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Emerging immunotherapy and tumor microenvironment for advanced sarcoma: a comprehensive review

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Sarcomas are heterogeneous mesenchymal malignancies classified as soft-tissue sarcomas (STS) and bone sarcomas. Advanced cases respond poorly to standard therapies, highlighting the need for novel strategies. Immunotherapies, including PD-1/PD-L1 inhibitors, adoptive cellular therapies, vaccines, and oncolytic viruses, have shown promise in specific sarcoma subtypes. This review explores these approaches, emphasizing the prognostic significance of immune cells within the tumor microenvironment (TME), such as tumor-associated macrophages (TAMs) and tumor-infiltrating lymphocytes (TILs), and their correlation with clinical outcomes. We also discuss challenges in immunotherapy efficacy, the importance of biomarker-driven personalized therapies, and the potential of a combination regimen with chemotherapy, radiation, and cytokine agents. Overall, this review highlights the evolving role of immunotherapy in advanced sarcomas, the critical influence of the TME, and the need to optimize synergistic treatment approaches to enhance patient outcomes.

KEYWORDS

sarcoma, immunotherapy, adoptive T cell therapy, vaccine, immune checkpoint inhibitors

Introduction

Sarcomas are heterogeneous malignancies arising from mesenchymal precursors encompassing bone, cartilage, fat, and muscle. Although rare in adults, comprising about 1% of global cancer diagnoses, sarcomas account for nearly 15% of pediatric malignancies (1). The World Health Organization recognizes over 70 subtypes, typically classified into two primary categories: soft-tissue sarcoma (STS) and bone sarcoma, each with unique

biology and clinical behaviors (2, 3). For localized disease, the current standard treatment is surgical resection often combined with radiotherapy. Nevertheless, approximately half of patients with high-grade tumors later develop metastasis, yielding a median overall survival (OS) of 14–19 months (4). For unresectable or advanced cohorts, standard first-line systemic therapy is doxorubicin alone or in combination with the alkylating drug ifosfamide (5). Second-line settings, such as novel chemotherapeutic agents trabectedin (6), eribulin (7), and tyrosine kinase inhibitors (TKIs) like pazopanib (8) are useful therapy options for specific sarcoma subtypes. Notably, their significance for enhancing OS remains uncertain. These therapies only yield limited durable response, with objective response rates (ORR) of 10-20% and median progression-free survival (PFS) of 4 months, highlighting the crucial need for more effective treatment options.

Specific challenges in sarcoma treatment

Immunotherapies, especially immune checkpoint inhibitors (ICIs), have achieved considerable benefit in certain sarcoma subtypes. Multiple trials are investigating ICI combinations with other therapies. However, specific challenges remain due to sarcoma heterogeneity, limited targetable antigens, and a lack of subtype-specific trials. ICIs generally demonstrate lower efficacy in sarcomas than in other solid tumors, with basket trials often grouping diverse subtypes, which complicates the identification of effective treatments for rare forms (9). Additionally, immunosuppressive tumor microenvironments (TME), low tumor mutational burdens (TMB), and weak immunogenicity of tumor-associated antigens (TAAs) hinder treatment success. Despite these limitations, combining ICI with other medications has shown promising synergistic advantages. Emerging approaches, such as adoptive cell transfer and oncolytic viruses (OVs), offer new opportunities to address these challenges and may enhance therapeutic outcomes for sarcoma patients.

This article reviews the current evidence supporting the utility of immunotherapy in advanced sarcoma, as well as the existing immunotherapy strategies (Figure 1), including anti-PD-1/PD-L1 therapy, adoptive T-cell therapy (ACT), vaccines, oncolytic virus, and cytokine-based immunotherapy.

Abbreviations: AS, Angiosarcoma; ASPS, Alveolar soft-part sarcoma; CAR, Chimeric antigen receptor; CR, Complete response; CTLA4, Cytotoxic T-lymphocyte-associated protein 4; DCs, Dendritic cells; FDA, Food and Drug Administration; GIST, Gastrointestinal stromal tumor; HIV, Human immunodeficiency virus; KS, Kaposi's sarcoma; LAG-3, Lymphocyte activation gene 3; MSI, Microsatellite instability; New York esophageal squamous cell carcinoma 1 gene; ORR, Objective response rate; OS, Overall survival; PD-1, Programmed cell death 1; PD-L1, Programmed death ligand 1; PFS, Progression free survival; RCC, Renal cell carcinoma; SS, synovial sarcoma; STS, Soft-tissue sarcoma; TCR, T cell receptor; TIL, Tumor-infiltrating lymphocyte; TLS, Tertiary lymphoid structures; TMB, Tumor mutational burden; TME, Tumor microenvironment; Treg cells, Regulatory T cells; T-VEC, Talimogene Laherparepvec; UPS, Undifferentiated pleomorphic sarcoma.

Immunological characteristic in different sarcoma subtype

Sarcomas are generally considered "immunological quiet", characterized by a low TMB, immunosuppressive TME, reduced T-cell infiltration, and increased HIF-1α, macrophages, and neutrophils. However, certain subtypes like alveolar soft-part sarcoma (ASPS), synovial sarcoma (SS), and undifferentiated pleomorphic sarcoma (UPS) display an immunologically "hot" phenotype: higher TMB, elevated PD-L1 expression, and presence of tertiary lymphoid structures (TLS), correlating with improved responses to checkpoint inhibitors (10).

