International Immunopharmacology 148 (2025) 114070

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Efficacy of immune checkpoint inhibitors in the treatment of soft tissue sarcoma: A systematic review and meta-analysis of clinical trials

Yang Cao [a,1], Wei Wang [a,1], Hairong Xu [b,1], Hang Yi [c,1], Yinyan Gao [d], Mingzhong Wan [e], Mingzhao Wang [a], Tong Chen [a], Yanchao Chen [a], Yihebali Chi [a], Shuqing Wei [f], Shi Jin [g], Ming Bai [h], Xin Li [h], Yibo Gao [i,*], Xiaohui Niu [b,*], Yutao Liu [a,*]

[a] Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China
[b] Department of Orthopedic Oncology Surgery, Beijing Jishuitan Hospital, Capital Medical University, No.31 Xin Jie Kou East Street, Xi Cheng District, Beijing 100035, China
[c] Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China
[d] Department of Epidemiology and Biostatistics, Xiangya School of Public Health, Central South University, Changsha, Hunan, China
[e] Shantou University Medical College, Shantou 515041, China
[f] Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, General Internal Medicine, Taiyuan, Shanxi 030013, China
[g] National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen 518116, China
[h] Department of Medical Oncology, the First Hospital of China Medical University, Shenyang, Liaoning Province 110001, China
[i] Central Laboratory & Shenzhen Key Laboratory of Epigenetics and Precision Medicine for Cancers, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen 518116, China

ARTICLE INFO

Keywords:
Soft-tissue sarcoma
Immune checkpoint inhibitors
Meta-analysis
Efficacy

ABSTRACT

Background: Soft tissue sarcomas (STS) are a heterogeneous group of tumors with diverse clinical and molecular characteristics, characterized by limited treatment options and poor prognosis. Immune checkpoint inhibitors (ICIs) have emerged as promising therapies for STS, yet comprehensive evaluations of their efficacy, especially in combination with other treatments, are scarce.
Methods: We conducted a systematic review and *meta*-analysis of clinical trials on ICIs in STS treatment, sourced from PubMed, Embase, and the Cochrane Central Register of Controlled Trials up to May 31, 2024. The studies included both monotherapy and combination therapies with ICIs. We assessed the methodological quality using the Cochrane Risk of Bias 2 tool and the Methodological Index for Non-Randomized Studies. Data synthesis involved random-effects *meta*-analysis to determine pooled proportions and 95% confidence intervals (CIs) for objective response rates (ORR), disease control rates (DCR), and high-grade treatment-related adverse events (TRAEs).
Results: The analysis included 38 studies with 1349 patients covering 24 STS subtypes. The overall ORR was 16% (95% CI 0.12–0.21), DCR was 64% (95% CI 0.57–0.70), and the rate of Grade 3–5 TRAEs was 19% (95% CI 0.13–0.27). Treatments combining ICIs with tyrosine kinase inhibitors (TKIs) showed the highest efficacy (ORR 28%, 95% CI 0.18–0.40), albeit with increased adverse events. ORRs in first-line treatments were substantially higher (28%) compared to second-line treatments or beyond (11%). Subtypes like alveolar soft part sarcoma (ASPS), angiosarcoma (AS), and epithelioid sarcoma (ES) exhibited favorable responses exceeding 30%.
Conclusions: This systematic review and *meta*-analysis indicate that ICIs, particularly when combined with TKIs, provide substantial therapeutic benefits in treating STS, significantly enhancing response rates in specific subtypes such as ASPS and AS. The results underscore the transformative potential of ICIs in STS treatment strategies. However, the variability across subtypes and treatment lines emphasizes the need for further randomized

* Corresponding authors.
E-mail addresses: gaoyibo@cicams.ac.cn (Y. Gao), niuxiaohui@263.net (X. Niu), liuyutao@cicams.ac.cn (Y. Liu).
[1] Authors contributed equally to this work.

https://doi.org/10.1016/j.intimp.2025.114070
Received 23 November 2024; Received in revised form 3 January 2025; Accepted 7 January 2025
Available online 17 January 2025

controlled trials to refine and personalize therapeutic approaches, ensuring optimal outcomes for patients with these diverse malignancies.

1. Introduction

Sarcomas, a heterogeneous group of tumors with distinct clinical and molecular characteristics, account for 1 % of adult malignancies and 15 % of pediatric oncological cases, predominantly classified into soft tissue sarcomas (STS) and sarcoma of bone. Soft tissue sarcomas can develop from fat, muscle, nerve, vascular, and other connective tissues, predominantly occurring in the trunk, limbs, viscera, and retroperitoneum. Currently, more than 60 histological subtypes of soft tissue sarcoma have been identified [1,2]. Common subtypes of STS include liposarcoma (LPS), leiomyosarcoma (LMS), and undifferentiated pleomorphic sarcoma (UPS); however, 20 % of patients are diagnosed with ultra-rare STS that have an annual incidence of fewer than 1 cases per million [3].

The cornerstone of STS management remains surgical intervention, yet many patients present with advanced stages where surgery is unfeasible, thus resorting to chemotherapy as the first-line treatment, including single-agent chemotherapy (dacarbazine, doxorubicin, epirubicin, or ifosfamide) or anthracycline-based combination regimens [1,4]. However, most sarcomas exhibit low sensitivity to chemotherapy drugs [5]. Previous studies indicate that the median survival for first-line chemotherapy ranges from 8 to 13 months, while for second-line chemotherapy, it is only between 2 and 6.6 months [6]. This underscores a pressing need for novel therapeutic strategies.

Immune checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1), its ligand (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) have achieved significant results in solid tumors, prompting increased research into their application in the field of sarcomas [7]. Pembrolizumab has been recommended for subsequent treatment in patients with certain subtypes of advanced or metastatic STS, including myxofibrosarcoma (MFS), UPS, cutaneous angiosarcoma, and undifferentiated sarcomas [1]. Advancements in genetic sequencing, targeted therapy, and the development of novel chemotherapy agents have also driven improvements in treatment protocols [8]. To enhance efficacy, combination therapies involving dual ICIs, ICIs with chemotherapy, targeted treatments, and other immunotherapies are continually being developed.

Despite the proliferation of clinical trials examining the utility of ICIs in STS, a cohesive synthesis of these studies, particularly those contrasting monotherapies and combination therapies across diverse sarcoma subtypes, remains lacking. A *meta*-analysis published in July 2021 on a similar topic [9], made an initial attempt to address this, but more than half of the studies included were conference abstracts, which may compromise the quality assessment. Moreover, a substantial amount of new primary research has been published since that analysis. Therefore, we conducted an updated systematic review and *meta*-analysis to assimilate recent studies, providing a refined perspective on the efficacy and safety of ICIs in STS treatment, and to guide clinical decision-making by identifying subtypes most responsive to immunotherapy.

2. Materials and methods

This systematic review and *meta*-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The detailed protocol has been registered on PROSPERO (CRD42024544710). The main outcome was the objective response rate (ORR), while secondary outcomes included disease control rate (DCR), progression-free survival (PFS), 3-month and 6-month PFS rates, overall survival (OS), and toxicity.

2.1. Eligibility criteria

Articles meeting the following criteria were considered for inclusion: ① Studies focusing on patients with histopathologically confirmed diagnosis of unresectable locally advanced or metastatic STS, including, but not limited to alveolar soft part sarcoma (ASPS), epithelioid sarcoma (ES), MFS, malignant peripheral nerve sheath tumor, rhabdomyosarcoma, LPS, angiosarcoma (AS), synovial sarcoma (SS), solitary fibrous tumor, clear cell sarcoma, LMS, and UPS. ② The intervention should be ICIs, used either alone or in combination with other treatments such as chemotherapy or targeted therapy. For single-arm trials, there is no control group; in two-arm or multi-arm trials, the control group should receive monotherapy with ICIs. ③ Outcome measures included ORR, DCR, PFS, rates of PFS at 3 and 6 months, OS, and related toxicities. Studies involving other types of tumors but providing separate subgroup analyses for STS with the necessary outcome measures can also be included. ④ The study design was clinical trials, whether randomized or not. ⑤ The publication language was limited to English.

Animal models, cell lines, case reports, case series, reviews, conference abstracts, and protocols were excluded.

2.2. Information sources and search strategy

We searched the following databases: PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), with the last update on May 31, 2024. The detailed search strategy is provided in Appendix Table S1-S3, primarily focusing on the keywords “sarcoma” and “immune checkpoint inhibitor”. Additionally, references from the included studies were also screened.

2.3. Literature selection

All records from the three databases were imported to the Endnote 21 (USA, Clarivate Analytics) for selection. Titles and/or abstracts, followed by full texts of these potentially eligible studies were independently assessed by two review team members (Y.C. and Y.G.). Any disagreements were resolved through discussion.

2.4. Data collection process and data items

Data extraction from all studies was conducted using a standardized form by two review team members (Y.C. and M.W). Y.C. handled the initial data extraction, while M.W. verified the accuracy of the collected data. Extracted details included the author, publication year, study design, median follow-up period, number of patients, patient demographics (median age (range) and percentage of female patients), tumor subtype, and specific treatment interventions (regimen, dosage, and duration). Outcome data collected comprised the ORR, DCR, PFS, 3-month and 6-month PFS rates, OS, and treatment-related adverse events (TRAE). The Response Evaluation Criteria in Solid Tumours (RECIST) was utilized as the evaluation method. For the time-related outcomes such as PFS, OS, and median follow-up, durations expressed in weeks were converted to months using the formula: months = weeks × 0.23.

Notably, the ORR was calculated as the number of responses (complete response (CR) + partial response (PR)) divided by the number of evaluable patients in the study, rather than by the total number of subjects (intent-to-treat analysis). This approach (per-protocol analysis) would provide a more accurate measure of treatment efficacy under ideal conditions [11].

2.5. Risk of bias assessment

The methodological quality of randomized trials was assessed by two reviewers (Y.C. and M.W.) using the Cochrane Risk of Bias 2 tool (RoB2) [12]. For non-randomized studies, we utilized the Methodological Index for Non-Randomized Studies (MINORS) [13]. Two reviewers independently conducted the assessments. Any disagreements between them were resolved through discussions with the involvement of a third researcher (Y.G.).

2.6. Synthesis methods

In our analysis, when at least three studies used the same type of intervention and comparator with the same outcome measure, a random-effect *meta*-analysis was conducted to pool the effect size with 95 % Confidence Intervals (CIs).

Due to the inclusion of only two randomized controlled trials (RCT), a *meta*-analysis was not performed for these studies. For ORRs, DCRs and Grade 3–5 TRAE (%), we used the *metaprop* function in Stata 16 (USA, StataCorp LLC) to calculate the pooled proportions and their 95 % CIs. The Freeman-Tukey double arcsine transformation was applied to compute the weighted aggregate estimates and to perform back-transformation on these estimates, ensuring that results with zero events were included [14]. This facilitated the inclusion and accurate analysis of all relevant data, regardless of the study's event rates. For 3-month and 6-month PFS rates, we used the *metan* function. The findings from these analyses were visualized through forest plots. Heterogeneity among the study outcomes was assessed using the I^2 statistic, with a value greater than 50 % indicates substantial heterogeneity [15].

Subgroup analyses were conducted to explore potential reasons for heterogeneity, specifically focusing on intervention types, lines of therapy, and patient characteristics where feasible. In our *meta*-analysis, we included studies covering both first-line and ≥2nd-line treatments. However, some studies included mixed patient populations across treatment lines, complicating clear classification. To address this, studies were categorized as first-line if ≤20 % of patients were receiving ≥2nd-line treatments and as ≥2nd-line if ≤20 % were in first-line therapy.

Additionally, we conducted six sensitivity analyses: ① ORR calculated by dividing the number of responses (CR + PR) by the total number of subjects in the study. ② Exclusion of smaller trials with fewer than 40 participants; ③ Exclusion of Phase I, I/II studies, and randomized Phase II studies, thus only analyzing Phase II single-arm studies; ④ Exclusion of studies that did not use the RECIST v.1.1 criteria to assess the best tumor response; ⑤ Exclusion of studies where any patients received first-line treatments, focusing our analysis exclusively on studies that enrolled patients undergoing ≥ second line therapies; ⑥ Exclusion of studies that used unapproved drugs.

3. Results

3.1. Study selection

The study selection process is illustrated in Fig. 1. The database search initially identified 1918 citations. After removing duplicates, 1604 citations were screened by titles and abstracts, with 1490 studies being excluded. The remaining 114 full texts were examined in more detail, resulting in 34 studies included. Additionally, one eligible study identified through the backward citation searches. Ultimately, 35 studies were included in the review. The final sample included seven phase I studies [16–22], three phase I/II studies [23–25], two randomized phase II studies each with two treatment arms [26,27], and 23 single-arm phase II studies [6,28–49].

3.2. Study characteristics

Table 1 offers a detailed overview of the 35 studies. It details each treatment arm of the two RCT separately, and separately describes the Phase I and Phase II study results of Broto (2020). Consequently, these were treated as individual studies in the analysis, leading to a total of 38 distinct studies being evaluated.

The collective dataset encompasses 1349 patients. The median age ranged from 30 to 69 years, with the proportion of females varying between 30 % and 66.7 %. The included studies primarily originated from the US (n = 18), followed by China (n = 7). Of the 1140 patients with clearly defined histological subtypes, a total of 24 different subtypes were covered. LMS emerged as the most common subtype (231 patients, 20.3 %), followed by ASPS (168 patients, 14.7 %), and UPS (162 patients, 14.2 %). LPS was also frequently observed, comprising 159 patients (13.9 %), including subtypes such as dedifferentiated liposarcoma (DDLPS) with 62 patients (5.4 %). Most studies were conducted in settings of second-line treatment or beyond (n = 24, 63.2 %). Additionally, a significant number of studies included treatment regimens with pembrolizumab (n = 10, 26.3 %).

