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REVIEW

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New strategies in soft tissue sarcoma treatment

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Abstract

Soft tissue sarcomas (STS) have long been a formidable challenge in oncology, partly because of their rarity and diversity, which complicates large-scale studies and slows the advent of new treatments. Traditionally anchored by anthracycline-based chemotherapy, the landscape of STS treatment hasn't shifted dramatically in the past twenty years. However, recent strides in research are starting to paint a more hopeful picture. Leveraging advanced molecular profiling, researchers are now tailoring treatments to the unique genetic makeup of tumors, with targeted therapies showing promise. Innovations such as NTRK inhibitors for NTRK-rearranged sarcomas and gamma-secretase inhibitors for desmoid tumors are changing clinical practices. The rise of immunotherapy, including novel agents like LAG-3 inhibitors and bifunctional proteins that target both TGF-β and PD-L1, offers new avenues for treatment, particularly when combined with traditional therapies like chemotherapy. Meanwhile, the approval of epigenetic treatments for specific sarcoma subtypes heralds a new wave of strategy based on histological specificity, which could lead to more personalized and effective care. While challenges remain, the field of STS treatment is evolving, driven by a deeper understanding of the disease's biological underpinnings and a commitment to innovative research approaches.

Keywords Soft tissue sarcoma (STS), Combination therapy, Immunotherapy, Adoptive cell transfer, Tertiary lymphoid structure (TLS), Target therapy, Clinical trial

Introduction

Soft tissue sarcomas (STS) represent a heterogeneous group of cancers, comprising over 100 distinct histotypes and accounting for less than 1% of all adult solid tumors [1]. The primary management strategy for localized disease typically involves surgery, often complemented by perioperative radiotherapy and/or chemotherapy, tailored based on factors such as histotype, grading, and tumor location. Surgical interventions, especially when performed in specialized referral centers, have shown to improve outcomes in patients with localized disease [2]. However, despite optimal local treatment, up to 40% of STS patients develop metastatic disease, which often results in fatal progression [2].

The standard first-line treatment for these cancers involves anthracycline-based regimens, which are used across nearly all subtypes and result in a median progression-free survival (mPFS) of approximately six months [2, 3]. Upon disease progression, second-line treatments such as gemcitabine, dacarbazine, ifosfamide, eribulin, and pazopanib are selected based on tumor histotype, contributing to an average median overall survival (mOS) of 20 months [3, 4].

The rarity and histological diversity of STS present significant challenges in treatment. Despite gradual improvements in survival over the past two decades,

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advances have been limited, largely due to the lack of novel therapeutic strategies and difficulties in conducting large, homogeneous studies in such a rare and diverse group of cancers [3].

This review aims to provide a comprehensive overview of the latest advancements in systemic therapies for STS, including chemotherapies, targeted agents, and immunotherapies, with the ultimate goal of enhancing patient survival. These innovative strategies are summarized in Table 1.

Chemotherapy strategies

Since the initial observation of doxorubicin activity in patients with advanced sarcomas in 1973 and despite numerous trials, no chemotherapy regimen has demonstrated a superior overall survival benefit compared to this established standard of care (Table 2). Recent developments, however, have shifted this paradigm, particularly with the emergence of a histotype-tailored approach for investigating new chemotherapy regimens. The potential of this strategy was recently highlighted in the LMS-04 study, conducted across centers of the French Sarcoma Group [21].

LMS-04 is a phase 3, multicenter, randomized study that compared the combination of trabectedin and

Table 1 New systemic therapeutic strategies for patients with advanced soft-tissue sarcomas