The sarcoma TME comprises immune cells, stromal cells (including cancer-associated fibroblast, CAF), and endothelial cells. These components interact with tumor cells, influencing progression, immunotherapy response, and clinical outcomes. The specific immune contexture in sarcoma is often marked by predominate tumor-associated macrophages (TAM), dysfunctional tumor-infiltrating lymphocytes (TIL) with reduced CD8+ T and NK cell activity, increased regulatory T cells (Tregs), limited B cells, and impaired dendritic cell (DC) function.

TAMs

TAMs are abundant myeloid cells in TME that contribute to immune suppression, angiogenesis, and metastasis. They present antigens via surface MHC molecules and secret immunomodulatory cytokines, fostering a pro-tumoral milieu and enhancing vascular remodeling (11). In sarcomas, TAM densities often exceed those of TILs (12–14). These macrophages predominantly display an M2-type (immunosuppressive), marked by high expression of SIRPα, CD47, CD68, CD163, and CSF1R (14, 15–17), which collectively promote phagocytosis resistance and immunosuppression.

Clinically, high TAM infiltration predicts poorer outcomes in both soft–tissue and bone sarcomas (14, 18–20). In a cohort of 188 STS patients, high TAM levels were independently associated with an increased risk of local recurrence (20). In 75 sarcoma specimens, greater numbers of CD163+/CD204+ macrophages at tumor margins correlated with reduced disease–free survival (18). Similarly, undifferentiated leiomyosarcomas with dense $CD163^+$/$CD68^+$ infiltration exhibited worse overall survival (19). In chondrosarcoma, CD68+ CD163+ TAMs are the main immune population (21), and a high CD68+/CD8+ ratio independently forecasts metastatic presentation and poor prognosis.

TILs

STS generally have fewer TILs and exhibit lower CD4+/CD8+ ratios compared to other immunoreactive cancer (22). High-grade sarcoma,

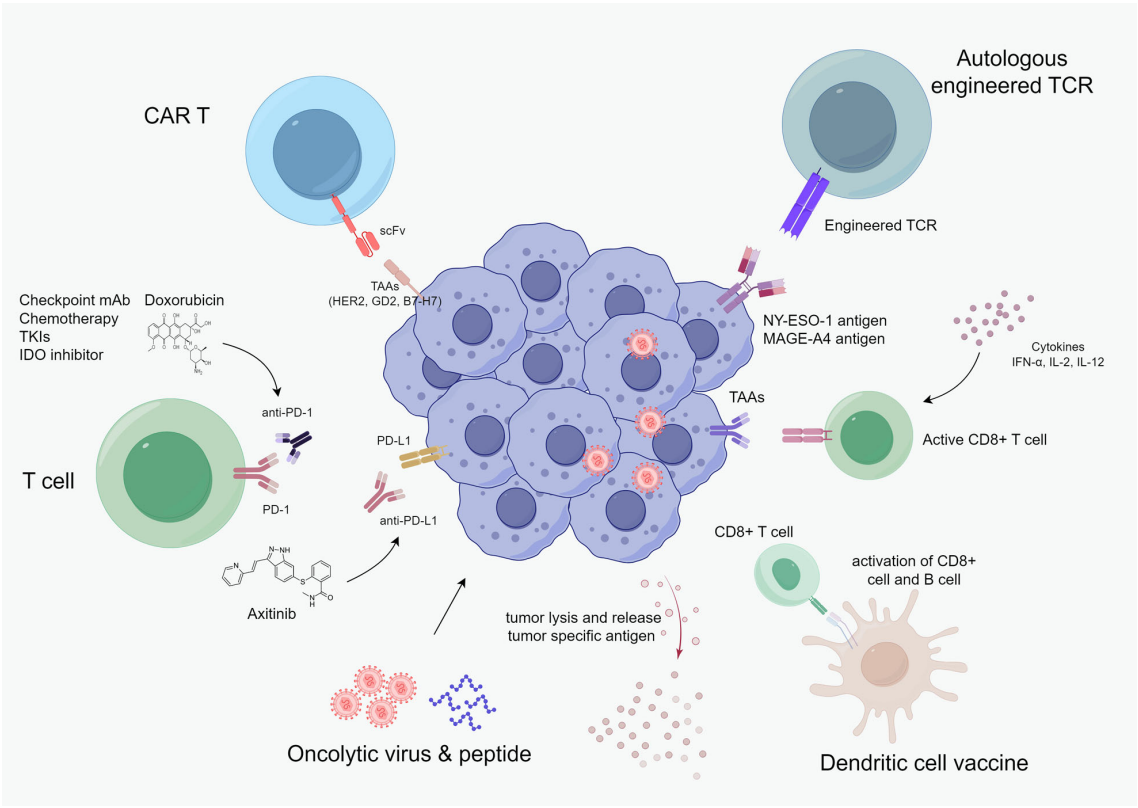

FIGURE 1
Current cancer immunotherapy landscape in advanced sarcoma, including checkpoint monoclonal antibodies, chemotherapy, TKI, adoptive cellular therapy, oncolytic virus & peptide, vaccine, and cytokine-based therapy.

such as leiomyosarcoma, exhibits higher infiltration of CD3+, CD8+, and FOXP3+ T-cells (13), while infiltrating CD20+ B-cells, though rarely detected in STS, are correlated to improved outcomes (23).

CD8+ T cells

CD8+ T cells are critical for antitumor immunity but become dysfunctional in sarcoma through upregulation of inhibitory receptors. In the primary UPS cohort, approximately one-third of cases exhibit high CD3+/CD8+ densities associated with favorable survival outcomes (24). In SS, greater CD8+ or FOXP3+ infiltration corresponds to improved OS (25). However, in angiosarcoma, neither PD-1/PD-L1 expression nor CD8+ levels predict outcomes, underscoring the subtype-specific complexity (26). Although gastrointestinal stromal tumor (GIST), myxofibrosarcoma, and pleomorphic sarcoma all feature high CD8+ densities, but lack of co–stimulatory ligands in GIST limits cytotoxic efficacy (27).