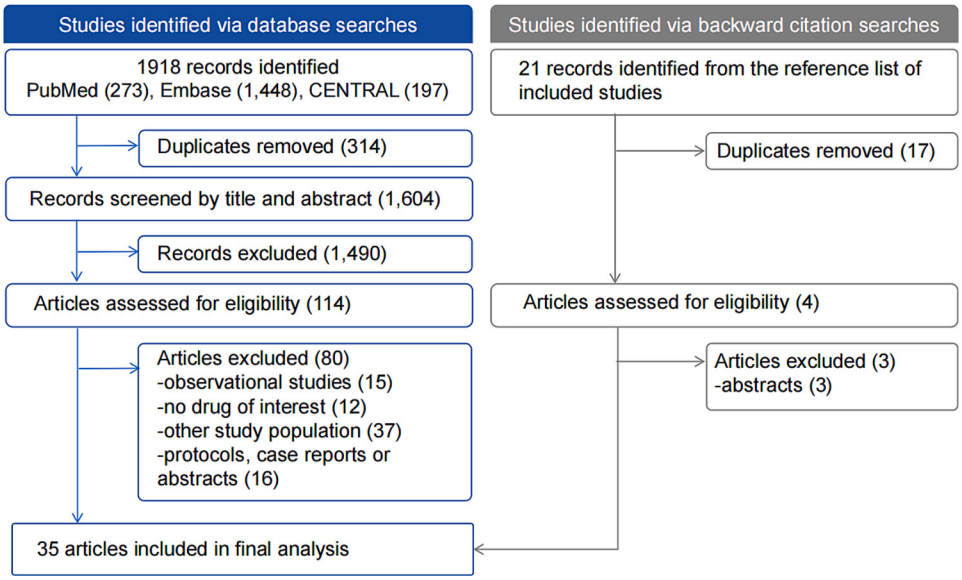

Fig. 1. Flow diagram for study selection.

Table 1
Overview of included studies.

Study	Design	Patients	Sample size	Median age (range)	Female percentage (%)	Histologic subtype	Treatment line	Treatment	Primary end-point	ORR (%)[b]	DCR (%)
ICI monotherapy											
Lakhani 2024	phase I dose escalation and expansion	advanced Sarcoma	35	44 (18–86)	46.0	SS (14/35)UPS (6/35) Rhabdomyosarcoma (3/35)Others (12/35)	≥second line	retifanlimab 3 mg/kg Q2W; continued for ≤ 2 years	safety	3.70	40.74
Day 2023	phase I dose escalation and expansion	advanced STS	20	57 (26–85)	50.0	NA	unknown	nofazinlimab 200 mg Q3W; continued for ≤ 2 years	ORR	25.00	68.75
Blay 2023	phase II single-arm	unresectable locally advanced or metastatic sarcomas,	97	51 (35–65)	45.0	Chordoma (34/97) ASPS (14/97)SMRT (12/97)DSRCT (8/97)CCS (3/97) SFT (3/97)ES (6/97)MLS (3/97)U-LMS (2/97)AS (1/97)FS (1/97) others (10/97)	≥second line	pembrolizumab 200 mg Q3W; continued for ≤ 2 years	12-week ORR	17.53	53.61
Chen 2023	phase II single-arm	advanced ASPS[a]	52	NA	50.0	ASPS (52/52)	unknown	atezolizumab 15 mg/kg Q3W	ORR	36.54	90.38
Chawla 2022	phase II randomized	locally advanced, relapsed, or metastatic SS or MLS	44	NA	43.2	MLS (14/43)SS (29/43)	≥second line	atezolizumab 1200 mg Q3W; continued for ≤ 2 years	PFS, OS	0.00[c]	40.50
Naing 2021	dose-finding and first-in-human study	advanced UPS	20	63 (33–80)	40.0	UPS (20/20)	unknown	pacmilimab 10 mg/kg Q2W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	safety, ORR	5.88	29.41
Shi 2020	phase II single-arm	unresectable, recurrent, or metastatic ASPS	37	30 (19–52)	59.5	ASPS (37/37)	unknown	geptanolimab 3 mg/kg Q2W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	ORR	37.84	86.49
Yang 2020	phase I dose escalation and expansion	metastatic or recurrent ASPS	12	NA	NA	ASPA (12/12)	unknown	toripalimab 3 mg/kg or 10 mg/kg Q2W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	safety	25.00	91.67
Tamura 2019	phase II single-arm	STS not curable by surgical or radiation therapy	21	51 (36-77)	52.0	DDLPS (2/21)MLS (2/21)PLS (1/21)other LPS (3/21)LMS (3/21) Myofibrosarcoma (2/21)UPS (1/21)AS (1/21)others (6/21)	≥second line	nivolumab 240 mg Q2W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	ORR	0.00	47.62
D'Angelo 2018	phase II randomized	locally advanced unresectable or metastatic STS	43	56 (21–76)	48.8	LMS (15/43)LPS (3/43)SS (2/43)UPS (5/43)ASPS	≥second line	nivolumab 3 mg/kg Q2W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	ORR	7.90	NA

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Patients	Sample size	Median age (range)	Female percentage (%)	Histologic subtype	Treatment line	Treatment	Primary end-point	ORR (%)[b]	DCR (%)
						(1/43)ES (1/43)SFT (1/43)MPNST (1/43) others (14/43)					
Ben-Ami 2017	phase II single-arm	advanced Leiomyosarcoma of the Uterus	12	55 (29–73)	NA	LMS(12/12)	≥second line	nivolumab 3 mg/kg Q2W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	ORR	0.00	NA
Tawbi 2017	phase II single-arm	metastatic or surgically unresectable locally advanced sarcoma	42	53 (18–81)	36.0	LMS(10/40)DDLPS (10/40)UPS (10/40)SS (10/40)	≥second line	pembrolizumab 200 mg Q3W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	ORR	17.50	55.00
Maki 2013	phase II single-arm	advanced synovial sarcomas	6	38 (23–57)	66.7	SS(6/6)	≥second line	ipilimumab 3 mg/kg Q3W; for three cycles	ORR	0.00	0.00
Dual Checkpoint Inhibitors											
Kelly 2023	phase II single-arm	metastatic or locally advanced sarcoma	30	54 (24–78)	40.0	LMS (5/30)UPS (5/30)MFS (2/30)DDLPS (2/30) PLS (1/30)EHE (3/30)AS (2/30)SFT (1/30)DSRCT (1/30)other (8/30)	≥second line	epacadostat 100 mg bid + pembrolizumab 200 mg Q3W; continued until patients had CR, PD, or unacceptable toxicity or after 12 months of therapy	24-week ORR	3.33[d]	46.67
Xie 2023	phase Ib single-arm	refractory ASPS	6	NA	NA	ASPS(6/6)	≥second line	TQB2858 1200 mg Q3W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	ORR	33.30	66.70
Somaiah 2022	phase II single-arm	advanced or metastatic sarcoma	57	48 (35–59)	46.0	LPS (6/57)ASPS (10/57)Chordoma (5/57)UPS (5/57) SS (5/57)AS (5/57)LMS (5/57)other (16/57)	≥second line	durvalumab 1500 mg + tremelimumab 75 mg for four cycles, followed by durvalumab Q4W for up to 12 months	12-week PFS rate	12.28[e]	47.37
Wagner 2021	phase II single-arm	metastatic or unresectable angiosarcoma	16	68 (25–81)	38.0	AS(16/16)	unknown	nivolumab 240 mg Q2W + ipilimumab 1 mg/kg Q6W; until tumor progression	ORR	28.57	42.86
D'Angelo 2018	phase II randomized	locally advanced unresectable or metastatic STS	42	57 (27–81)	54.8	AS (3/42)LMS (14/42)LPS (2/42)SS (2/42) UPS (6/42)ASPS (1/42)MPNST (1/42)MFS (1/42)Others (12/42)	≥second line	nivolumab 3 mg/kg and ipilimumab 1 mg/kg Q3W followed by nivolumab 3 mg/kg Q2W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	ORR	12.20	NA

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Patients	Sample size	Median age (range)	Female percentage (%)	Histologic subtype	Treatment line	Treatment	Primary end-point	ORR (%)[b]	DCR (%)
Anti-PD1 + TKI											
Cho 2024	phase II single-arm	locally advanced or metastatic STS	47	51 (22–72)	53.2	LMS (12/47)MPNST (5/47)SS (4/47)MFS (4/47)DSRCT (4/47)UPS (4/47)DDLPS (3/47)CCS (2/47)ESS (2/47)ASPS (2/47) AS (2/47)Other (3/47)	≥second line	pazopanib 800 mg Qd + durvalumab 1500 mg Q3W until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	ORR	30.43	89.13
Liu 2022	phase II single-arm	locally advanced or metastatic STS	30	33 (19–67)	46.7	ASPS (12/30)SS (7/30)UPS (5/30)LMS (4/30) FS (1/30)ES (1/30)	unknown	anlotinib 12 mg Qd + TQB2450 1200 mg Q3W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	ORR	36.67	76.67
Broto 2020	phase Ib single-arm	advanced STS	16	38 (25–78)	37.0	SS (2/16)UPS (2/16)CCS (4/16)AS (2/16)ASPS (3/16)Other (3/16)	unknown	nivolumab 3 mg/kg Q2W + sunitinib 37.5 mg or 25 mg	the recommended dose for phase II	50.00	71.43
Broto 2020	phase II single-arm	advanced STS	52	43 (19–77)	42.0	SS (9/52)UPS (8/52) CCS (7/52)SFT (7/52)ES (7/52)AS (5/52)ASPS (4/52)EMC (4/52) EHE (1/52)	unknown	sunitinib 37.5 mg as induction and then 25 mg + nivolumab 3 mg/kg Q2W	6-month PFS rate	13.04	84.78
Wilky 2019	phase II single-arm	advanced or metastatic sarcomas	33	44 (27–62)	45.0	ASPS(12/33) UPS(5/33) ULMS(4/33) Non-ULMS(2/33) DDLPS(2/33) ES(1/33) MPNST (1/33) EHE (1/33) AS(1/33) SS (1/33) other(3/33)	≥second line	axitinib 5 mg bid + pembrolizumab 200 mg Q3W thereafter for up to 2 years	3-month PFS rate	25.00	53.13
Anti-PD1 + chemotherapy											
Haddox 2024	phase II single-arm	locally advanced or metastatic STS	57	NA (29–80)	57.9	DDLPS(17/57)PLS (2/57)MLS (1/57)LMS (19/57)UPS (8/57)AS (3/57)	unknown	pembrolizumab 200 mg + eribulin 1.4 mg/m2 (day 1, 8) Q3W; until progression, unacceptable toxicity, or completion of 2 years of treatment	12-week PFS rate	19.64	58.93

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Patients	Sample size	Median age (range)	Female percentage (%)	Histologic subtype	Treatment line	Treatment	Primary end-point	ORR (%)[b]	DCR (%)
						MPNST (1/57)MFS (1/57)Other (5/57)					
Tian 2024	phase II single-arm	locally advanced or metastatic STS	40	NA	30.0	UPS(10/40)ES (8/40)FS (7/40)AS (5/40) MFS (3/40)MPNST (2/40)LMS (2/40)SS (2/40)DDLPS (1/40)	≥second line	nab-paclitaxel 260 mg/m2 Q3W for up to six cycles + camrelizumab 200 mg Q3W for up to 1 year	ORR, PFS, safety	22.50	50.00
Gordon 2023	phase II single-arm	locally advanced unresectable or metastatic STS	92	NA	56.4	LPS(12/92)LMS (23/92)UPS (9/92) Rhabdomyosarcoma (5/92)SS (5/92)CCS (4/92) MFS (4/92)MPNST (3/92)MLS (3/92)DSRCT (1/92)others (23/92)	First-Line	ipilimumab 1 mg/kg + nivolumab 3 mg/kg + trabectedin 1.2 mg/m2; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	ORR	25.32	87.34
Tian 2022	phase II single-arm	locally advanced or metastatic STS	38	NA	47.4	UPS (16/38)SS (4/38)DDLPS (3/38)LMS (3/38)MFS (2/38)MLS (2/38) AS(2/38)ES (2/38) Rhabdomyosarcoma (1/38)MPNST (1/38)CCSS (1/38) others(1/38)	≥second line	sintilimab 200 mg + doxorubicin 35 mg/m2 Q3W up to six cycles while sintilimab treatment continued for up to 2 years	safety, ORR	39.47	71.05
Toulmonde 2022	phase Ib single-arm	locally advanced or metastatic STS	16	66 (25–75)	62.5	LMS (6/16)DDLPS (2/16)UPS (2/16)SS (1/16)MPNST (1/16)SFT (1/16)PLS (1/16)ES (1/16)Others (1/16)	≥second line	trabectedin 1.2 mg/m2 + durvalumab 1120 mg Q3W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	ORR	7.14	64.29
Wagner 2022	phase I/II single-arm	metastatic or unresectable LMS or LPS	35	59 (NA, NA)	57.0	ULMS(6/35)non-ULMS (18/35)DDLPS (9/35)MLS (1/35)PLS (1/35)	≥second line	1.5,1.2,1.0 mg/m2 trabectedin + avelumab 800 mg	safety, ORR	12.12	60.61