Category	Target	Drug tested	Phase	Setting	Main results	Reference
ADC	AXL	Mipasetamab-uzoptirine	1b	Advanced STS	PR = 9,5% ; SD = 47,6%	[5]
ADC	GD2	M3554	1	Advanced STS	Ongoing	[6]
ADC	B7H3	HS-20,093	2	Advanced STS and OS	STS : ORR = 25% PFS = 7,1 months	[7]
Bifunctional fusion protein	TGF- β and PD-L1	Bintrafusp alfa + doxorubicin	2	First-line advanced TLS + STS	Ongoing	NCT04874311
ICI	PD-1 + LAG3	Nivolumab + Relatlimab	2	TLS + advanced STS	Ongoing	NCT04095208
ICI	PD-1 + CTLA-4	Balstilimab + Zalifrelimab	2	Advanced STS	6 months-NPR = 46,4%	[8]
ICI	PD-1	Nivolumab + doxorubicin/dacarbazine	2	Leiomyosarcoma	mPFS = 8,7 months	[9]
TKI	EGFR	Afatinib	2	Advanced chordoma	First line cohort 12months-PFS = 40%	[10]
TKI + ICI	VEGFR + PD-1 + CTLA-4	Cabozantinib + nivolumab + ipilimumab	2	Advanced STS	Combination mPFS = 5,3 m Cabozantinib mPFS = 3,5 m	[11]
TKI + ICI	VEGFR + PD-L1	Anlotinib + TQB2450	2	Advanced ASPS	ORR = 79,3%	[12]
TKI + ICI	VEGFR + PD-1	Sunitinib + Nivolumab	2	DDCS	ORR = 26%	[13]
TCR-T	MAGE-A4	Afami-cel	2	Advanced SS or myxoid/round cell LPS	mOS = 15,4months	[11]
TRK inhibitors	NTRK	Larotrectinib	2	NTRK-fusion STS	ORR = 58%	[14]
TRK inhibitors	NTRK	Entrectinib	2	NTRK-fusion STS	ORR = 57,7%	[15]
Epigenetic modulator	EZH2	Tazemetostat	1	INI1-negative ES	DCR = 26%	[16]
Epigenetic modulator	EZH2	Tazemetostat + doxorubicin	3	Advanced ES	Ongoing	[17]
MDM2 inhibitor	MDM2	BI907828	3	First-line advanced DDLPS	Ongoing	[18]
Gamma secretase inhibitors	NOTCH pathway	Nirogacestat	3	Desmoid tumors	ORR = 41%	[19]
CDK9 inhibitor	CDK9	KB-0742	1/2	Advanced STS	DCR = 42,9% in TFF positive STS	[20]

ADC antibody drug conjugate, *ICI* immune checkpoint inhibitor, *TKI* tyrosine kinase inhibitor

Table 2 Main randomized trials comparing doxorubicin to other drugs or combinations in STS

Control arm	Experimental arm	Study type	Setting	Number of patients	Primary Endpoint	Control Arm (months or %)	Experimental Arm (months or %)	Reference
Doxorubicin 75 mg/m^2 q3w	Doxorubicin 60 mg/m^2 + Trabectedin (1,1 mg/m^2) q3w	Phase III	First-line LMS	150	PFS	6,2	12,2	[21]
Doxorubicin 75 mg/m^2 q3w	Doxorubicin 75 mg/m^2 + Olaratumab 20 mg/kg q3w	Phase III	First-line	509	OS	20,4	19,7	[22]
Doxorubicin75mg/m^2 q3w	Pazopanib 800 mg/day	Phase II	First-line > 60 years	120	PFS	5,3	4,4	[23]
Doxorubicin 75 mg/m^2 q3w	Doxorubicin 75 mg/m^2 q3w + evofosfamide 300 mg/m^2 d1d8 q3w	Phase III	First-line	640	OS	19	18,4	[24]
Doxorubicin 75 mg/m^2 q3w	Gemcitabine 675 mg/m^2 d1d8 Docetaxel 75 mg/m^2 d8 q3w	Phase III	First-line	257	PFS	5,8	5,9	[25]
Doxorubicin 75 mg/m^2 q3w	Doxorubicin 75 mg/m^2 + palifosfamide 150 mg/m2/d IV days 1 to 3 q3w	Phase III	First-line	447	PFS	5,2	6	[26]
Doxorubicin 75 mg/m^2 q3w	Doxorubicin 60 mg/m^2 + Trabectedin 1,1 mg/m^2 3-hour IV q3w	Phase II	First-line	115	PFS	5,5	5,7	[27]
Doxorubicin 75 mg/m^2 q3w	Trabectedin 3-hour 1,3 mg/m^2 IV or 24-hour 1,5 mg/m^2 IV q3w	Phase IIb	First-line	133	PFS	5,5	2,8 (3 h) and 3,1 (24 h)	[28]
Doxorubicin 75 mg/m^2 q3w	Doxorubicin 75 mg/m^2 + Ifosfamide 10 g/m^2 q3w	Phase III	First-line	455	OS	12,8	14,3	[29]
Doxorubicin 75 mg/m^2 q3w (+/- Ifosfamide 6–9 g/m^2)	Trabectedin 24-hour 1,5 mg/m^2 IV q3w	Phase III	First-line TRS	121	PFS	8,8	16,1	[30]
Doxorubicin 75 mg/m^2 q3w	Docetaxel 100 mg/m^2 q3w	Phase II	First and second-line	86	ORR	30%	0%	[31]
Doxorubicin 75 mg/m^2 q3w	CYVADIC (cyclophosphamide 500 mg/m^2, vincristine 1,5 mg/m^2, doxorubicin 50 mg/m^2, dacarbazine 750 mg/m^2) q4w	Phase III	Fist-line	405	PFS	10,7	11,2	[32]
Doxorubicin 70 mg/m^2 q3w	Doxorubicin 70 mg/m^2 + Vindesine 3 mg/m^2 q3w	Phase III	First-line	298	ORR	17%	18%	[33]
Doxorubicin 75 mg/m^2 q3w	BI907828 (p53-MDM2 inhibitor)	Phase II/III	First-line DDLPS					Ongoing