Correlative biomarker studies highlight that combined immune parameters best predict clinical benefit. In the SARC028 trial, pre–treatment densities of activated CD8+ T cells and PD-L1+ TAMs correlated with pembrolizumab response (28). Co-presence of CD8+ TILs and neoantigens further improved survival compared to either factor alone (29). Likewise, trials of interleukin-2 pathway agonists plus nivolumab demonstrated that CD8+ infiltration together with PD-1 expression correlated with increased ORR (23, 30).

Tregs

Tregs facilitate tumor immune evasion by secreting IL-10 and TGF-β, expressing CTLA-4 and PD-1, and thereby inhibiting effector T cell responses. Treg infiltration varies across sarcoma subtypes, with GIST showing the highest density of FOXP3+ density (36%) among sarcomas (12). The prognostic significance of Tregs in STS is undefined due to the lack of sample number and heterogeneity. In one cohort of 163 STS samples, 11.7% were PD-L1 positive and 25.2% showed high FOXP3+ infiltration, both metrics independently predicted poor prognosis in multivariate analysis (31). Another study linked high Treg levels with increased local recurrence risk, regardless of surgical margin status (32).

Biomarkers of immunotherapy response

TMB and dMMR

TMB correlates with ICI efficacy, as higher TMB generates more neoantigen, enhancing immune recognition (33). The FDA defines TMB-high as ≥ 10 mutations per megabase (Mb), which predicts a stronger response to PD-1 blockade (34). However, most STS subtypes exhibit median TMB below three mutations per Mb, and only ~2% qualify as TMB-high, making it an impractical biomarker

in STS (35, 36). Analysis of 1,407 sarcomas in the GENIE database confirmed low TMB across sarcoma categories, with TMB-high in 3.8% of STS and 0.6% of bone sarcomas (37). Specific histologies (e.g., angiosarcoma) exhibit higher TMB, with 63.4% of aggressive cases meeting the high threshold (38, 39). Conversely, translocation-driven subtypes (e.g., SS) typically display low TMB, though rare high-TMB cases (~6.3%) have been reported (40).

A phase II trial (NCT02834013) of ipilimumab and nivolumab in angiosarcoma reported a 25% ORR, rising to 60% in cutaneous scalp and face tumors (41). Among seven TMB-evaluated patients, only the single TMB-high case responded. Similarly, PD-1 blockade benefits patients with cutaneous head and neck angiosarcomas, regardless of TMB elsewhere, suggesting anatomical context may outweigh mutational burden (42).

MMR deficiency (dMMR) machinery is associated with high mutational load and predicts PD-1 blockade efficacy (39). However, dMMR remains exceptionally rare (~1%) in STS, further constraining its role as a predictive biomarker.

PD-L1 expression

Unlike many carcinomas, PD-L1 levels in sarcomas are highly variable and only modestly predictive of ICI response. Immunohistochemistry studies report PD–L1 positivity in 12-23% of STS cases, depending on the subtype and antibody used (12, 43). In SARC028, a higher density of PD-L1+TAMs and infiltrating CD8+ T cell correlated with ICB response; nonetheless, only 2 of 40 PD-L1+ sarcomas responded (28). PD-L1 expression often increases as the tumor progresses and generally portends a worse prognosis. One small SS series found lower PD-L1 in recurrent versus diagnostic specimens (44). Radiotherapy can increase PD-L1 expression when given preoperatively (45). Overall, dynamic and context–dependent PD-L1 regulation in the sarcoma microenvironment limits its reliability as a stand–alone biomarker.

B cell and TLS

B cell subtypes in the TME play dual roles: antigen-presenting B cells within TLS activate CD4+ and CD8+ T cells to mount antitumor responses (46–48), whereas regulatory B cells secrete immunosuppressive cytokines (49, 50). High-immune-infiltrate STS samples are enriched for B-cell-rich TLS, which strongly predicts better response rates and survival in pembrolizumab-treated cohorts. TLS are organized immune cell clusters that resemble secondary lymphoid organs. They play a critical role in generating delayed immune response by recruiting TILs. The spatial structure of TLS, including germinal centers, cellular composition, and tumor location affects patient prognosis (51).

Transcriptomic profiling of STS has defined five immune phenotypes, including immune-low, immune-high, and highly vascularized groups (23). The immune-high/TLS-rich class exhibited superior survival and a 30% ORR in Phase II pembrolizumab trials, compared to 2.4% overall (52). Similar TLS–related benefits have been observed in melanoma, RCC, and other ICI-treated malignancies, highlighting their potential as pan-cancer predictors of ICB response (53–55).

IDO

Indoleamine 2,3-dioxygenase (IDO) catalyzes tryptophan to kynurenine, creating an immunosuppressive niche that impairs effector T cells and promotes Tregs activation (56, 57). In a study of 371 primary STS patients, IDO was detected on endothelial cells in 23% and on tumor cells in 41%; 56% of samples exhibited elevated kynurenine (58). Higher kynurenine levels, but not PD-L1 expression, are associated with worse OS. A phase II trial of pembrolizumab in selected STS subtypes achieved only a 6% partial response. The reason was likely due to high baseline infiltration of IDO1+ macrophages (59). The treatment further increased the plasma kynurenine/tryptophan ratio, suggesting the IDO1-mediated immunosuppression as a resistance mechanism.