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Patients	Sample size	Median age (range)	Female percentage (%)	Histologic subtype	Treatment line	Treatment	Primary end-point	ORR (%)[b]	DCR (%)
Italiano 2022	phase II single-arm	advanced nonresectable/ metastatic STS with tertiary lymphoid structures	35	69 (20–89)	45.7	LPS(12/35)LMS (4/35)UPS (6/35) ES(3/35)others (10/35)	unknown	cyclophosphamide 50 mg bid + pembrolizumab 200 mg Q3W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	6-month PFS rate	30.00	63.33
Livingston 2021	phase II single-arm	unresectable or metastatic STS	30	NA	53.3	LMS (10/30)LPS (7/30)UPS (4/30)AS (2/30)SS (1/30) Rhabdomyosarcoma (1/30)EAS (1/30)others (4/30)	first-line	doxorubicin (60 mg/m2 on cycle 1 with escalation to 75 mg/m2 on cycle 2 as tolerated) + pembrolizumab 200 mg Q3W for 24 months	safety	36.67	80.00
Pollack 2020	phase I/II single-arm	metastatic/unresectable sarcoma	37	58 (26–80)	41.0	LMS (11/37)DDLPS (4/37) UPS (3/37)EHE (2/37)ES (1/37)ASPS (1/37)AS (1/37)PLS (1/37)MFS (1/37) SFT (2/37)others (10/37)	unknown	pembrolizumab 200 mg + doxorubicin 45 or 75 mg/m2 Q3W for up to 6 cycles, pembrolizumab treatment continued for up to 2 years	ORR	19.44	80.56
Toulmonde 2018	phase II single-arm	locally advanced or metastatic STS	57	60 (19–84)	42.0	LMS (15/57)UPS (16/57)GIST (10/57)ESS (3/57) MFS (2/57)SFT (1/57)SS (1/57)AS (1/57)MLS (1/57)PLS (1/57)DDLPS (2/57) Others (4/57)	≥second line	cyclophosphamide 50 mg bid + pembrolizumab 200 mg Q3W	6-month ORR, 6-month DCR	2.00	34.00
ICI + immunomodulator											
Toulmonde 2024	phase II single-arm	advanced, 'cold' STS, characterized by an absence of tertiary lymphoid structures	14	63 (37–79)	57.2	LMS(6/14)AS (2/14)DDLPS (1/14)MLS (1/14)ES (1/14)ESS (1/14)UPS (1/14)others (1/14)	≥second line	JX-594 + Cyclophosphamide 50 mg bid + avelumab10 mg/kg Q2W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	6-month PFS rate	7.14	42.86
Chawla 2023	phase II single-arm	metastatic or locally advanced sarcoma	50	NA	54.0	UPS(3/50)LMS (15/50)SS (8/50)DDLPS (4/50)MLS (4/50)CCCS (1/50)	≥second line	trabectedin 1.2 mg/m2 Q3W + nivolumab 3 mg/kg Q2W + intratumoral talimogene laherparepvec Q2W	12-month PFS rate	7.69	84.62

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Patients	Sample size	Median age (range)	Female percentage (%)	Histologic subtype	Treatment line	Treatment	Primary end-point	ORR (%)[b]	DCR (%)
						DSRCT (1/50)ES (1/50) Rhabdomyosarcoma (1/50)others (12/50)					
Zhou 2023	phase I	unresectable recurrent or metastatic soft-tissue sarcoma	13	NA	NA	NA	≥second line	MASCT-I + camrelizumab 200 mg Q3W + apatinib 250 mg Qd; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal or end of the study	safety	30.77	76.92
Chawla 2022	phase II randomized	locally advanced, relapsed, or metastatic SS or MLS	45	NA	42.2	MLS(12/45)SS (33/45)	≥second line	CMB305 + atezolizumab 1200 mg Q3W; continuing up to 2 years	PFS, OS	2.30[c]	55.80
Kelly 2020	phase II single-arm	metastatic or locally advanced sarcoma	20	64 (24–90)	60.0	LMS(5/20)AS (3/20)UPS (2/20)ASPS (1/20)SS (1/20)MPNST (1/20) ES (1/20)MFS (1/20)others (5/20)	≥second line	pembrolizumab 200 mg + T-VEC Q3W; until confirmed disease progression, unacceptable toxicity, voluntary withdrawal, end of the study or had received the maximum duration of therapy (12 months)	24-week ORR	35.00	70.00

STS: Soft tissue sarcoma; ASPS: Alveolar soft-part sarcoma; AS: Angiosarcoma; CCS: Clear cell sarcoma; DSRCT: Desmoplastic small round cell tumor; DDLPS: Dedifferentiated liposarcomas; ES: Epithelioid sarcoma; EAS: Epithelioid angiosarcoma; EMC: Extraskeletal myxoid chondrosarcoma; EHE: Epithelioid hemangioendothelioma; ESS: Endometrial stromal sarcoma; FS: Fibrosarcoma; GIST: Gastrointestinal stromal tumour; HE: Hemangioendothelioma; LMS: Leiomyosarcoma; ULMS: Uterine leiomyosarcoma; MFS: Myxofibrosarcomas; MPNST: Malignant peripheral nerve sheath tumor; MLS: Myxoid liposarcoma; PLS: Pleomorphic liposarcoma; SS: Synovial sarcoma; SFT: Solitary fibrous tumor; SMRT: SMARCA4-deficient malignant rhabdoid tumour; UPS: Undifferentiated pleomorphic sarcoma; ORR: objective response rate; DCR: disease control rate; NA: not available;

a: Three pediatric patients were enrolled; their ages ranged from 12 to 17 years.

b: Best tumor response per RECIST v.1.1 in evaluable patients.

c: On the basis RECIST v1.1 modified to use irRC.

d: The best ORR at 24 weeks by RECIST v1.1.

e: Best overall response was reported by irRECIST.

Table S6 provides the additional outcomes included in this review. It reports the PFS (34 studies), 3-month PFS rates (8 studies), 6-month PFS rates (15 studies), OS (21 studies), and grade 3–5 treatment-related adverse events percentage (G3-5 TRAE %) (20 studies).

3.3. Risk of bias in studies

Appendix Tables S4 and S5 presents the results of risk of bias assessments. For the single arm trials, the overall risk of bias is generally low. However, the scores for "unbiased assessment of the study endpoint" were notably low, indicating that most studies did not strictly adhere to blind evaluations of objective endpoints or double-blind evaluations of subjective endpoints. The highest scores were awarded for "prospective collection of data" and "endpoints appropriate to the aim of the study". Regarding the two RCTs, D'Angelo et al. (2018) was assessed as low risk, while Chawla et al. (2022) showed some concerns.

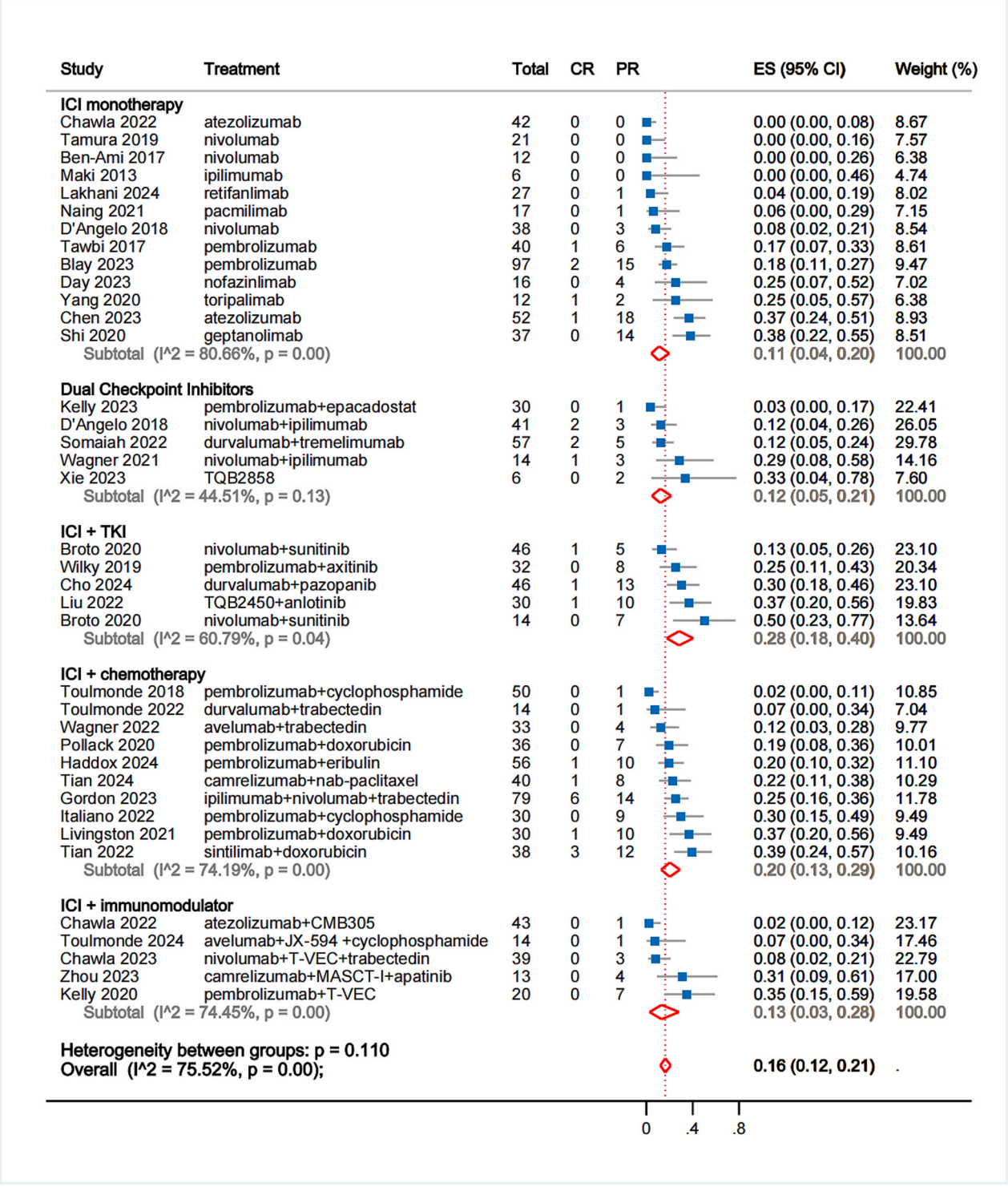

Fig. 2. Objective response rates per treatment group. Objective response rate was defined as the number of responses (complete response (CR) + partial response (PR)) divided by the evaluable subjects in the study.

3.4. The efficacy of ICIs in the treatment of sarcomas

All studies were included in the *meta*-analysis of ORR, resulting in a pooled ORR of 0.16 (95 % CI 0.12–0.21), with significant heterogeneity (I^2 = 75.52 %) (Fig. 2). Additionally, 35 studies were included in the *meta*-analysis of DCR, yielding a pooled DCR of 0.64 (95 % CI 0.57–0.70), also with significant heterogeneity (I^2 = 82.24 %) (Fig. S1).

Table S6 presents additional outcomes. Median progression-free survival (mPFS) was reported in 34 studies, with a median mPFS of 4.1 months (range: 1.4 to 20.8 months). Median overall survival (mOS) was reported in 21 studies, with a median mOS of 18 months (range: 8.8 to 34.7 months). Grade 3–5 TRAEs were reported in 20 studies, with a median incidence of 18.75 % (range: 0 to 57.1 %). Fig. S2 presents the results of the *meta*-analysis for 3-month and 6-month PFS rates. The pooled 3-month PFS rate was 60.32 % (95 % CI 50.18–70.46, 8 studies, I^2 = 67.8 %). The pooled 6-month PFS rate was 37.21 % (95 % CI 24.68–49.74, 15 studies, I^2 = 93.2 %).

This review included only two RCTs. D'Angelo et al. (2018) evaluated nivolumab alone and combined with ipilimumab, finding that while nivolumab alone was minimally effective, the combination therapy was beneficial for certain subtypes like UPS, LMS, and MFS, with a manageable safety profile [26]. Chawla et al. (2022) found that combining CMB305 with atezolizumab did not significantly improve mPFS (2.6 vs. 1.6 months) or OS (18 months for both) over atezolizumab alone in SS or myxoid liposarcoma patients [27].

3.4.1. Subgroup analysis: Response rates per treatment group

Fig. 2 and Fig. S1 shows the subgroup analyses stratified by treatment groups. In this review, 30 treatment regimens were divided into five groups. ICI monotherapy achieved an ORR of 0.11 (95 % CI 0.04–0.20, 13 studies, I^2 = 80.66 %) and a DCR of 0.57 (95 % CI 0.42–0.72, 11 studies, I^2 = 87.29 %). The efficacy of dual checkpoint inhibitors and the combination of ICIs with immunomodulators appears similar to that of ICI monotherapy. Regimens that combined ICIs with chemotherapy agents resulted in an ORR of 0.20 (95 % CI 0.13–0.29, 10 studies, I^2 = 74.19 %) and a DCR of 0.66 (95 % CI 0.54–0.77, 10 studies, I^2 = 83.3 %). ICI combined with tyrosine kinase inhibitor (TKI) had the best curative effect, with ORR and DCR of 0.28 (95 %CI 0.18–0.40, 5 studies, I^2 = 60.79 %) and 0.77 (95 %CI 0.63–0.88, 5 studies, I^2 = 72.48 %), respectively. Aside from the Dual Checkpoint Inhibitors group, substantial heterogeneity exists within other groups and between different groups.