q3w : every three weeks q4w : every four weeks d1 : on day 1 d8 : on day 8 IV : intravenous, *LMS* leiomyosarcoma, *DDLPS* dedifferentiated liposarcomas, *TRS* translocation-related sarcomas, *PFS* progression-free survival, *OS* overall survival, *ORR* objective response rate

doxorubicin versus doxorubicin alone in uterine and non-uterine leiomyosarcoma patients. Significantly, this study revealed, for the first time, a survival benefit with the combination treatment, doubling the median progression-free survival (mPFS) of doxorubicin alone (12.2 vs. 6.2 months, HR 0.41 [95% CI 0.29–0.58]; $p<0.0001$). However, it is noteworthy that the combination group exhibited higher hematologic toxicity, particularly grade 3–4, albeit manageable.

Another intriguing combination strategy is being explored in the SUNRISELMS trial [NCT05269355], a phase 2/3 double-blind study evaluating the efficacy and safety of adding unesbulin, an oral microtubule polymerization inhibitor, to dacarbazine in unresectable or metastatic, relapsed, or refractory leiomyosarcomas. This ongoing trial follows the phase 1b trial [34], which demonstrated good tolerance and promising efficacy in pretreated leiomyosarcomas, with a disease control rate (DCR) of 58.6% at 12 weeks.

Antibody-drug conjugates

Antibody-drug conjugates (ADCs) represent a significant advance in targeted cancer therapy, merging the specificity of monoclonal antibodies with the potent cytotoxicity of small molecule drugs. By harnessing the targeting capability of antibodies, ADCs deliver toxic agents directly to tumor cells, minimizing the impact on healthy tissues and enhancing therapeutic efficacy. This targeted approach reduces the systemic toxicity associated with conventional chemotherapy, potentially improving patient outcomes and quality of life.

ADCs are composed of three main components: an antibody specific to tumor antigens, a cytotoxic drug, and a linker that connects the drug to the antibody. The design of each component is critical. The antibody must target an antigen that is predominantly expressed on cancer cells, ensuring high specificity. The linker technology is equally vital, as it must be stable in the bloodstream to prevent premature release of the toxin but cleavable within the tumor environment to release the cytotoxic agent once the ADC reaches its target.

The innovative aspect of ADCs lies in their ability to exploit the natural properties of antibodies to seek out and bind to specific antigens expressed on the surface of cancer cells. Once an ADC binds to its target antigen, it is internalized by the cancer cell, whereupon the linker is cleaved, releasing the cytotoxic drug. This allows the drug to exert its lethal effect at the heart of the tumor cell, maximizing tumor cell kill while sparing normal cells.

The development of ADCs has been bolstered by advances in engineering more stable linkers and more potent cytotoxins, which can kill cancer cells at lower doses. Innovations in antibody engineering and linker chemistry have expanded the therapeutic window of ADCs, enabling the treatment of a broader range of cancers with improved safety profiles.

One of the ADCs making waves in clinical trials is Mipasetamab uzoptirine (Mipa), targeting AXL, a receptor tyrosine kinase implicated in various tumor processes, including growth, metastasis, and resistance to agents. AXL overexpression is associated with poor prognosis in several cancers, making it a valuable target for ADC therapy. Mipa comprises a humanized anti-AXL antibody linked to a potent cytotoxic drug, SG3199, via a cleavable linker, designed to deliver the drug specifically to AXL-expressing tumor cells.

The clinical potential of Mipa was explored in a Phase 1b trial involving patients with advanced sarcomas. This trial aimed to evaluate the safety, tolerability, pharmacokinetics, and efficacy of Mipa in patients who have exhausted standard-of-care therapies. Approximately 196 patients were expected to enroll, receiving Mipa in a regimen that allowed for dose adjustments based on tolerability and response.