Although combining the IDO1 inhibitor epacadostat with pembrolizumab showed early promise in melanoma, the subsequent phase III KEYNOTE-252 trial failed (60), possibly due to compensatory upregulation of TDO or IDO2. A small phase II study using the same combination in sarcoma also yielded limited benefit (61). These results emphasized the need to elucidate the IDO/kynurenine signal in the sarcoma TME and to refine dosing and combinatorial strategies before deploying IDO pathway inhibitors as clinical biomarkers or therapeutic partners.

Immune checkpoint blockage for advanced sarcomas

ICI monotherapy or combined with other ICIs

Early trials using ICI monotherapy demonstrate unsatisfactory activity (62, 63). In the pioneering phase II SARC028 trial, 84 STS patients treated with pembrolizumab had an ORR of 18%. The best activity was observed in UPS of 40% and dedifferentiated liposarcoma cohorts of 20%, while osteosarcoma showed only a 5% response (64). A subsequent basket trial for rare sarcomas reported an ORR of 6.2% in the pembrolizumab monotherapy group, with no complete responses (65). Pooled analyses of anti-PD1/PD-L1 therapy in advanced STS showed an ORR of 15.1% and a non-progression rate (NPR) of 58.5% (66). The UPS and ASPS displayed the best response, while leiomyosarcoma and osteosarcoma had the lowest response rates. Nivolumab alone showed similarly modest activity, with a 12% response rate in certain sarcoma subtypes. A combination of nivolumab and CTLA-4 inhibitor ipilimumab demonstrated an improved response. In the Alliance A091401 trial for metastatic sarcoma, the combination therapy had a 16% ORR compared to 5% for nivolumab alone (67, 68) (Table 1).

Neoadjuvant nivolumab or ipilimumab also showed significant efficacy in resectable high–grade sarcomas. In

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TABLE 1 Key clinical trials of ICI monotherapy or combination in sarcomas.

NCT number	Clinical Trial	Phase	Study agent/ combination	Sarcoma subtype/ evaluable patients	ORR (%)	Outcomes/details
ICI monotherapy or combination with other ICI						
NCT02301039	Tawbi et al. SARC028, 2017 (64)	Phase II	pembrolizumab	40 STS cohort; 40 BS cohort	18% in STS 5% in BS	STS patients, PFS: 18 weeks; OS: 49weeks. BS patients, PFS: 8 weeks; OS: 52weeks.
NCT03012620	Blay et al. AcSé Pembrolizumab, 2023 (65)	Phase II (basket trial)	pembrolizumab	98 rare STS (34 chordoma, 14 ASPS, 12 SMARCA4-deficient, 8 DSCRT, 31 others)	6.2% at week 12	PFS 2.75 ms; OS 19.7 ms
NCT02500797	D'Angelo et al. Alliance A091401, 2018 (68)	Phase II	nivolumab plus ipilimumab vs nivolumab	42 sarcomas (3 AS, 4 BS, 14 LMS, 2 LPS, 6 SCS, 2 SS, 6 UPS/MFH, 1 unspecified, 4 others); 43 sarcomas (5 BS, 15 LMS, 3 LPS, 2 unspecified, 5 SCS, 2 SS, 5 UPS, 6 others)	16% vs 5%	PFS: 4.1 ms vs 1.7 ms, OS: 14.3 ms vs 10.7 ms
NCT03307616	Roland et al., 2024 (69)	Phase II	neoadjuvant nivolumab or nivolumab/ ipilimumab	17 DDLPS and 10 UPS	pathologic response was 8.8% in DDLPS and 89% in UPS	24-month relapse-free survival was 38% in DDLPS and 78% in UPS
NCT03141684	Chen et al., 2023 (70)	Phase II	atezolizumab	52 ASPS	37%	PFS: 20.8 ms
ICIs combination with chemotherapy or TKI						
NCT02888665	Pollack et al., 2020 (71)	Phase I/II	pembrolizumab plus doxorubicin	37 anthracycline-naive sarcoma (11 LMS and others)	13% for phase II patients and 19% overall	PFS: 8.1ms, OS: 27.6 ms
N/A	Livingston et al., 2021 (72)	Phase II	pembrolizumab plus doxorubicin	30 STS	36.7%	PFS: 5.7 ms; OS: 17 ms
N/A	Reichard et al. NITRA-SARC, 2023 (73)	Phase II	nivolumab plus trabectedin	Group A-lipo- or leiomyosarcomas: 43 STS (28 LMS and 15 LPS); Group B-non-L-sarcomas: 49 STS (12 UPS, 11 SCS, 6 FMS, 5 SS, 4 EpS)	overall PFS rate 6-months: 47.6% vs 14.6%	PFS: 5.5 ms vs 2.3 ms; OS: 18.7 ms vs 5.6 ms
NCT03138161	Gordon et al. SAINT, 2023 (74)	Phase I/II	nivolumab/ ipilimumab plus trabectedin	26 LMS, 14 LPS, 9 UPS, 7 RMS, 5 SS, 24 others	6 CR, 14 PR, 49 SD, 25.3% best response rate	PFS: 6.7ms, OS: 24.6 ms
NCT03899805	Haddox et al., 2024 (75)	Phase II	pembrolizumab plus eribulin	57 STS (19 LMS, 20 LPS, 18 UPS/other)	2 PR in LMS cohort; 3 PR in LPS; 1 CR and 5 PR in other cohort	12 week PFS rate was 36.8% for LMS, 69.6% for LPS, and 52.6% for UPS/other
NCT02636725	Wilky et al., 2019 (76)	Phase II	Pembrolizumab plus axitinib	33 STS (12 ASPS, 6 LMS, 5 High-grade PS, 2 DDLPS, 8 other histotypes)	The overall 3-month PFS rate: 65·6%	PFS: 4.7 ms; OS: 18.7 ms
NCT03277924	Martin-Broto et al. IMMUNOSARC 2020 (77)	Phase I/II	nivolumab + sunitinib	52 STS (9 SS, 8 UPS, 7 clear cell sarcoma, 7 SFT, 7 EpS, 5 AS, 4 ESMCS, 4 ASPS, 1 EHET)	the 6-month PFS rate: 48%	PFS: 5.6 ms; mOS: 24 ms
N/A	Liu et al., 2022 (78)	Phase II	benmelstobart (anti-PD-L1) plus anlotinib	30 STS (12 ASPS, 7 SS, 5 UPS, 4 LMS, 2 others)	36.6%	PFS: 7.8 ms; OS: not reached
NCT03798106	Cho et al., 2024 (55)	Phase II	durvalumab plus pazopanib	47 STS (12 LMS, 5 MPNST, 4 SS, 4 MFS, 4 UPS, 4 DSRCT, 14 others)	30.4%	PFS 7.7 ms, 1-year OS of 71.7%