Fig. S3A displays the subgroup analysis results for the ICI monotherapy group, which was segmented into three categories: anti-PD L1, anti-PD 1, and anti-CTLA-4. Among these, the anti-PD 1 group demonstrated an ORR of 0.13 (95 % CI 0.05–0.22, 9 studies, I^2 = 72.44 %). Fig. S3B showed that the anti-PD 1 + chemotherapy subgroup achieved an ORR of 0.22 (95 % CI 0.12–0.35, 7 studies, I^2 = 80.63 %). Fig. S3C

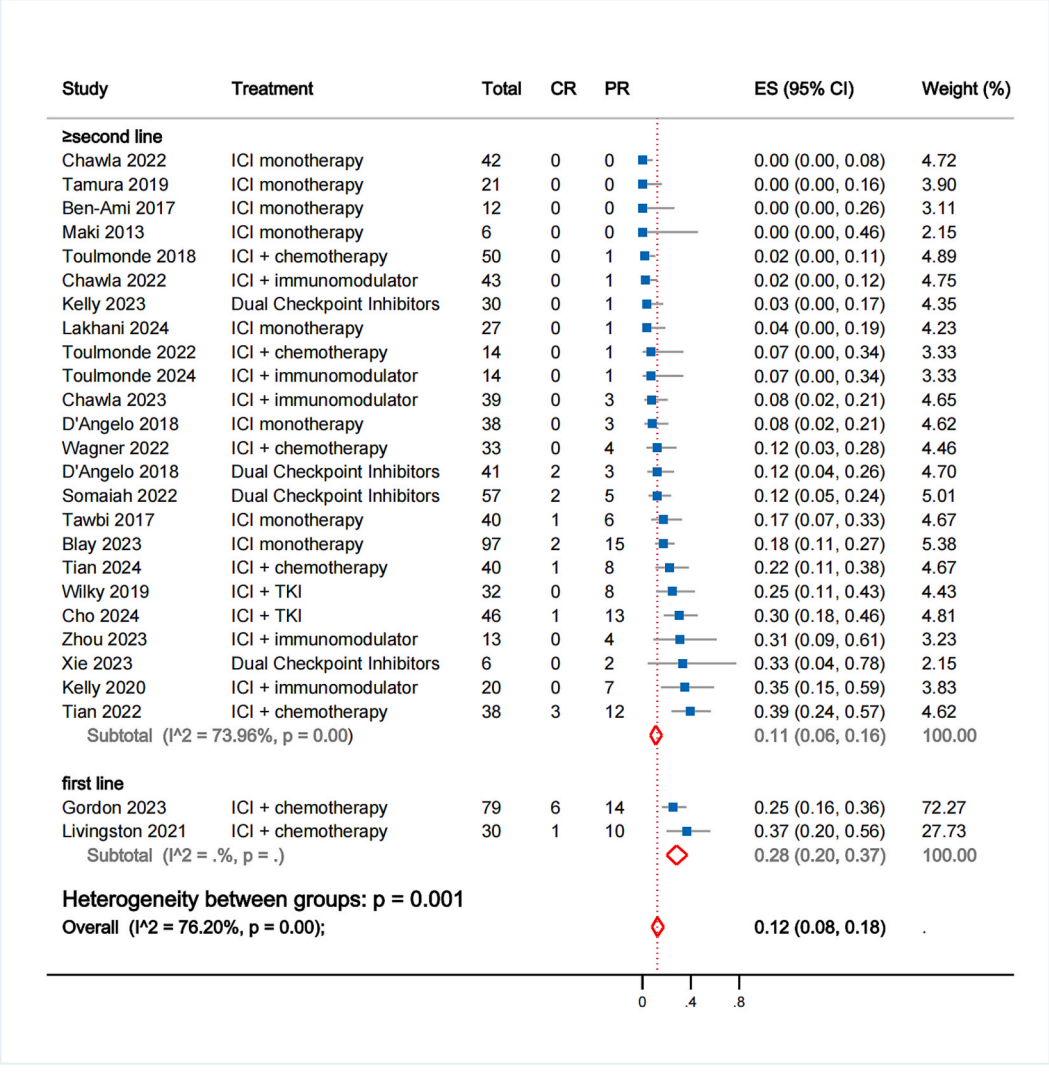

Fig. 3. Objective response rates by treatment line.

revealed that the combination of ICI with doxorubicin was more effective, with an ORR of 0.31 (95 % CI 0.19–0.45, 3 studies, I^2:NA).

3.4.2. Subgroup analysis: Response rates by treatment line

Fig. 3 and Fig. S4 display the efficacy of first-line and ≥second-line treatments. For first-line treatments, the ORR was 0.28 (95 % CI 0.20–0.37, 2 studies, I^2: NA) and the DCR was 0.86 (95 % CI 0.78–0.92, 2 studies, I^2: NA). In contrast, for ≥second-line treatments, both ORR and DCR were significantly lower, at 0.11 (95 % CI 0.06–0.16, 24 studies, I^2 = 73.96 %) and 0.56 (95 % CI 0.48–0.64, 21 studies, I^2 = 75.65 %), respectively.

3.4.3. Subgroup analysis: Response rates per histologic subtypes

Subgroup analysis of histological subtypes involved 24 subtypes, encompassing 1140 patients. Data for each subtype were extracted and pooled according to treatment groups: ICI monotherapy, Dual Checkpoint Inhibitors, ICI + TKI, ICI + chemotherapy, and ICI + immunomodulator. The pooled results for all subtypes are displayed in Fig. 4.

No objective responses were observed in patients with Epithelioid Hemangioendothelioma, MFS, or Rhabdomyosarcoma, likely due to the small sample sizes in these subtypes. Although one patient with Epithelioid Angiosarcoma achieved a PR, this outcome is not statistically significant due to the limited number of patients. The highest ORR among histological subtypes was observed in ASPS at 0.41 (95 % CI 0.22–0.62), while among treatment groups, the combination of ICI with TKI therapy demonstrated the most effective results, achieving an ORR of 0.64 (95 % CI 0.45–0.80) (Fig. S5A). AS and ES both showed favorable ORRs of 0.31. AS treatments with ICI + immunomodulator were particularly effective, achieving an ORR of 0.60 (95 % CI 0.15–0.95) (Fig. S5B). For ES, the highest efficacy was seen with ICI +

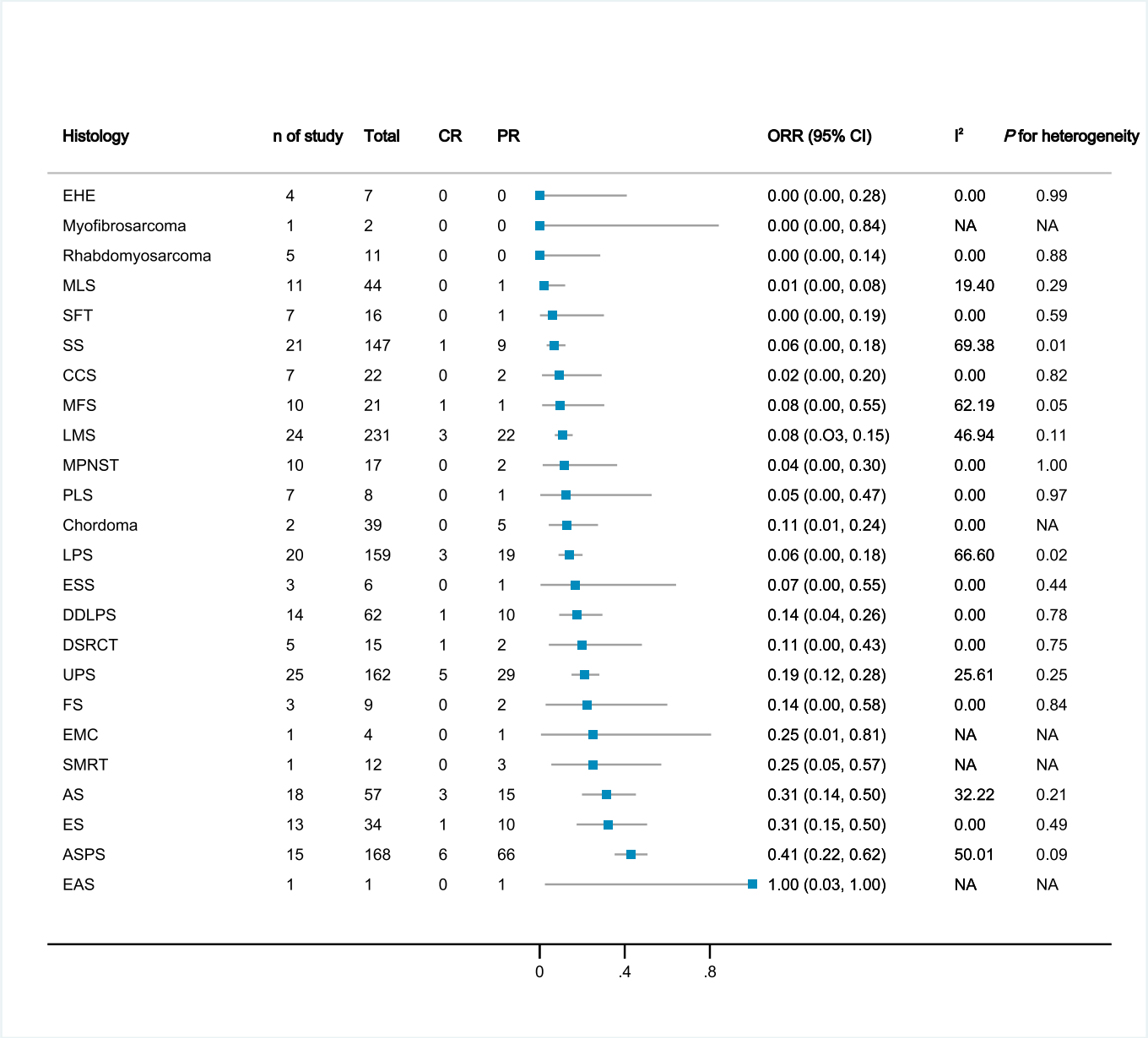

Fig. 4. Objective response rates per histologic subtypes. ASPS: Alveolar soft-part sarcoma; AS: Angiosarcoma; CCS: Clear cell sarcoma; DSRCT: Desmoplastic small round cell tumor; DDLPS: Dedifferentiated liposarcomas; ES: Epithelioid sarcoma; EAS: Epithelioid angiosarcoma; EMC: Extraskeletal myxoid chondrosarcoma; EHE: Epithelioid hemangioendothelioma; ESS: Endometrial stromal sarcoma; FS: Fibrosarcoma; LMS: Leiomyosarcoma; MFS: Myxofibrosarcomas; MPNST: Malignant peripheral nerve sheath tumor; MLS: Myxoid liposarcoma; PLS: Pleomorphic liposarcoma; SS: Synovial sarcoma; SFT: Solitary fibrous tumor; SMRT: SMARCA4-deficient malignant rhabdoid tumour; UPS: Undifferentiated pleomorphic sarcoma; LPS: Liposarcoma. Unknown or unspecified subtypes were not calculated.

chemotherapy, with an ORR of 0.47 (95 % CI 0.21–0.73) (Fig. S5C). For UPS, ICI combined with an immunomodulator achieved the highest ORR of 0.50 (95 % CI 0.12–0.88) (Fig. S5H).

LMS and SS exhibited ORRs below 10 %. However, some treatment regimens demonstrated superior efficacy over others. For LMS, ICI + chemotherapy and Dual Checkpoint Inhibitors showed better efficacy with ORRs of 0.15 (95 %CI 0.09–0.23) and 0.13 (95 %CI 0.03–0.32), respectively (Fig. S5D). For SS, ICI + TKI and ICI + chemotherapy were more effective, with ORRs of 0.17 (95 %CI 0.05–0.39) and 0.29 (95 %CI 0.08–0.58), respectively (Fig. S5G). LPS treatments typically had low efficacy, with an overall ORR of 0.06 (95 %CI 0.00–0.18). The ICI + chemotherapy regimen was more effective, achieving an ORR of 0.23 (95 %CI 0.14–0.33) and significantly outperforming other strategies (Fig. S5E). For specific subtypes, myxoid liposarcoma had a minimal response (ORR 0.01 [95 %CI 0.00–0.08]), while DDLPS responded better, especially to ICI + chemotherapy (ORR 0.21 [95 %CI 0.10–0.37]) and ICI + immunomodulator (ORR 0.20 [95 %CI 0.01–0.72]) treatments (Fig. S5F).

3.4.4. Subgroup analysis: G3-5TRAE (%) per treatment group

Safety analysis included 20 studies and 659 patients. Across all treatment groups, the rate of G3-5 TRAEs was 0.19 (95 % CI 0.13–0.27, 20 studies, I^2 = 80.09 %) (Fig. 5). For ICI monotherapy and ICI + immunomodulator, the toxicity was manageable, with G3-5 TRAE rates of 0.11 (95 % CI 0.04–0.21) and 0.14 (95 % CI 0.06–0.24) respectively. Dual Checkpoint Inhibitors showed slightly higher toxicity at 0.19 (95 % CI 0.11–0.28). ICI + TKI and ICI + chemotherapy groups experienced substantial toxicity, with rates of 0.39 (95 % CI 0.30–0.49) and 0.31 (95 % CI 0.22–0.41) respectively. For the ICI + TKI treatment combination, common grade 3–4 TRAEs include neutropenia and transaminitis.

3.4.5. Sensitivity analysis

Sensitivity analysis excluding studies where any patients received first-line treatments, focusing exclusively on studies enrolling patients undergoing ≥ second-line therapies, resulted in a decreased ORR of 0.09 (95 % CI 0.04–0.17, 15 studies, I^2 = 77.69 %), indicating poorer efficacy in ≥second-line treatments (Fig. S10). Results from other sensitivity analyses did not significantly alter (Fig. S6-9, 11).

