcinoma (TRAMUNE): an open-label, multicenter phase Ib study. Clin Cancer Res 28(9):1765–1772
50. Tian Z, Dong S, Zuo W, Li P, Zhang F, Gao S, Yang Y, Li C, Zhang P, Wang X et al (2022) Efficacy and safety of sintilimab plus doxorubicin in advanced soft tissue sarcoma: a single-arm, phase II trial. Front Pharmacol 13:987569
51. Somaiah N, Conley AP, Parra ER, Lin H, Amini B, Solis Soto L, Salazar R, Barreto C, Chen H, Gite S et al (2022) Durvalumab plus tremelimumab in advanced or metastatic soft tissue and bone sarcomas: a single-centre phase 2 trial. Lancet Oncol 23(9):1156–1166
52. McKean M, Tolcher AW, Reeves JA, Chmielowski B, Shaheen MF, Beck JT, Orloff MM, Somaiah N, Van Tine BA, Drabick JJ et al (2022) Newly updated activity results of alrizomadlin (APG-115), a novel MDM2/p53 inhibitor, plus pembrolizumab: phase 2 study in adults and children with various solid tumors. J Clin Oncol 40(16):9517
53. D'Angelo SP, Richards AL, Conley AP, Woo HJ, Dickson MA, Gounder M, Kelly C, Keohan ML, Movva S, Thornton K et al (2022) Pilot study of bempegaldesleukin in combination with nivolumab in patients with metastatic sarcoma. Nat Commun. https://doi.org/10.1038/s41467-022-30874-8
54. Livingston MB, Jagosky MH, Robinson MM, Ahrens WA, Benbow JH, Farhangfar CJ, Foureau DM, Maxwell DM, Baldrige EA, Begic X et al (2021) Phase II study of pembrolizumab in combination with doxorubicin in metastatic and unresectable soft-tissue sarcoma. Clin Cancer Res 27(23):6424–6431
55. Wilky BA, Trucco MM, Subhawong TK, Florou V, Park W, Kwon D, Wieder ED, Kolonias D, Rosenberg AE, Kerr DA et al (2019) Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. Lancet Oncol 20(6):837–848
56. Burgess MA, Bolejack V, Schuetze S, Van Tine BA, Attia S, Riedel RF, Hu JS, Davis LE, Okuno SH, Priebat DA et al (2019) Clinical activity of pembrolizumab (P) in undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated/pleomorphic liposarcoma (LPS): Final results of SARC028 expansion cohorts. J Clin Oncol 37:11015
57. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S et al (2019) Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non–small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol 37(7):537–546
58. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob J-J, Rutkowski P, Cowey CL, Lao CD, Schadendorf D, Wagstaff J, Dummer R et al (2018) Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 19(11):1480–1492
59. Huang AC, Postow MA, Orlowski RJ, Mick R, Bengsch B, Manne S, Xu W, Harmon S, Giles JR, Wenz B et al (2017) T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. Nature 545(7652):60–65
60. Vanhersecke L, Bougouin A, Crombé A, Brunet M, Sofeu C, Parrens M, Pierron H, Bonhomme B, Lembege N, Rey C et al (2023) Standardized pathology screening of mature tertiary lymphoid structures in cancers. Lab Invest 103(5):100063
61. Petitprez F, de Reyniès A, Keung EZ, Chen TW-W, Sun C-M, Calderaro J, Jeng Y-M, Hsiao L-P, Lacroix L, Bougoüin A et al (2020) B cells are associated with survival and immunotherapy response in sarcoma. Nature 577(7791):556–560
62. Roland CL, Nassif Haddad EF, Keung EZ, Wang WL, Lazar AJ, Lin H, Chelvanambi M, Parra ER, Wani K, Guadagnolo BA et al (2024) A randomized, non-comparative phase 2 study of neoadjuvant immune-checkpoint blockade in retroperitoneal dedifferentiated liposarcoma and extremity/truncal undifferentiated pleomorphic sarcoma. Nat Cancer 5(4):625–641
63. Italiano A, Bessede A, Pulido M, Bompas E, Piperno-Neumann S, Chevreau C, Penel N, Bertucci F, Toulmonde M, Bellera C

et al (2022) Pembrolizumab in soft-tissue sarcomas with tertiary lymphoid structures: a phase 2 PEMBROSARC trial cohort. Nat Med 28(6):1199–1206
64. Lin H, Wei S, Hurt EM, Green MD, Zhao L, Vatan L, Szeliga W, Herbst R, Harms PW, Fecher LA et al (2018) Host expression of PD-L1 determines efficacy of PD-L1 pathway blockade-mediated tumor regression. J Clin Invest 128(2):805–815
65. Keung EZ, Burgess M, Salazar R, Parra ER, Rodrigues-Canales J, Bolejack V, Van Tine BA, Schuetze SM, Attia S, Riedel RF et al (2020) Correlative analyses of the SARC028 trial reveal an association between sarcoma-associated immune infiltrate and response to pembrolizumab. Clin Cancer Res 26(6):1258–1266
66. Chalmers ZR, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, Schrock A, Campbell B, Shlien A, Chmielecki J et al (2017) Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 9(1):34