OS, Overall survival; PFS, Progression-free survival; STS, soft tissue sarcoma; BS, bone sarcoma; NPR, non-progression rate; N/A, unmentioned.

retroperitoneal dedifferentiated liposarcoma (DDLPS) and UPS, 89% of resected specimens showed pathologic response (69). The two-year OS rate exceeded 80% in both cohort and heightened intratumoral B cell infiltration correlated with superior survival. Similarly, a phase II study in classical Kaposi sarcoma (cKS) achieved an 87% response rate (6/13 evaluable patients) with combined nivolumab and low-dose ipilimumab (79).

Emerging novel PD−1/PD−L1 inhibitors have shown promising efficacy in ASPS. Toripalimab, a high-affinity anti-PD-1 antibody, demonstrated a 25.0% ORR in a phase I trial of advanced ASPS, with a median PFS of 11.1 months and OS of 34.7 months (80). Atezolizumab, an anti-PD-L1 agent, achieved a 37% ORR and 20.8 months median PFS in a phase II ASPS cohort (70). Though combination strategies with CTLA−4 blockade increased toxicity, pharmacodynamic analyses indicated that even tumors lacking baseline PD-1/PD-L1 expression may convert to an ICI-responsive phenotype during treatment. These data affirm that dual−checkpoint approaches and novel agents can overcome inherent sarcoma resistance, but also underscore the need for refined biomarker−driven patient selection.

Combination of ICIs plus chemotherapy

Combination regimens of ICIs and chemotherapy have demonstrated promising results in advanced sarcoma, particularly in anthracycline−naive and high−grade subtypes. In the first phase 1/2 trial combining pembrolizumab with doxorubicin in anthracycline-naive sarcoma, the study did not meet its primary endpoint for ORR (19% overall), but achieved a PFS of 8.1 months and OS of 27.6 months, both favorably compared with prior studies (71). The following phase II trial in unresectable STS confirmed the combination's manageable safety profile, reporting a 36.7% ORR and an 80.0% disease control rate (DCR) (72). PD-L1 expression was linked to improved ORR, but not to PFS or OS.

Alkylating agent metronomic cyclophosphamide has also been combined with PD-1 inhibitors. Despite strong preclinical synergy, a phase II trial showed limited activity in STS, possibly owing to IDO1-expressing TAMs (59). Combining IDO inhibition with pembrolizumab yielded only a 3.3% ORR at 24 weeks (61).

Trabectedin is a marine-derived alkylating agent approved for anthracycline-resistant liposarcoma or leiomyosarcoma. It can destroy cancer cells and expose tumor neoantigens to immune recognition. Trabectedin combined with low-dose cyclophosphamide modulates macrophage polarization in the sarcoma microenvironment, reducing M2 macrophages and increasing CD8+ T cells that correlated with improved prognosis (81, 82). In a cohort of 92 patients, trabectedin plus nivolumab extended median PFS to 9.8 months versus 4.4 months, and OS to 24.6 months versus 13.9 months compared to earlier data (73). First−line regimens combining trabectedin with ipilimumab/nivolumab achieved a best response of 25.3% and an 87.3% DCR (74). A seven−year follow−up confirmed durable safety and efficacy, with 25% of participants alive at the study cutoff (83).

Finally, eribulin, a microtubule-binding agent, activates the cGAS-STING signal and remodels immune infiltration. In combination with pembrolizumab, eribulin produced a 12-month PFS rate of 36.8% in leiomyosarcoma, 69.6% in liposarcoma, and 52.6% in UPS (75). High serum levels of IL-4 and IFN-α were linked to therapeutic benefits. Collectively, these studies underscore the potential of chemo−immunotherapy combinations to convert immunologically "cold" sarcomas into more responsive tumors, warranting further biomarker−driven optimization.

Combination of ICI and TKI target therapy

Combining ICIs with anti-angiogenic TKIs has shown synergistic effects in treating advanced sarcoma. This synergy is partly attributed to the normalization of tumor vasculature, which enhances the effector cell infiltration, and converts the suppressive TME into an active state (84).

ASPS, a rare subtype resistant to cytotoxic therapy, often harbors the *ASPSCR1-TFE3* fusion, leading to upregulation of HIF-1α and VEGF. TKI has been the most active option for ASPS, whereas the majority could develop resistance. A phase II trial combining pembrolizumab with the VEGF inhibitor axitinib in advanced sarcoma reported an ORR of 25% and a median PFS of 4.7 months (76). Notably, ASPS patients achieved an ORR of 54.5% and a median PFS of 12.4 months. The observed outcomes in ASPS likely reflect the contribution of PD-1 blockade, as axitinib monotherapy yielded no responses in four ASPS.