4. Discussion

This review included 38 studies with 1349 patients. We comprehensively evaluated the efficacy of ICI therapy for STS, including the use of ICI alone and in combination with chemotherapy, targeted therapy, and other treatment regimens. The *meta*-analysis found that the overall ORR of all treatment combinations was 16 %. Compared with single-drug therapy, combination therapy shows better efficacy, especially the combination of ICI and TKI, with an ORR of 28 %. However, the incidence of adverse events is also relatively high. In addition, our study also revealed that there were significant differences in the efficacy of ICI treatment among different treatment lines and sarcoma subtypes, with first-line treatment being more effective than second-line or more-line treatment, and the efficacy of ASPS, AS, and ES subtypes being better than other subtypes. These findings provide important references for

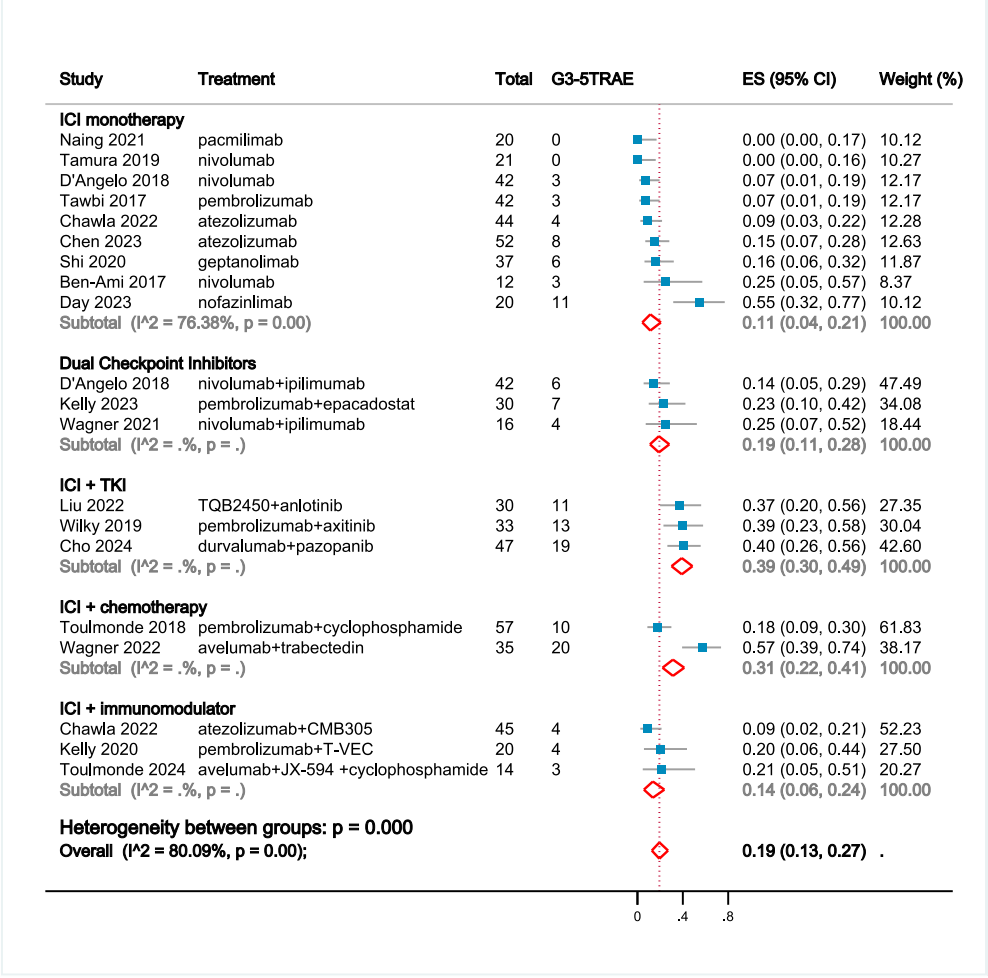

Fig. 5. G3-5TRAE (%) per treatment group.

more precise selection of treatment options in clinical practice.

In the context of metastatic or unresectable diseases, standard treatment typically includes single-agent doxorubicin, or chemotherapy in combination with gemcitabine and docetaxel, with reported response rates between 10 % and 25 % [46]. A *meta*-analysis conducted in 2018 found that, compared to single-agent chemotherapy, multi-drug chemotherapy regimens were associated with improved OS (HR: 0.79) and PFS (HR: 0.86). This analysis included 3210 patients with assessable responses, 631 (19.6 %) of them achieved partial or complete remission, which is comparable to the ORR (20 %) of the ICI plus chemotherapy treatment plan in this study, but lower than the ORR (31 %) of ICI combined with doxorubicin [50]. Additionally, another *meta*-analysis explored the effects of TKIs in advanced sarcoma patients, showing that TKIs have advantages in improving ORR, DCR, as well as PFS and OS. However, only 67 out of 911 patients (7.4 %) achieved objective remission, which is significantly lower than the ORR (28 %) of ICI combined with TKIs in our study [51]. A *meta*-analysis reported in 2021 on the activity of ICIs in STS indicated an ORR of 14 % for all treatment plans, including single-agent as well as combinations with chemotherapy and targeted therapies [9], slightly lower than the conclusion of our study. This discrepancy may arise from the inclusion of novel combination treatment plans in our study, and additionally, our study included more clinical trials and patients, which may also have influenced the results of analysis.

The EORTC 62012 study compared the efficacy of doxorubicin alone versus doxorubicin combined with ifosfamide as first-line treatment for patients with advanced STS, showing an ORR of 26 % for the combination group and 14 % for the monotherapy group [52]. Another single-arm phase II clinical study of anlotinib combined with doxorubicin as first-line treatment for advanced STS patients showed an ORR of 13.3 % [53]. Both are lower than the ORR (28 %) of first-line treatment in this study, suggesting the potential of immunotherapy (especially ICI combined with chemotherapy) for first-line treatment of STS.

A randomized phase II study comparing gemcitabine combined with dacarbazine versus dacarbazine alone for STS patients previously treated showed an ORR of only 4 % for the monotherapy group, while the combination therapy group had an ORR of 12 % [54], comparable to the ORR (11 %) of second-line treatment in this study. Pazopanib, anlotinib, and regorafenib can be considered as second-line treatment options for unresectable or advanced STS [1]. The PALETTE (EORTC 62072) study included 369 patients with metastatic STS who had failed standard chemotherapy and had not received treatment with angiogenesis inhibitors, with ORRs of 6 % and 0 % for the pazopanib and placebo groups, respectively [55]. In the REGOSARC study, the ORRs for regorafenib and placebo groups were 4.5 % and 1.1 %, respectively [56]. Both are lower than the ORR (11 %) of second-line treatment in this study. In a phase II study of anlotinib as second-line treatment for advanced STS, the ORR of anlotinib was 13 % [57], which is comparable to the results of this study. In summary, the efficacy of chemotherapy and targeted monotherapy is poor in the context of second-line treatment, and immunotherapy is worth further exploration.

The analysis of this study highlights the potential of combining ICIs with TKIs in the treatment of STS, especially in the ASPS subtype, where a significant therapeutic advantage is demonstrated. Vascular endothelial growth factor not only promotes tumor angiogenesis, leading to tumor growth and metastasis, but also suppresses immune responses in the tumor microenvironment [41]. Anti-angiogenic therapy can normalize blood vessels in a short time and reduce the number of immune cells that exert immunosuppressive functions [40]. Therefore, the strategy of combining anti-angiogenic and immunotherapy provides new clinical prospects for the treatment of specific subtypes of soft tissue sarcoma. ASPS is a rare type of soft tissue sarcoma, accounting for <1 % of all soft tissue sarcomas, and it shows significant resistance to traditional chemotherapy [3,30]. Strong evidence suggests that the immunological characteristics of ASPS include a high level of tumor-infiltrating immune cells, which is closely related to the clinical efficacy of immunotherapy [39], Chen AP et al. reported that atezolizumab was effective at inducing sustained responses in approximately one third of patients with advanced ASPS [30]. However, it is important to acknowledge the limited activity of ICI monotherapy in ASPS. The OSCAR study, a phase II trial evaluating nivolumab monotherapy in CCS and ASPS, demonstrated a low ORR (4.0 %) in the ASPS cohort (n = 14) [58]. This observation highlights the need for more effective treatment strategies in this subtype. In our analysis, the ORR for ASPS was the highest among all histological subtypes, at 41 %. Among treatment combinations, the combination of ICI and TKI showed the best effect, with an ORR of 64 %. The ORR for ASPS patients treated with TQB2450 in combination with anlotinib reached 75 % [40]. A phase II trial published in 2024 showed that the ORR further increased to 79.3 % in ASPS patients who had not previously received TKI or immunotherapy with this combined treatment regimen [59]. Future clinical trials need to further verify the efficacy of the combination of ICI and TKI in ASPS.

Advanced-stage AS is composed of an aggressive subgroup of sarcomas, characterized by poor prognosis and short duration of sustained response [60]. A study of sorafenib in recurrent or metastatic angiosarcoma showed an ORR of 14 % [61]. In this study, the efficacy of ICIs in AS reached 31 %, ICIs combined with immunomodulators were particularly effective, achieving an ORR of 60 %. The efficacy of ICIs combined with TKIs was also good, reaching 50 %, significantly higher than previous results, indicating that further exploration of combined immunotherapy modalities in AS is valuable. However, the primary tumor site influences ICI efficacy in AS. The Angiosarcoma Project has shown that AS of the head, neck, face, and scalp (HNFS) may be more sensitive to ICI treatment due to high tumor mutation burden and a dominant ultraviolet damage mutational signature, with two cases of exceptional response to anti-PD-1 therapy reported in HNFS patients [62]. The primary site, especially HNFS, should be considered when evaluating ICI treatment for AS. Future research should explore the relationship between primary site, tumor mutation burden, mutational signatures, and ICI response.

ES is a rare sarcoma, the incidence of which is <1 % of all sarcomas. It mainly occurs in young and middle-aged men aged 20–40 years [63]. The largest retrospective series of systemic therapy in ES included 115 patients from 17 sarcoma centers and found a response rate of 22 % for anthracycline-based regimens and 27 % for gemcitabine-based regimens, with pazopanib showing no objective response [64]. A retrospective multicenter real-world study involving 74 patients with ES demonstrated the actual effectiveness of conventional chemotherapy with an ORR of 15 % for first-line treatment and 9 % for second-line and beyond [65]. These studies suggest that the efficacy of chemotherapy is limited, whereas in this study, ES showed a more favorable ORR of 31 %. Moreover, the highest efficacy was observed with the combination of ICIs and chemotherapy, with an ORR of 47 %, thus future research can further explore the integration of chemotherapy with immunotherapy in ES.

LMS accounts for 15 %–20 % of all newly diagnosed soft tissue tumors in adults. It is common in retroperitoneum and uterus [66]. A phase III study involving 423 patients with advanced LMS compared the efficacy of trabecotidine and dacarbazine. The results showed that the ORR of the two groups were 10 % and 7 % respectively [67], which was equivalent to the ORR (8 %) of LMS in this study. However, this study also found that ICI plus chemotherapy and dual checkpoint inhibitors showed relatively good efficacy with ORR of 15 % and 13 %, respectively, suggesting that there is a certain potential to explore the treatment of immune combination in LMS.

LPS are among the more common STS subtypes, accounting for approximately 15 %–20 % of all STSs [68]. A Phase III study involving 154 patients with advanced LPS compared the efficacy of trabecotidine and dacarbazine, and showed that the ORR of the two groups was 9 % and 6 %, respectively, which was comparable to the ORR of 6 % in this study [67]. However, the ICI + chemotherapy regimen was found to be the most effective in LPS patients in this study, achieving an ORR of 23

%, much higher than other treatment regiments. This study also analyzed the histological subtype of DDLPS, which is a high-grade and aggressive disease insensitive to radiotherapy and chemotherapy [68]. Our results showed that patients with DDLPS also achieved a good ORR (21 %) using ICI plus chemotherapy. Therefore, it is very valuable to further explore the combination of immunotherapy combined chemotherapy in patients with LPS.

SS represent a unique subset of STS and account for 5–10 % of all STS, differs from other STS by the relatively young age at diagnosis and clinical presentation [69]. Pooled data from 15 trials on advanced STS demonstrated significantly better response to chemotherapy compared to other STS (27.8 vs 18.8 %) [70]. In this study, the ORR of SS was only 6 %, even though the combination of ICI + chemotherapy achieved 29 % ORR. Therefore, whether to provide immunotherapy for SS needs careful consideration.

For UPS, Maki and colleagues studied 19 patients diagnosed with UPS who received gemcitabine or gemcitabine combined with docetaxel, and 32 % of them had documented responses [71]. In the multicenter phase II study (SARC028), the ORR for UPS patients treated with pembrolizumab was 40 %, whereas in a subsequent cohort expansion trial, the ORR declined to 23 % [72]. In this study, the ORR of UPS is 19 %, and the highest ORR of ICI combined with immunomodulators is 0.50, which is applied to 6 patients, representing a small sample size. ICI plus chemotherapy ORR 26 % but equivalent to immunotherapy or chemotherapy alone, but may cause greater toxicity due to combination therapy.

5. Strengths and limitations

This article comprehensively incorporates the latest research and employs systematic methodologies to select studies, assess their quality, and synthesize data, providing a holistic overview of the efficacy and safety of ICI in the treatment of STS. However, despite stringent inclusion and exclusion criteria, the evidence relied upon exhibits certain limitations. Primarily, this study predominantly relies on single-arm phase II clinical trials designed for preliminary evaluation of treatment regimens. These trials often lack a randomized control group, which may lead to results being influenced by patient selection bias or other uncontrolled confounding factors. Additionally, the typically small sample sizes of these trials might result in insufficient statistical power, limiting the generalizability of the conclusions. Secondly, due to the distinct heterogeneity in trial design and execution, such as variations in drug dosages, treatment combinations, and baseline characteristics of patients, these factors can affect the reliability and consistency of the results. Although we conducted extensive subgroup analyses on treatment regimens, lines of therapy, and disease subtypes, substantial heterogeneity still exists among the subgroups. Furthermore, while we conducted literature searches across three major databases to cover relevant studies as broadly as possible, limitations due to language and database scope might have prevented the inclusion of all pertinent research.

6. Future directions

The findings of this study provide important insights for future research directions. Our research reveals the following key points, which are instructive for the design and implementation of future research:

Firstly, this study mainly relies on data from single-arm phase II clinical trials. Although such studies can provide preliminary efficacy information, there are obvious limitations. Therefore, future research should include RCTs, which can not only verify short-term efficacy, but also explore the long-term efficacy and safety of different treatment options, thereby ensuring the broad applicability and reliability of research results. In addition, future research should explore more innovative treatment combinations, such as combining existing drugs with emerging targeted drugs or immune modulators, especially for those subtypes that have poor traditional treatment effects, new treatment options may bring breakthrough therapeutic effects. Further research is needed to explore the appropriate drug dose to balance the safety and effectiveness of treatment. Several randomized controlled clinical trials are currently underway in sarcoma patients, including the treatment regimen of PD-1 blockade combined with pazopanib compared to pazopanib alone (NCT05679921), the treatment regimen of nivolumab combined with ipilimumab compared to pazopanib (RARImmune, NCT04741438), and the treatment regimen of pembrolizumab combined with radiotherapy compared to radiotherapy alone (SU2CSARC032, NCT03092323).