Preliminary data from this study have been recently presented [5]. As of February 2024, 24 patients with sarcoma were enrolled across four dose cohorts: 7.5 mg, 11 mg, 13 mg, and 15 mg. These patients were not selected based on AXL expression but rather their clinical need and previous treatment history. The efficacy assessment revealed that two patients (9.5%) achieved a partial response (PR), ten patients (47.6%) maintained stable disease (SD) and eight patients (38.1%) showed disease progression (PD). Significant tumor reductions were noted in several patients, particularly at higher dose levels, highlighting Mipa's potential therapeutic benefit. The treatment was generally well-tolerated, with adverse events more frequent at higher doses. Common side effects included anemia, fatigue, and skin-related issues such as palmar-plantar erythrodysesthesia and erythema. Notably, one patient experienced acute liver failure, although it was deemed not related to the study drug. The maximum tolerated dose was not established within the study's scope, as the non-tolerated dose was not reached. Pharmacokinetic data indicated that Mipa exposures tend to increase with the dose, showing moderate-to-marked interpatient variability. The rapid clearance of the drug suggests no significant accumulation, which supports the Q3W dosing schedule. Mipasetamab uzoptirine has shown a promising safety profile and clinical activity in a challenging patient population with advanced sarcomas. All patients tested expressed AXL in their tumor cells, with varying levels of expression correlated with response rates. The study continues to explore the optimal dosing regimen and extends to investigate potential combinations with other agents like gemcitabine.

Besides AXL, other targets can represent good candidates for innovative ADC-based therapeutic strategies. GD2, a disialoganglioside, is prevalent across various tumor types, especially in sarcomas, where it is expressed in more than 90% of cases. This high expression rate makes GD2 an attractive target for ADC-based therapies, which combine the specificity of monoclonal antibodies with the potent cytotoxicity of linked drugs. The ADC in question, M3554, harnesses a recombinant human IgG1 monoclonal antibody linked to exatecan, a topoisomerase I inhibitor, via a beta-glucuronidase-cleavable linker [6]. This configuration allows M3554 to bind selectively to GD2-expressing cancer cells, facilitating the internalization of the complex and subsequent release of the cytotoxic payload within the lysosomal compartment of the tumor cell. This targeted approach aims to maximize tumor cell kill while minimizing the systemic exposure to the cytotoxic agent, potentially reducing the treatment-related side effects compared to conventional chemotherapy. One of the critical aspects of M3554's development is its modified effector function, designed to reduce the severe pain associated with GD2-targeting through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), observed with other GD2-targeting antibodies. This modification is anticipated to improve the tolerability and patient compliance, addressing one of the significant barriers faced by previous therapies targeting this pathway. Preclinical studies have shown that M3554 displays potent antitumor efficacy in patient-derived xenograft (PDX) models of sarcomas, suggesting that it could provide a significant therapeutic advantage over existing treatments. An upcoming Phase 1 study of M3554 will aim to establish

the safety profile, determine the maximum tolerated dose, and assess the preliminary efficacy in patients with soft tissue sarcomas.

Immunotherapy

STS played a pivotal role as the first model illustrating the potential of immunotherapy in cancer treatment, tracing back to the 19th century when William Coley observed sarcoma regression following bacterial infection clearance [35]. In the present landscape of immuno-oncology, significant strides have been made, with approvals for administration granted in various solid tumors, including melanoma, non-small cell lung cancer, and renal cell carcinoma, among others. However, despite this progress, the application of immunotherapy in STS remains a complex challenge. An analysis of combined data from nine clinical trials exploring immune checkpoint inhibitors (ICIs) in sarcomas involving 384 patients revealed an overall objective response rate (ORR) of 15.1% [36]. Nevertheless, upon excluding alveolar soft-part sarcoma, a rare subtype known for its heightened responsiveness to PD-1/PD-L1 monoclonal antibodies [37], the ORR diminished to 9.8% [36]. These disappointing results are mainly due to the high number of subtypes, some of which are ultrarare [37] and scattered information available about the tumor microenvironment (TME) for the various subtypes of sarcomas [38].

In an exhaustive analysis of the STS microenvironment, Petitprez et al. [39] introduced an immune classification of STS grounded in transcriptomic data, delineating five distinct sarcoma immune classes (SIC) characterized by varying levels of immune infiltration. The identification of tertiary lymphoid structures (TLS) emerged as a defining feature of the immune-high class, correlating with enhanced outcomes, and serving as a predictor for responses to immunotherapy. TLS are ectopic lymphoid formations that develop within non-lymphoid tissues, mirroring the structural and functional characteristics of lymph nodes [40]. These structures contain B-cell follicles and germinal centers surrounded by a T-cell region. In the context of antitumor immunity, TLS play a crucial role by fostering interactions between immune cells, promoting the activation and maturation of B and T cells, and enhancing local immune responses [40]. In the first biomarker-driven immunotherapy trial conducted in patients with STS, the existence of TLS has been correlated with improved outcomes and heightened responsiveness to immune-checkpoint inhibition. Notably, patients with TLS-positive STS exhibited an objective response rate of 30%, comparable to the rates observed in approved indications such as lung cancer and melanomas [41] (Fig. 1).