Sunitinib can activate immune cell subsets, inducing IFN-γ-producing effector T cells via DCs, and synergize with PD-1 blockade (85). Sunitinib plus nivolumab (ImmunoSarc-I trail) demonstrated an ORR of 21% and an 18-month OS rate of 100% (77). Due to high toxicity, this regimen used a lower dose of sunitinib. A subsequent phase II trial (NCT03277924) showed potential activity in several other subtypes (86, 87). Angiosarcoma patients exhibited a higher efficacy, with a PR rate of 33%, and a median PFS of 3.93 months.

Anlotinib is a multi-kinase angiogenetic inhibitor that is recommended as a first-line treatment for metastatic ASPS (88). A combination of anlotinib and novel PD-L1 antibody TQB2450 (Benmelstobart) exhibited a favorable efficacy in metastatic STS patients unresponsive to chemotherapy (78). Among the 30 enrolled patients, the ORR was 36.7%, and median PFS was 7.8 months. In an expanded ASPS cohort, this combination showed an ORR of 79.3%, including 3 CR and 20 PR (89). TLS emerged as a potential predictive marker for immunotherapy efficacy in ASPS.

A phase II trial (NCT03798106) combining durvalumab with pazopanib in metastatic STS met its pre-specified endpoint (55). The ORR was 30.4% and mPFS was 7.7 months. High CD20+ B cell infiltration and vessel density led to a longer PFS and improved response. Infiltrated CD20+ B cell was identified as an independent predictor of PFS.

To summarize, these combined regimens of anti-angiogenic inhibitors and ICIs demonstrate synergistic anti-tumor effects and promising activity in patients with ASPS and some vascular subtypes. However, all these researches are limited by inadequate sample sizes and the absence of controlled arms, which restrict the ability to identify molecular markers of response. Further investigations with larger, well-designed trials are required to validate these findings and explore predictive biomarkers.

Real-world efficacy of ICI in advanced sarcoma

Several retrospective studies have reported the real-world efficacy of immunotherapy, in advanced STS, either alone or

combined with anti-angiogenic therapy (90–93). These studies reported variable outcomes, influenced by patient characteristics and sarcoma subtypes. Liu et al. (90) reported a 19.4% ORR with pembrolizumab monotherapy in advanced STS, alongside a median PFS of 2.9 months and OS of 12.0 months. Although certain subtypes like ASPS and UPS are considered more responsive to ICIs, real-world data remain limited due to patients' poorer health status and extensive prior treatment. Notably, treatment duration and ECOG performance status were independent predictors of PFS and OS. In another study, Nasr et al. assessed the ICI efficacy in metastatic UPS and other high-grade pleomorphic sarcomas (91). The median PFS was 2.9 months, with a 6-month PFS of 32%, and a median OS of 12.9 months. Prior radiotherapy and ICI type was independently associated with PFS. These findings align with the broader literature, suggesting the ICI effectiveness in advanced STS.

Combining ICIs with anti-angiogenic therapy has shown enhanced efficacy. One real-world study (93) reported an ORR of 48.1% and a median PFS of 8.9 months with such a combination. ASPS cohorts exhibited a higher PR rate (71.4%), indicating significant benefit. Another analysis (92) confirmed the potential of this combination, reporting an ORR of 17.6% and a median PFS of 5.8 months. Patients with ASPS or clear cell sarcoma (CCS) had significantly longer median PFS (16.2 months) compared to other subtypes (4.4 months). Multivariate analyses identified ECOG status and treatment line as key predictors of both PFS and OS.

Collectively, combined ICIs with anti-angiogenic therapy offer promising clinical benefits for STS, particularly in subtypes like ASPS and CCS. However, response rates vary due to patient characteristics and treatment history. Factors like ECOG status and treatment timing significantly influence outcomes. Challenges remain in optimizing therapy sequencing, understanding synergetic mechanisms, and tailoring strategies to specific patient subsets. Current decisions often rely on clinical experience, emphasizing the need for larger prospective studies and biomarker identification to address STS heterogeneity and improve treatment outcomes.

Adoptive T-cell therapy

ACT represents a promising immunotherapeutic strategy that harnesses engineered T cells to target TAAs expressed by cancer cells. Three classical ACTs methods are clinically developed, TCR-T, CAR-T, and TILs.

TCR-T

Letetresgene autoleucel (lete-cel) is an autologous engineered TCR therapy targeting NY-ESO-1 antigen and specific HLA-A*02 alleles. In a phase II trial (NCT03967223) (94), 87 patients with metastatic SS or myxoid round cell liposarcoma (MRCLS) expressing NY-ESO-1 were treated with lete-cel at doses of 1-15×10^9 transduced cells. The ORR was 39% for SS and 41% for MRCLS, with a median response duration of 10.6 months. Another phase I trial (NCT04318964) reported a novel TCR-T therapy targeting NY-ESO-1 in sarcoma (95). Twelve patients received cell infusions and low doses of IL-2 injection post-adoptive transfer. The ORR was 41.7%, with a median PFS of 7.2 months and a median duration of 13.1 months. The regimen exhibited favorable efficacy and safety profiles.

Afamitresgene autoleucel (afami-cel), an autologous TCR-T product targeting MAGE-A4 in HLA-A*02-positive patients. In the phase II SPEARHEAD-1 trial, afami-cel achieved an ORR of 43.2% with a median response duration of six months in patients with unresectable or metastatic SS who had received prior chemotherapy (96). Common adverse events included cytokine release syndrome, nausea, and fatigue. Afami-cel received accelerated approval from the U.S. FDA, making it the first TCR-based cell therapy for rare sarcoma subtypes (97).