Future studies should also prioritize the exploration of biomarkers. Although our data demonstrate significant differences in efficacy between various treatment regimens and subtypes, the specific underlying reasons remain unclear. Shi et al. found that the proportion of $CD4^+$ T cells at baseline was negatively correlated with patient response [31]. Cho et al. found that the infiltration of $CD20^+$ B cells was the only independent predictor of prolonged PFS [39]. Another study found that the presence of tumor-infiltrating lymphocytes in tumors is associated with poor PFS [25]. There is also evidence that the tertiary lymphoid structure (TLS) may become a potential predictor for evaluating the efficacy of immunotherapy in patients with sarcoma. In the PEMBROSARC study, TLS was observed in tumor samples from all patients who achieved PR [45]. However, although the expression of PD-L1 is associated with improved ORR, it does not improve OS or PFS [6,46]. In addition, higher serum levels of IFNα and IL4 are associated with clinical benefit [42]. Future research should focus on identifying biomarkers that can predict treatment efficacy, which is crucial for personalized therapy. By pinpointing patients who are likely to benefit from specific treatment plans, we can optimize treatment strategies to enhance efficiency and cost-effectiveness. Further studies on biomarkers will also deepen our understanding of sarcoma biology and pathogenic mechanisms, thereby advancing the development of new targeted therapies.

7. Conclusions

In conclusion, this systematic review and *meta*-analysis reveals that ICIs, particularly when combined with other drugs, offer significant promise in treating STS. The superior efficacy of these combinations in specific sarcoma subtypes highlights the potential for ICIs to transform treatment paradigms. However, the variability in response across different subtypes and treatment lines underscores the need for more comprehensive, randomized controlled trials to refine and personalize treatment strategies, ensuring optimized outcomes for patients with these diverse and challenging malignancies.

8. Contributors

Conception and design: CY, WW, XHR, and HY. Collection and/or assembly of data: CY, WW, XHR, GYY, YH and WanMZ. Data analysis and interpretation: CY, YH, GYY, WangMZ and WanMZ. Manuscript writing: CY, WW, YH, CT, CYC and GYY. Final approval of manuscript: CY, YH, GYY, WangMZ, CYHBL, WSQ, JS, BM and LX. Guarantor: GYB, NXH and LYT. CY, WW, XHR and YH contributed equally as co-first authors.

CRediT authorship contribution statement

Yang Cao: Writing – original draft, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Wei Wang:** Writing – original draft, Data curation, Conceptualization. **Hairong Xu:** Writing – original draft, Methodology, Data curation. **Hang Yi:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Yinyan Gao:** Validation, Software, Methodology, Conceptualization. **Mingzhong Wan:** Methodology, Formal analysis. **Mingzhao Wang:** Methodology, Conceptualization. **Tong Chen:**

Validation, Software. **Yanchao Chen:** Methodology, Conceptualization. **Yihebali Chi:** Validation, Methodology. **Shuqing Wei:** Writing – review & editing, Validation. **Shi Jin:** Writing – original draft, Visualization. **Ming Bai:** Writing – review & editing, Conceptualization. **Xin Li:** Writing – review & editing, Visualization. **Yibo Gao:** Writing – review & editing, Visualization, Funding acquisition, Conceptualization. **Xiaohui Niu:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Yutao Liu:** Writing – review & editing, Visualization, Methodology, Funding acquisition, Conceptualization.

Funding

Medical Oncology Innovation Team of Cancer Hospital Chinese Academy of Medical Sciences (CICASM-MOIT-202404), the National Natural Science Foundation of China (82122053), Shenzhen Science and Technology Program (ZDSYS20220606101604009), Shenzhen High-level Hospital Construction Fund, Shenzhen Key Medical Discipline Construction Fund (No. SZXK075), and Sanming Project of Medicine in Shenzhen (SZSM202211011).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The lead authors (C.Y. and W.W.) had full access to all the data in the study and had final responsibility for the decision to submit the paper for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2025.114070.

Data availability

Data will be made available on request.

References

[1] M. von Mehren, J.M. Kane, M. Agulnik, M.M. Bui, J. Carr-Ascher, E. Choy, M. Connelly, S. Dry, K.N. Ganjoo, R.J. Gonzalez, A. Holder, J. Homsi, V. Keedy, C. M. Kelly, E. Kim, D. Liebner, M. McCarter, S.V. McGarry, N.W. Mesko, C. Meyer, A. S. Pappo, A.M. Parkes, I.A. Petersen, S.M. Pollack, M. Poppe, R.F. Riedel, S. Schuetze, J. Shabason, J.K. Sicklick, M.B. Spraker, M. Zimel, L.E. Hang, H. Sundar, M.A. Bergman, S.T. Sarcoma, Version 2.2022, J. Natl. Compr. Canc. Netw. 20 (2022) 815–833, https://doi.org/10.6004/jnccn.2022.0035.

[2] R.L. Siegel, K.D. Miller, N.S. Wagle, A. Jemal, Cancer statistics, 2023, CA: A Cancer J. Clin. 73 (2023) 17–48. doi: 10.3322/caac.21763.

[3] S. Stacchiotti, A.M. Frezza, J.-Y. Blay, E.H. Baldini, S. Bonvalot, J.V.M.G. Bovée, D. Callegaro, P.G. Casali, R.C. Chiang, G.D. Demetri, E.G. Demicco, J. Desai, M. Eriksson, H. Gelderblom, S. George, M.M. Gounder, A. Gronchi, A. Gupta, R.L. Haas, A. Hayes-Jardon, P. Hohenberger, K.B. Jones, R.L. Jones, B. Kasper, A. Kawai, D.G. Kirsch, E.S. Kleinerman, A. Le Cesne, J. Lim, M.D. Chirlaque López, R. Maestro, R. Marcos-Gragera, J.M. Broto, T. Matsuda, O. Mir, S.R. Patel, C.P. Raut, A.R.A. Razak, D.R. Reed, P. Rutkowski, R.G. Sanfilippo, M. Sbaraglia, I.-M. Schaefer, D.C. Strauss, K.S. Hall, W.D. Tap, D.M. Thomas, W.T.A. van der Graaf, W. J. van Houdt, O. Visser, M. von Mehren, A.J. Wagner, B.A. Wilky, Y.-J. Won, C.D. M. Fletcher, A.P. Dei Tos, A. Trama, Ultra-rare sarcomas: a consensus paper from the connective tissue oncology society community of experts on the incidence threshold and the list of entities, Cancer 127 (2021) 2934–2942. doi: 10.1002/cncr.33618.

[4] B. Seddon, S.J. Strauss, J. Whelan, M. Leahy, P.J. Woll, F. Cowie, C. Rothermundt, Z. Wood, C. Benson, N. Ali, M. Marples, G.J. Veal, D. Jamieson, K. Küver, R. Tirabosco, S. Forsyth, S. Nash, H.-M. Dehbi, S. Beare, Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial, Lancet Oncol. 18 (2017) 1397, https://doi.org/10.1016/S1470-2045(17)30622-8.

[5] F. Tang, Y. Tie, Y.-Q. Wei, C.-Q. Tu, X.-W. Wei, Targeted and immuno-based therapies in sarcoma: mechanisms and advances in clinical trials, Biochim. Biophys. Acta (BBA) – Rev. Cancer 1876 (2021) 188606, https://doi.org/10.1016/j.bbcan.2021.188606.

[6] E.M. Gordon, S.P. Chawla, W.A. Tellez, E. Younesi, S. Thomas, V.S. Chua-Alcala, H. Chomoyan, C. Valencia, D.A. Brigham, A. Moradkhani, D. Quon, A. Srikureja, S. G. Wong, W. Tseng, N. Federman, 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 (2023) 906, https://doi.org/10.3390/cancers15030906.

[7] M.M. Lynch, B.A. Alexiev, B.A. Schroeder, S.M. Pollack, Combinations of chemotherapy and PD-1/PD-L1 inhibitors in sarcoma, Curr. Treat. Options Oncol. 23 (2022) 1861–1876, https://doi.org/10.1007/s11864-022-01036-1.

[8] B. Hoffner, A.D. Elias, V.M. Villalobos, Targeted therapies in the treatment of sarcomas, Target Oncol. 13 (2018) 557–565, https://doi.org/10.1007/s11523-018-0583-0.

[9] M. Saerens, N. Brusselaers, S. Rottey, A. Decruyenaere, D. Creytens, L. Lapeire, Immune checkpoint inhibitors in treatment of soft-tissue sarcoma: a systematic review and meta-analysis, Eur. J. Cancer 152 (2021) 165–182, https://doi.org/10.1016/j.ejca.2021.04.034.

[10] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, Rev. Esp. Cardiol. (Engl. Ed.) 74 (2021) (2020) 790–799, https://doi.org/10.1016/j.rec.2021.07.010.

[11] S. I, C. Av, Intention-to-treat analysis in clinical trials: principles and practical importance, Revista Portuguesa de Cardiologia: Orgao Oficial Da Sociedade Portuguesa de Cardiologia = Portuguese Journal of Cardiology: An Official Journal of the Portuguese Society of Cardiology 21 (2002). https://pubmed.ncbi.nlm.nih.gov/12522981/ (accessed June 19, 2024).

[12] J.A.C. Sterne, J. Savović, M.J. Page, R.G. Elbers, N.S. Blencowe, I. Boutron, C. J. Cates, H.-Y. Cheng, M.S. Corbett, S.M. Eldridge, J.R. Emberson, M.A. Hernán, S. Hopewell, A. Hróbjartsson, D.R. Junqueira, P. Jüni, J.J. Kirkham, T. Lasserson, T. Li, A. McAleenan, B.C. Reeves, S. Shepperd, I. Shrier, L.A. Stewart, K. Tilling, I. R. White, P.F. Whiting, J.P.T. Higgins, RoB 2: a revised tool for assessing risk of bias in randomised trials, BMJ 366 (2019) l4898, https://doi.org/10.1136/bmj.l4898.

[13] K. Slim, E. Nini, D. Forestier, F. Kwiatkowski, Y. Panis, J. Chipponi, Methodological index for non-randomized studies (minors): development and validation of a new instrument, ANZ J. Surg. 73 (2003) 712–716, https://doi.org/10.1046/j.1445-2197.2003.02748.x.

[14] V.N. Nyaga, M. Arbyn, M. Aerts, Metaprop: a Stata command to perform meta-analysis of binomial data, Arch. Public Health 72 (2014) 39, https://doi.org/10.1186/2049-3258-72-39.

[15] J.P.T. Higgins, J. Thomas, J. Chandler, M. Cumpston, Analysing data and undertaking meta-analysis, Cochrane Handbook for Systematic Reviews of Interventions (2019) 241–284.

[16] Y. Zhou, M. Li, B. Zhang, C. Yang, Y. Wang, S. Zheng, L. Tang, C. Zhou, G. Qian, Y. Huang, W. Yu, H. Li, Y. Wang, A. He, Z. Shen, J. Zhang, X. Li, Q. Yang, H. Hu, Y. Yao, A pilot study of multi-antigen stimulated cell therapy-I plus camrelizumab and apatinib in patients with advanced bone and soft-tissue sarcomas, BMC Med. 21 (2023) 470, https://doi.org/10.1186/s12916-023-03132-x.

[17] N. Lakhani, R. Cosman, U. Banerji, D. Rasco, M. Tomaszewska-Kiecana, E. Garralda, D. Kornacki, J. Li, C. Tian, N. Bourayou, J. Powderly, A first-in-human phase I study of the PD-1 inhibitor, retifanlimab (INCMGA00012), in patients with advanced solid tumors (POD1UM-101), ESMO Open 9 (2024) 102254, https://doi.org/10.1016/j.esmoop.2024.102254.

[18] D. Day, J.J. Park, J. Coward, B. Markman, C. Lemech, J.C. Kuo, A. Prawira, M. P. Brown, S. Bishnoi, D. Kotasek, R.M. Strother, R. Cosman, R. Su, Y. Ma, Z. Yue, H. Hu, R. Wu, P. Li, A.N. Tse, A first-in-human phase 1 study of nofazinlimab, an anti-PD-1 antibody, in advanced solid tumors and in combination with regorafenib in metastatic colorectal cancer, Br. J. Cancer 129 (2023) 1608–1618, https://doi.org/10.1038/s41416-023-02431-7.

[19] A. Naing, F. Thistlethwaite, E.G.E.D. Vries, F.A.L.M. Eskens, N. Uboha, P.A. Ott, P. LoRusso, J. Garcia-Corbacho, V. Boni, J. Bendell, K.A. Autio, M. Randhawa, G. Durm, M. Gil-Martin, M. Stroh, A.L. Hannah, H.-T. Arkenau, A. Spira, CX-072 (pacmilimab), a Probody® PD-L1 inhibitor, in advanced or recurrent solid tumors (PROCLAIM-CX-072): an open-label dose-finding and first-in-human study, J. Immunother. Cancer 9 (2021) e002447, https://doi.org/10.1136/jitc-2021-002447.

[20] Safety and clinical efficacy of toripalimab, a PD-1 mAb, in patients with advanced or recurrent malignancies in a phase I study, Eur. J. Cancer 130 (2020) 182–192, https://doi.org/10.1016/j.ejca.2020.01.028.

[21] L. Xie, X. Liang, J. Xu, X. Sun, K. Liu, K. Sun, Y. Li, X. Tang, X. Li, X. Zhan, X. Niu, W. Guo, Exploratory study of an anti-PD-L1/TGF-β antibody, TQB2858, in patients with refractory or recurrent osteosarcoma and alveolar soft part sarcoma: a report from Chinese sarcoma study group (TQB2858-Ib-02), BMC Cancer 23 (2023) 868, https://doi.org/10.1186/s12885-023-11390-4.

[22] M. Toulmonde, M. Brahmi, A. Giraud, C. Chakiba, A. Bessede, M. Kind, E. Toulza, M. Pulido, S. Albert, J.-P. Guégan, S. Cousin, S. Mathoulin-Pelissier, R. Perret, S. Croce, J.-Y. Blay, I. Ray-Coquard, A. Floquet, A. Italiano, 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 (2022) 1765–1772, https://doi.org/10.1158/1078-0432.CCR-21-2258.

[23] J. Martin-Broto, N. Hindi, G. Grignani, J. Martinez-Trufero, A. Redondo, C. Valverde, S. Stacchiotti, A. Lopez-Pousa, L. D'Ambrosio, A. Gutierrez, H. Perez-Vega, V. Encinas-Tobajas, E. de Alava, P. Collini, M. Peña-Chilet, J. Dopazo, I. Carrasco-Garcia, M. Lopez-Alvarez, D.S. Moura, J.A. Lopez-Martin, Nivolumab and sunitinib combination in advanced soft tissue sarcomas: a multicenter, single-arm, phase Ib/II trial, J. Immunother. Cancer 8 (2020) e001561, https://doi.org/10.1136/jitc-2020-001561.

[24] M.J. Wagner, Y. Zhang, L.D. Cranmer, E.T. Loggers, G. Black, S. McDonnell, S. Maxwell, R. Johnson, R. Moore, P.H. de Viveiros, L. Aicher, K.S. Smythe, Q. He, R.L. Jones, S.M. Pollack, A phase 1/2 trial combining avelumab and trabectedin for advanced liposarcoma and leiomyosarcoma, Clin. Cancer Res. 28 (2022) 2306–2312, https://doi.org/10.1158/1078-0432.CCR-22-0240.

[25] S.M. Pollack, M.W. Redman, K.K. Baker, M.J. Wagner, B.A. Schroeder, E. T. Loggers, K. Trieselmann, V.C. Copeland, S. Zhang, G. Black, S. McDonnell, J. Gregory, R. Johnson, R. Moore, R.L. Jones, L.D. Cranmer, Assessment of doxorubicin and pembrolizumab in patients with advanced anthracycline-naive sarcoma, JAMA Oncol. 6 (2020) 1–5, https://doi.org/10.1001/jamaoncol.2020.3689.

[26] S.P. D'Angelo, M.R. Mahoney, B.A. Van Tine, J. Atkins, M.M. Milhem, B. N. Jahagirdar, C.R. Antonescu, E. Horvath, W.D. Tap, G.K. Schwartz, H. Streicher, A non-comparative multi-center randomized phase II study of nivolumab +/− ipilimumab for patients with metastatic sarcoma (Alliance A091401), Lancet Oncol. 19 (2018) 416–426, https://doi.org/10.1016/S1470-2045(18)30006-8.

[27] S.P. Chawla, B.A. Van Tine, S.M. Pollack, K.N. Ganjoo, A.D. Elias, R.F. Riedel, S. Attia, E. Choy, S.H. Okuno, M. Agulnik, M. von Mehren, M.B. Livingston, V. L. Keedy, C.F. Verschraegen, T. Philip, G.C. Bohac, S. Yurasov, A. Yakovich, H. Lu, M. Chen, R.G. Maki, Phase II randomized study of CMB305 and atezolizumab compared with atezolizumab alone in soft-tissue sarcomas expressing NY-ESO-1, J. Clin. Oncol. 40 (2022) 1291–1300, https://doi.org/10.1200/JCO.20.03452.

[28] C.M. Kelly, C.R. Antonescu, T. Bowler, R. Munhoz, P. Chi, M.A. Dickson, M. M. Gounder, M.L. Keohan, S. Movva, R. Dholakia, H. Ahmad, M. Biniakewitz, M. Condy, H. Phelan, M. Callahan, P. Wong, S. Singer, C. Ariyan, E.K. Bartlett, A. Crago, S. Yoon, S. Hwang, J.P. Erinjeri, L.-X. Qin, W.D. Tap, S.P. D'Angelo, Objective response rate among patients with locally advanced or metastatic sarcoma treated with talimogene laherparepvec in combination with pembrolizumab, JAMA Oncol. 6 (2020) 402–408, https://doi.org/10.1001/jamaoncol.2019.6152.

[29] J.-Y. Blay, S. Chevret, A. Le Cesne, M. Brahmi, N. Penel, S. Cousin, F. Bertucci, E. Bompas, T. Ryckewaert, P. Soibinet, P. Boudou-Rouquette, E. Saada Bouzid, P. Soulie, T. Valentin, J.-P. Lotz, D. Tosi, Z. Neviere, M. Cancel, I. Ray-Coquard, L. Gambotti, F. Legrand, A. Lamrani-Ghaouti, C. Simon, C. Even, C. Massard, Pembrolizumab in patients with rare and ultra-rare sarcomas (AcSé Pembrolizumab): analysis of a subgroup from a non-randomised, open-label, phase 2, basket trial, Lancet Oncol. 24 (2023) 892–902, https://doi.org/10.1016/S1470-2045(23)00282-6.

[30] A.P. Chen, E. Sharon, G. O'Sullivan-Coyne, N. Moore, J.C. Foster, J.S. Hu, B.A. Van Tine, A.P. Conley, W.L. Read, R.F. Riedel, M.A. Burgess, J. Glod, E.J. Davis, P. Merriam, A.R. Naqash, K.K. Fino, B.L. Miller, D.F. Wilsker, A. Begum, K.V. Ferry-Galow, H.A. Deshpande, G.K. Schwartz, B.H. Ladle, S.H. Okuno, J.C. Beck, J. L. Chen, N. Takebe, L.K. Fogli, C.L. Rosenberger, R.E. Parchment, J.H. Doroshow, Atezolizumab for advanced alveolar soft part sarcoma, N. Engl. J. Med. 389 (2023) 911–921, https://doi.org/10.1056/NEJMoa2303383.

[31] Y. Shi, Q. Cai, Y. Jiang, G. Huang, M. Bi, B. Wang, Y. Zhou, G. Wang, H. Ying, Z. Tao, C. Shi, Q. Guo, C. Gao, Activity and safety of geptanolimab (GB226) for patients with unresectable, recurrent, or metastatic alveolar soft part sarcoma: a phase II, single-arm study, Clin. Cancer Res. 26 (2020) 6445–6452, https://doi.org/10.1158/1078-0432.CCR-20-2819.

[32] K. Tamura, K. Hasegawa, N. Katsumata, K. Matsumoto, H. Mukai, S. Takahashi, H. Nomura, H. Minami, Efficacy and safety of nivolumab in Japanese patients with uterine cervical cancer, uterine corpus cancer, or soft tissue sarcoma: multicenter, open-label phase 2 trial, Cancer Sci. 110 (2019) 2894–2904, https://doi.org/10.1111/cas.14148.

[33] E. Ben-Ami, C.M. Barysauskas, S. Solomon, K. Tahlil, R. Malley, M. Hohos, K. Polson, M. Loucks, M. Severgnini, T. Patel, A. Cunningham, S.J. Rodig, F. S. Hodi, J.A. Morgan, P. Merriam, A.J. Wagner, G.I. Shapiro, S. George, Immunotherapy with single agent nivolumab for advanced leiomyosarcoma of the uterus: results of a phase 2 study, Cancer 123 (2017) 3285–3290, https://doi.org/10.1002/cncr.30738.

[34] H.A. Tawbi, M. Burgess, V. Bolejack, B.A. Van Tine, S.M. Schuetze, J. Hu, S. D'Angelo, S. Attia, R.F. Riedel, D.A. Priebat, S. Movva, L.E. Davis, S.H. Okuno, D. R. Reed, J. Crowley, L.H. Butterfield, R. Salazar, J. Rodriguez-Canales, A.J. Lazar, I. I. Wistuba, L.H. Baker, R.G. Maki, D. Reinke, S. Patel, Pembrolizumab in advanced soft tissue and bone sarcomas: results of SARC028, a multicentre, single arm, phase 2 trial, Lancet Oncol. 18 (2017) 1493–1501, https://doi.org/10.1016/S1470-2045(17)30624-1.

[35] R.G. Maki, A.A. Jungbluth, S. Gnjatic, G.K. Schwartz, D.R. D'Adamo, M.L. Keohan, M.J. Wagner, K. Scheu, R. Chiu, E. Ritter, J. Kachel, I. Lowy, L.J. Old, G. Ritter, A pilot study of anti-CTLA4 antibody ipilimumab in patients with synovial sarcoma, Sarcoma 2013 (2013) 168145, https://doi.org/10.1155/2013/168145.

[36] C.M. Kelly, L.-X. Qin, K.A. Whiting, A.L. Richards, V. Avutu, J.E. Chan, P. Chi, M. A. Dickson, M.M. Gounder, M.L. Keohan, S. Movva, B.A. Nacev, E. Rosenbaum, T. Adamson, S. Singer, E.K. Bartlett, A.M. Crago, S.S. Yoon, S. Hwang, J.P. Erinjeri, C.R. Antonescu, W.D. Tap, S.P. D'Angelo, A phase 2 study of epacadostat and pembrolizumab in patients with advanced sarcoma, Clin. Cancer Res. 29 (2023) 2043–2051, https://doi.org/10.1158/1078-0432.CCR-22-3911.

[37] N. Somaiah, A.P. Conley, E.R. Parra, H. Lin, B. Amini, L. Solis Soto, R. Salazar, C. Barreto, H. Chen, S. Gite, C. Haymaker, E.F. Nassif, C. Bernatchez, A. Mitra, J. A. Livingston, V. Ravi, D.M. Araujo, R. Benjamin, S. Patel, M.A. Zarzour, S. Sabir, A.J. Lazar, W.-L. Wang, N.C. Daw, X. Zhou, C.L. Roland, Z.A. Cooper, J. Rodriguez-Canales, A. Futreal, J.-C. Soria, I.I. Wistuba, P. Hwu, Durvalumab plus tremelimumab in advanced or metastatic soft tissue and bone sarcomas: a single-centre phase 2 trial, Lancet Oncol. 23 (2022) 1156–1166, https://doi.org/10.1016/S1470-2045(22)00392-8.

[38] M.J. Wagner, M. Othus, S.P. Patel, C. Ryan, A. Sangal, B. Powers, G.T. Budd, A. I. Victor, C.-T. Hsueh, R. Chugh, S. Nair, K.M. Leu, M. Agulnik, E. Sharon, E. Mayerson, M. Plets, C. Blanke, H. Streicher, Y.K. Chae, R. Kurzrock, Multicenter phase II trial (SWOG S1609, cohort 51) of ipilimumab and nivolumab in metastatic or unresectable angiosarcoma: a substudy of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART), J. Immunother. Cancer 9 (2021) e002990, https://doi.org/10.1136/jitc-2021-002990.

[39] H.J. Cho, K.-H. Yun, S.-J. Shin, Y.H. Lee, S.H. Kim, W. Baek, Y.D. Han, S.K. Kim, H. J. Ryu, J. Lee, I. Cho, H. Go, J. Ko, I. Jung, M.K. Jeon, S.Y. Rha, H.S. Kim, Durvalumab plus pazopanib combination in patients with advanced soft tissue sarcomas: a phase II trial, Nat. Commun. 15 (2024) 685, https://doi.org/10.1038/s41467-024-44875-2.

[40] J. Liu, T. Gao, Z. Tan, S. Li, J. Xu, C. Bai, R. Xue, L. Xie, L. Zhang, Z. Fan, W. Guo, Phase II study of TQB2450, a novel PD-L1 antibody, combination with anlotinib in patients with locally advanced or metastatic soft tissue sarcoma, Clin. Cancer Res. 28 (2022) 3473–3479, https://doi.org/10.1158/1078-0432.CCR-22-0871.

[41] B.A. Wilky, M.M. Trucco, T.K. Subhawong, V. Florou, W. Park, D. Kwon, E. D. Wieder, D. Kolonias, A.E. Rosenberg, D.A. Kerr, E. Sfakianaki, M. Foley, J. R. Merchan, K.V. Komanduri, J.C. Trent, Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial, Lancet Oncol. 20 (2019) 837–848, https://doi.org/10.1016/S1470-2045(19)30153-6.

[42] C.L. Haddox, M.J. Nathenson, E. Mazzola, J.-R. Lin, J. Baginska, A. Nau, J. L. Weirather, E. Choy, A. Marino-Enriquez, J.A. Morgan, G.M. Cote, P. Merriam, A. J. Wagner, P.K. Sorger, S. Santagata, S. George, Phase II study of eribulin plus pembrolizumab in metastatic soft-tissue sarcomas: clinical outcomes and biological correlates, Clin. Cancer Res. 30 (2024) 1281–1292, https://doi.org/10.1158/1078-0432.CCR-23-2250.

[43] Z. Tian, Y. Feng, Y. Yang, X. Liu, G. Qu, Y. Yang, X. Wang, J. Wang, P. Zhang, W. Yao, Combining nanoparticle albumin-bound paclitaxel with camrelizumab in advanced soft tissue sarcoma: activity, safety, and future perspectives, Front. Pharmacol. 15 (2024) 1335054, https://doi.org/10.3389/fphar.2024.1335054.

[44] Z. Tian, S. Dong, W. Zuo, P. Li, F. Zhang, S. Gao, Y. Yang, C. Li, P. Zhang, X. Wang, J. Wang, W. Yao, Efficacy and safety of sintilimab plus doxorubicin in advanced soft tissue sarcoma: a single-arm, phase II trial, Front. Pharmacol. 13 (2022) 987569, https://doi.org/10.3389/fphar.2022.987569.

[45] A. Italiano, A. Bessede, M. Pulido, E. Bompas, S. Piperno-Neumann, C. Chevreau, N. Penel, F. Bertucci, M. Toulmonde, C. Bellera, J.P. Guegan, C. Rey, C. Sautès-Fridman, A. Bougoüin, C. Cantarel, M. Kind, M. Spalato, B. Dadone-Montaudie, F. Le Loarer, J.Y. Blay, W.H. Fridman, Pembrolizumab in soft-tissue sarcomas with tertiary lymphoid structures: a phase 2 PEMBROSARC trial cohort, Nat. Med. 28 (2022) 1199–1206, https://doi.org/10.1038/s41591-022-01821-3.