Although TCR-based therapies targeting cancer-testis antigens (CTAs) show initial responses, many patients eventually experience disease progression. Future research should focus on understanding resistance mechanisms, overcoming HLA restrictions, and expanding the repertoire of targetable TAA.

CAR-T

CAR-T cell therapy has shown remarkable success in hematological malignancy, but faces challenges in solid tumors, including sarcomas, due to issues with T-cell trafficking, tumor heterogeneity, and the immunosuppressive TME. Current strategies aim to improve long-term efficacy by targeting conserved antigens that minimize toxicity to healthy tissues and enhancing CAR-T cell homing and persistence.

B7-H3

B7-H3 (CD276) is overexpressed in many pediatric solid tumors including pediatric sarcoma and neuroblastoma, with limited expression in normal tissue. In an analysis of 156 sarcoma specimens, 91% exhibited B7-H3 expression, with 61% showing high levels (98).

Clinical trials of B7-H3 targeted therapies, such as MGA271 (Fc-optimized humanized anti-B7H3 mAb) and MGC018 (B7-H3 ADC), have demonstrated antitumor activity but also raised concerns about toxicity (99).

B7-H3 CAR-T showed safety and good tolerability in early-phase trials for relapsed pediatric cancers, but limited efficacy (100, 101). The STRIvE-02 trial (NCT04483778) (102) reported no objective responses (n=9) after initial infusions. However, a single patient achieved a response following a second infusion, possibly due to prior radiation therapy enhancing CAR-T cell expansion. Combining radiation with CAR-T may modulate the TME to improve outcomes. Ongoing studies are exploring bispecific B7-H3xCD19 CAR-T cells and combinations with PD-1 inhibitors to enhance efficacy (103, 104).

To improve CAR-T cell homing, strategies involve engineering cells to express chemokine receptors like CXCR2 and CXCR6n.

Preclinical models have shown that CXCR2-modified B7-H3 CAR-T cells exhibit enhanced trafficking to osteosarcoma sites and improved cytolytic activity, leading to prolonged survival (105).

HER2

HER2 CAR-T cell therapy has demonstrated safety in advanced sarcomas, but limited efficacy due to poor CAR-T cell expansion and persistence. The HEROS 2.0 phase I trial allowed multiple HER2 CAR-T infusions, resulting in a 50% (7/14) clinical benefit (106). Three patients (21%) achieved complete remission, including one with long-term remission. Current studies are exploring combinations of HER2 CAR-T with ICIs like pembrolizumab or nivolumab (NCT04995003) to enhance CAR-T expansion and efficacy.

GD2

GD2 is highly expressed in neuroblastoma and pediatric tumors like Ewing sarcoma and osteosarcoma but minimally in normal tissues. GD2-targeting antibodies and GD2-targeted CAR-T cells have shown promising activity in relapsed neuroblastoma (107, 108). A phase I trial (NCT02107963) of third-generation GD2 CAR-T cells demonstrated feasibility and safety in osteosarcoma and neuroblastoma patients, but limited efficacy (109). Multi-omic analyses indicated that baseline CXCR3+ monocytes correlated with improved CAR T cell expansion, suggesting the peripheral immune environment influences therapy efficacy. Further research is needed to clarify myeloid-driven resistance mechanisms and enhance GD2 CAR-T cell efficacy in pediatric sarcoma.

Collectively, CAR-T therapy holds promise for treating solid tumors like sarcomas, despite the challenges exist. Strategies incorporating chemokine receptor modification, targeting tumor stroma, combination therapies, cytokine support, and metabolic reprogramming are being explored to enhance CAR-T cell persistence and antitumor activity (110). Continued research and clinical trials are essential to optimize these approaches and improve outcomes for sarcoma patients.

TILs therapy in sarcoma

TILs are immune cells within tumors capable of recognizing various cancer-associated antigens. In metastatic melanoma, TIL therapy has shown an ORR of 30-60% (111–113). For advanced STS patients, several ongoing trials are exploring TIL monotherapy or combination strategies, but fewer efficacy were reported (114, 115).

Oncolytic virus therapy

OVs therapy represents a novel immunotherapeutic strategy that utilizes natural or genetically engineered viruses to selectively infect and lyse cancer cell. This approach remodels the TME, enhances tumor immunogenicity, and can sensitize tumors to other immunotherapies. Talimogene laherparepvec (T-VEC), an oncolytic HSV-1 virus, is currently approved for treating recurrent, unresectable melanoma. In STS, several OVs have demonstrated efficacy in preclinical models, but few have advanced to clinical trials. A phase II trial combining the oncolytic vaccinia virus JX-594 with low-dose cyclophosphamide in advanced STS showed no clinical benefit, as all patients experienced disease progressing within six months (116). Adding the PD-L1 inhibitor avelumab provided limited additional benefit (117), with only one angiosarcoma patient achieving a PR.

The success of T-VEC in melanoma has prompted investigations into its potential in sarcomas. A Phase Ib trial combining T-VEC with preoperative radiation in locally advanced STS demonstrated tolerability but limited efficacy, with only 5 of 23 patients achieving pathological CR (118). In a Phase II trial, T-VEC combined with pembrolizumab showed strong antitumor activity across sarcoma subtypes, achieving a 30% ORR at 24 weeks, with notable responses in angiosarcoma, where 71% of patients achieved PR (119, 120). OH2 is an oncolytic HSV-2 expressing GM-CSF. A combination of OH2 and anti-PD-1 therapy achieved a 16.7% ORR, with one CR and durable disease control in angiosarcoma (121).