[46] M.B. Livingston, M.H. Jagosky, M.M. Robinson, W.A. Ahrens, J.H. Benbow, C. J. Farhangfar, D.M. Foureau, D.M. Maxwell, E.A. Baldrige, X. Begic, J. T. Symanowski, N.M. Steuerwald, C.J. Anderson, J.C. Patt, J.S. Kneisl, E.S. Kim, Phase II study of pembrolizumab in combination with doxorubicin in metastatic and unresectable soft-tissue sarcoma, Clin. Cancer Res. 27 (2021) 6424–6431, https://doi.org/10.1158/1078-0432.CCR-21-2001.

[47] M. Toulmonde, N. Penel, J. Adam, C. Chevreau, J.-Y. Blay, A. Le Cesne, E. Bompas, S. Piperno-Neumann, S. Cousin, T. Grellety, T. Ryckewaert, A. Bessede, F. Ghiringhelli, M. Pulido, A. Italiano, Use of PD-1 targeting, macrophage infiltration, and IDO pathway activation in sarcomas, JAMA Oncol 4 (2018) 93–97, https://doi.org/10.1001/jamaoncol.2017.1617.

[48] M. Toulmonde, J.-P. Guegan, M. Spalato-Ceruso, F. Peyraud, M. Kind, L. Vanhersecke, F. Le Loarer, R. Perret, C. Cantarel, C. Bellera, A. Bessede, A. Italiano, 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 (2024) 38, https://doi.org/10.1186/s12943-024-01946-8.

[49] S.P. Chawla, W.A. Tellez, H. Chomoyan, C. Valencia, A. Ahari, N. Omelchenko, S. Makrievski, D.A. Brigham, V. Chua-Alcala, D. Quon, A. Moradkhani, E. M. Gordon, Activity of TNT: a phase 2 study using talimogene laherparepvec, nivolumab and trabectedin for previously treated patients with advanced sarcomas (NCT# 03886311), Front. Oncol. 13 (2023) 1116937, https://doi.org/10.3389/fonc.2023.1116937.

[50] A. Zer, R.M. Prince, E. Amir, A.R. Abdul Razak, Multi-agent chemotherapy in advanced soft tissue sarcoma (STS) – a systematic review and meta-analysis, Cancer Treat. Rev. 63 (2018) 71–78, https://doi.org/10.1016/j.ctrv.2017.12.003.

[51] W. Li, L. Liu, Z. Liang, H. Lai, J. Wu, H. Zhang, C. Fang, Efficacy of tyrosine kinase inhibitors in patients with advanced or metastatic sarcomas after prior chemotherapy: a meta-analysis, Medicine (Baltimore) 103 (2024) e37423, https://doi.org/10.1097/MD.0000000000037423.

[52] I. Judson, J. Verweij, H. Gelderblom, J.T. Hartmann, P. Schöffski, J.-Y. Blay, J. M. Kerst, J. Sufliarsky, J. Whelan, P. Hohenberger, A. Krarup-Hansen, T. Alcindor, S. Marreaud, S. Litière, C. Hermans, C. Fisher, P.C.W. Hogendoorn, A.P. dei Tos, W. T.A. van der Graaf, European organisation and treatment of cancer soft tissue and bone sarcoma group, 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 (2014) 415–423, https://doi.org/10.1016/S1470-2045(14)70063-4.
[53] Y. Zhou, Z. Wang, R. Zhuang, X. Guo, C. Zhang, Y. You, L. Chen, W. Liu, Y. Zhang, W. Lu, A phase II study of epirubicin combined with anlotinib followed by anlotinib in the first-line treatment of advanced unresectablesoft tissue sarcoma, JCO 39 (2021) e23536, https://doi.org/10.1200/JCO.2021.39.15_suppl.e23536.
[54] X. García-Del-Muro, A. López-Pousa, J. Maurel, J. Martín, J. Martínez-Trufero, A. Casado, A. Gómez-España, J. Fra, J. Cruz, A. Poveda, A. Meana, C. Pericay, R. Cubedo, J. Rubió, A. De Juan, N. Laínez, J.A. Carrasco, R. de Andrés, J.M. Buesa, Spanish Group for Research on Sarcomas, Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study, J. Clin. Oncol. 29 (2011) 2528–2533, https://doi.org/10.1200/JCO.2010.33.6107.
[55] W.T.A. van der Graaf, J.-Y. Blay, S.P. Chawla, D.-W. Kim, B. Bui-Nguyen, P. G. Casali, P. Schöffski, M. Aglietta, A.P. Staddon, Y. Beppu, A. Le Cesne, H. Gelderblom, I.R. Judson, N. Araki, M. Ouali, S. Marreaud, R. Hodge, M.R. Dewji, C. Coens, G.D. Demetri, C.D. Fletcher, A.P. Dei Tos, P. Hohenberger, EORTC Soft Tissue and Bone Sarcoma Group, PALETTE study group, Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial, Lancet 379 (2012) 1879–1886, https://doi.org/10.1016/S0140-6736(12)60651-5.
[56] O. Mir, T. Brodowicz, A. Italiano, J. Wallet, J.-Y. Blay, F. Bertucci, C. Chevreau, S. Piperno-Neumann, E. Bompas, S. Salas, C. Perrin, C. Delcambre, B. Liegl-Atzwanger, M. Toulmonde, S. Dumont, I. Ray-Coquard, S. Clisant, S. Taieb, C. Guillemet, M. Rios, O. Collard, L. Bozec, D. Cupissol, E. Saada-Bouzid, C. Lemaignan, W. Eisterer, N. Isambert, L. Chaigneau, A.L. Cesne, N. Penel, 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 (2016) 1732–1742, https://doi.org/10.1016/S1470-2045(16)30507-1.
[57] Y. Chi, Z. Fang, X. Hong, Y. Yao, P. Sun, G. Wang, F. Du, Y. Sun, Q. Wu, G. Qu, S. Wang, J. Song, J. Yu, Y. Lu, X. Zhu, X. Niu, Z. He, J. Wang, H. Yu, J. Cai, Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, patients with refractory metastatic soft-tissue sarcoma, Clin. Cancer Res. 24 (2018) 5233–5238, https://doi.org/10.1158/1078-0432.CCR-17-3766.
[58] T. Nishikawa, S. Kakunaga, K. Tamura, M. Ando, T. Ozaki, A. Kawai, T. Ueda, M. Kawasaki, S. Tomatsuri, N. Okamura, M. Kamikura, A. Hamada, A. Yoshida, A. Hirakawa, T. Shibata, K. Nakamura, K. Yonemori, Efficacy and safety of nivolumab monotherapy in patients with unresectable clear cell sarcoma and alveolar soft part sarcoma (OSCAR Trial/NCCH1510), Cancer 130 (2024) 3836–3844, https://doi.org/10.1002/cncr.35483.
[59] Z. Tan, Y. Wu, Z. Fan, J. Liu, T. Gao, C. Bai, R. Xue, S. Li, L. Zhang, X. Wang, A phase II study of anlotinib and an anti-PDL1 antibody in patients with alveolar soft part sarcoma: results of expansion cohorts, JCO 42 (2024) 11515, https://doi.org/10.1200/JCO.2024.42.16_suppl.11515.
[60] N. Hindi Muñiz, J. Martinez Trufero, G. Grignani, A. Sebio Garcia, 1922P - Immunosarc II master trial: phase II of sunitinib and nivolumab in vascular sarcomas cohort - A GEIS, ISG and UCL study, Ann. Oncol. 34 (2023) S1032–S1061.
[61] R.G. Maki, D.R. D'Adamo, M.L. Keohan, M. Saulle, S.M. Schuetze, S.D. Undevia, M. B. Livingston, M.M. Cooney, M.L. Hensley, M.M. Mita, C.H. Takimoto, A.S. Kraft, A.D. Elias, B. Brockstein, N.E. Blachère, M.A. Edgar, L.H. Schwartz, L.-X. Qin, C. R. Antonescu, G.K. Schwartz, Phase II study of sorafenib in patients with metastatic or recurrent sarcomas, J. Clin. Oncol. 27 (2009) 3133–3140, https://doi.org/10.1200/JCO.2008.20.4495.
[62] C.A. Painter, E. Jain, B.N. Tomson, M. Dunphy, R.E. Stoddard, B.S. Thomas, A. L. Damon, S. Shah, D. Kim, J. Gómez Tejeda Zañudo, J.L. Hornick, Y.-L. Chen, P. Merriam, C.P. Raut, G.D. Demetri, B.A. Van Tine, E.S. Lander, T.R. Golub, N. Wagle, The angiosarcoma project: enabling genomic and clinical discoveries in a rare cancer through patient-partnered research, Nat. Med. 26 (2020) 181–187, https://doi.org/10.1038/s41591-019-0749-z.
[63] M. Meissner, A. Napolitano, K. Thway, P. Huang, R.L. Jones, Pharmacotherapeutic strategies for epithelioid sarcoma: are we any closer to a non-surgical cure? Exp. Opin. Pharmacother. 24 (2023) 1395–1401, https://doi.org/10.1080/14656566.2023.2224500.
[64] A.M. Frezza, R.L. Jones, S. Lo Vullo, N. Asano, F. Lucibello, E. Ben-Ami, R. Ratan, P. Teterycz, K. Boye, M. Brahmi, E. Palmerini, A. Fedenko, B. Vincenzi, A. Brunello, I.M.E. Desar, R.S. Benjamin, J.Y. Blay, J.M. Broto, P.G. Casali, H. Gelderblom, G. Grignani, A. Gronchi, K.S. Hall, O. Mir, P. Rutkowski, A.J. Wagner, O. Anurova, P. Collini, A.P. Dei Tos, U. Flucke, J.L. Hornick, I. Lobmaier, T. Philippe, P. Picci, D. Ranchere, S.L. Renne, M. Sbaraglia, K. Thway, M. Wagrodzki, W.-L. Wang, A. Yoshida, L. Mariani, A. Kawai, S. Stacchiotti, Anthracycline, gemcitabine, and pazopanib in epithelioid sarcoma: a multi-institutional case series, JAMA Oncol. 4 (2018) e180219, https://doi.org/10.1001/jamaoncol.2018.0219.
[65] M.M. Gounder, P. Merriam, R. Ratan, S.R. Patel, R. Chugh, V.M. Villalobos, M. Thornton, B.A. Van Tine, A.H. Abdelhamid, J. Whalen, J. Yang, A. Rajarethinam, M.S. Duh, P.J. Bobbili, L. Huynh, T.I. Totev, A.K. Lax, S. Agarwal, G.D. Demetri, Real-world outcomes of patients with locally advanced or metastatic epithelioid sarcoma, Cancer 127 (2021) 1311–1317, https://doi.org/10.1002/cncr.33365.
[66] N. Devaud, O. Vornicova, A.R. Abdul Razak, K. Khalili, E.G. Demicco, C. Mitric, M. Q. Bernardini, R.A. Gladdy, Leiomyosarcoma: current clinical management and future horizons, Surg. Oncol. Clin. N. Am. 31 (2022) 527–546, https://doi.org/10.1016/j.soc.2022.03.011.
[67] S. Patel, M. von Mehren, D.R. Reed, P. Kaiser, J. Charlson, C.W. Ryan, D. Rushing, M. Livingston, A. Singh, R. Seth, C. Forscher, G. D'Amato, S.P. Chawla, S. McCarthy, G. Wang, T. Parekh, R. Knoblauch, M.L. Hensley, R.G. Maki, G. D. Demetri, Overall survival and histology-specific subgroup analyses from a phase 3, randomized controlled study of trabectedin or dacarbazine in patients with advanced liposarcoma or leiomyosarcoma, Cancer 125 (2019) 2610–2620, https://doi.org/10.1002/cncr.32117.
[68] A.T.J. Lee, K. Thway, P.H. Huang, R.L. Jones, Clinical and molecular spectrum of liposarcoma, J. Clin. Oncol. 36 (2018) 151–159, https://doi.org/10.1200/JCO.2017.74.9598.
[69] A.M. Gazendam, S. Popovic, S. Munir, N. Parasu, D. Wilson, M. Ghert, Synovial sarcoma: a clinical review, Curr. Oncol. 28 (2021) 1909–1920, https://doi.org/10.3390/curroncol28030177.
[70] M. Vlenterie, S. Litière, E. Rizzo, S. Marréaud, I. Judson, H. Gelderblom, A. Le Cesne, E. Wardelmann, C. Messiou, A. Gronchi, W.T. van der Graaf, Outcome of chemotherapy in advanced synovial sarcoma patients: review of 15 clinical trials from the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group; setting a new landmark for studies in this entity, Eur. J. Cancer 58 (2016) 62–72, https://doi.org/10.1016/j.ejca.2016.02.002.
[71] R.G. Maki, J.K. Wathen, S.R. Patel, D.A. Priebat, S.H. Okuno, B. Samuels, M. Fanucchi, D.C. Harmon, S.M. Schuetze, D. Reinke, P.F. Thall, R.S. Benjamin, L. H. Baker, M.L. Hensley, Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected], J. Clin. Oncol. 25 (2007) 2755–2763, https://doi.org/10.1200/JCO.2006.10.4117.
[72] M.A. Burgess, V. Bolejack, S. Schuetze, B.A. Van Tine, S. Attia, R.F. Riedel, J.S. Hu, L.E. Davis, S.H. Okuno, D.A. Priebat, S. Movva, D.R. Reed, S.P. D'Angelo, A. J. Lazar, E.-Z.-Y. Keung, D.K. Reinke, L.H. Baker, R.G. Maki, S. Patel, H.-A.-H. Tawbi, Clinical activity of pembrolizumab (P) in undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated/pleomorphic liposarcoma (LPS): final results of SARC028 expansion cohorts, JCO 37 (2019) 11015, https://doi.org/10.1200/JCO.2019.37.15_suppl.11015.