Oncolytic peptides, such as LTX-315, offer a non-viral approach to oncolysis by triggering anticancer immunity through remodeling the TME (122). A pilot trial evaluated LTX-315 in six heavily pretreated sarcoma patients, with four proceeding to adoptive cellular therapy (114). The treatment exhibited manageable toxicity and induced systemic immune responses, leading to disease stabilization in some patients. The best clinical response was a long-lasting stable disease in one patient, with tumor-reactive T cells detected in the blood. Further optimization is needed to improve clinical benefit. Subsequent studies found that LTX-315 triggers anticancer immunity by promoting MyD88-dependent DC maturation (115).

Vaccine therapy

Vaccine-based immunotherapy strategies are gaining traction in sarcoma, particularly those targeting cancer-testis antigens like NY-ESO-1. Personalized peptide vaccines have shown potential. A phase II trial reported a median OS of 9.6 months in refractory sarcoma patients, slightly exceeding the 8-month OS for second-line palliative chemotherapy. Some cases experienced lung metastasis reduction and prolonged stable disease (123). Combining long peptide antigen (LPA) vaccines with TCR-T has shown efficacy in - preclinical models resistant to checkpoint inhibitors (124). A phase I trial combining NY-ESO-1-specific TCR-T cells with a lymph node-targeted LPA vaccine in refractory SS showed durable tumor shrinkage lasting over two years and sustained TCR-T cell persistence in one patient (125).

DC vaccination could enhance antitumor immunity by inducing CD8+ T-cell responses and has shown promise (126). In

a phase I/II study of 35 advanced sarcoma patients, only one exhibited a PR, six had stable disease, and increased IFN-γ and IL-12 levels were observed post-treatment (127). Case studies also highlight durable responses, such as a pediatric Ewing's sarcoma patient surviving beyond two years post-DC vaccination, and a refractory SS patient showing over 2.5 years of disease control with NY-ESO-1-targeting lentiviral DC therapy (128, 129). DC vaccines can also enhance CAR-T cell therapy by improving persistence, tumor infiltration, and adaptive immune activation, and thereby leading to increased tumor cytolysis (128, 130). Combining DC vaccines with adoptive cellular therapy or ICIs offers potential strategies to amplify antitumor efficacy, warranting further exploration in sarcoma treatment.

CMB305 is a lentiviral-based prime-boost vaccine targeting NY-ESO-1. In a phase Ib study of 79 sarcoma patients, CMB305 achieved a DCR of 61.9% and a median OS of 26.2 months, although no objective responses were observed (131, 132). The vaccine elicited NY-ESO-1-specific antibodies and T-cell responses in half of the patients. In a phase II study, combining CMB305 with atezolizumab yielded a median progression-free survival (PFS) of 2.6 months and OS of 18 months, with select patients demonstrating anti-NY-ESO-1 responses and improved outcomes (133).

Cytokine-based therapy for sarcoma

Cytokines are soluble proteins mediating cellular interaction and immune response. Crucial cytokines like interleukins (ILs) and interferons (IFNs) modulate immune activity, and have been explored for their anti-tumor effects. IFNα was among the first agents used to treat HIV-related KS, showing tumor suppression in some patients (134). However, its clinical use is limited by low response and toxicity (135). While novel agents like liposomal doxorubicin and paclitaxel have supplanted IFNα as KS therapy, it may still have a role when combined with agents targeted angiogenic or HHV-8-encoded homologs (136).

IL-2 stimulates T and NK cells, promoting lymphocyte proliferation and activating lymphocytes into lymphokine-activated killer (LAK) cells, which can eradicate tumor cells independent of histocompatibility (137, 138). High-dose IL-2 has been approved for advanced melanoma but limited by severe toxicity (139). Small studies in sarcoma have shown IL-2, even conjunction with LAK cells or IFNs, offers limited antitumor effects (140–142). Nevertheless, IL-2-induced immune activation suggests potential efficacy for a subset of sarcoma.

IL-12, another potent anti-tumor cytokine, has shown promise in treating T-cell lymphoma and AIDS-related KS (143, 144). Like IL-2, the clinical application was limited by short half-life and toxicity. Recent studies on engineered IL-2 and IL-12 have demonstrated efficacy and safety in canine STS models by localizing effects and reducing systemic toxicity (145). Additionally, other cytokines like VEGFs, GM-CSFs, TGFs, and IFN-γ are under extensive study in clinical trials (146, 147).

Conclusion and future direction

In conclusion, immunotherapy holds significant promise for advanced sarcomas, yet many sarcoma subtypes remain poorly responsive to ICIs due to their 'cold' immune microenvironment. In this regard, a recent review highlights the need for a more refined selection of patients based on immune biomarkers such as TLS and PD-L1 expression (148). TLS has garnered considerable interest as a predictive biomarker of the response to ICI therapies, or possibly chemotherapy (149). Some studies supported the presence of TLS in sarcoma associated with enhanced T– and B–cell responses, underscoring their central role in shaping the immune landscape (150, 151). Additionally, responders to immunotherapy often exhibit higher PD–L1 levels on both TAMs and T cells (65). Unfortunately, most clinical trials to date have not stratified patients by these biomarkers, potentially leading to disappointing results. Future trials should perform a better stratification of patients to optimize outcomes across these heterogeneous tumors.

Moreover, it is also relevant to mention that combining genomic profiling with immunotherapy may further help refine patient selection and improve clinical outcomes in sarcomas (152–154). Next–generation sequencing in STS can identify specific molecular pathways linked to chemosensitivity, as shown in MFS and UPS analyses (155). This combined approach promises to personalize treatment and improve outcomes in heterogeneous sarcoma populations.

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Conflict of interest

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