These promising findings underscore the potential of immunotherapy as a more effective treatment option for certain sarcoma patients when compared to traditional cytotoxic chemotherapy. However, several pivotal questions remain. First, there is a need to explore strategies to further improve response rates to ICIs, specifically in sarcomas characterized by the presence of TLS. Additionally, addressing the challenge of achieving success with immunotherapy in the substantial 80% of patients who exhibit TLS-negative sarcoma is crucial for expanding the applicability of these therapeutic approaches. Last, a critical inquiry emerges regarding the generalizability of these findings to pediatric and adolescent and young adult cases of soft tissue and bone sarcomas, necessitating exploration of the potential benefits across diverse age groups within the sarcoma patient population.

Two ongoing randomized studies are currently exploring novel combinations to further enhance the response rate to PD-1 inhibition in patients with TLS-positive sarcomas. The CONGRATS study [NCT04095208] is investigating the combination of nivolumab with the LAG-3–blocking antibody relatlimab versus nivolumab alone in patients with advanced TLS-positive advanced or metastatic STS. Notably, LAG-3 in sarcomas is significantly upregulated in TLS-positive STS [39], and its expression has been associated with a poor outcome in

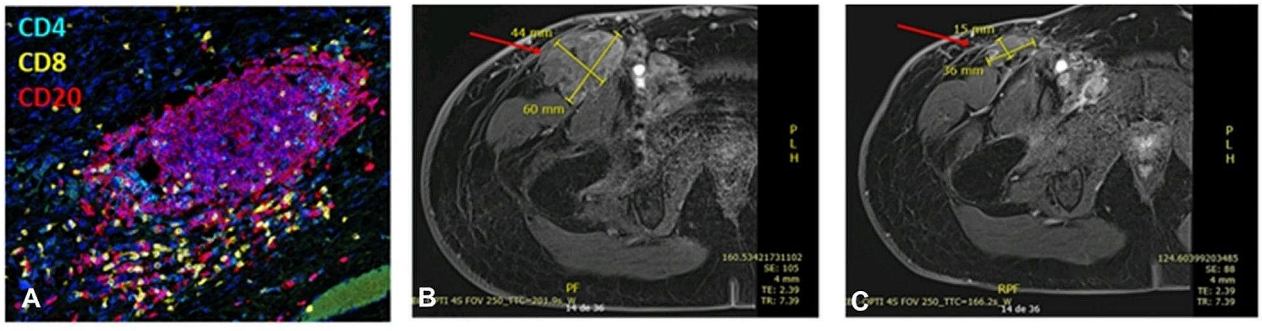

Fig. 1 **A** Representative example of tertiary lymphoid structure in a case of epithelioid sarcoma. **B** Locally advanced epithelioid sarcoma of the groin refractory to standard therapies. **C** Objective response after two infusions of pembrolizumab

comparison on transcriptomic analysis of over 600 complex genomics STS [42]. Recruitment for this study has recently concluded, and the results are anticipated in 2024.

Simultaneously, the TRUST study [NCT04874311] is exploring the combination of doxorubicin with a bifunctional fusion protein targeting TGF-β and PD-L1, bintrafusp alfa. Certain cytotoxic drugs, such as anthracyclines, the standard first-line treatment for advanced STS, can induce specific cellular responses beyond the typical apoptotic pathway, rendering tumor cell death immunogenic. Recent preclinical data from various tumor models demonstrated that appropriately selected immunogenic drugs, including anthracyclines, could sensitize tumors lacking T cell infiltration to host antitumor T cell immunity [43]. Moreover, instigating tumor infiltration by T cells sensitized tumors to checkpoint inhibition and durably controlled cancer. All these findings suggest that combining checkpoint blockade with immunogenic cytotoxic drugs can significantly expand the proportion of cancers responding to checkpoint therapy. Given that TGFB1 is highly overexpressed in TLS-positive sarcomas [39], the "proof of concept" in the TRUST study aims to prospectively demonstrate the high clinical benefit rate of PD-1/TGFB1 inhibition combined with doxorubicin versus doxorubicin alone in TLS-positive sarcomas. This study represents the first biomarker driven randomized investigation of an immunotherapy regimen in the first line setting for patients with advanced STS, and its results are eagerly anticipated in 2025.

For cold sarcomas, which constitute most cases, diverse therapeutic strategies are being explored to convert them into a "hot" and more responsive state to immune checkpoint inhibition. Notably, and as indicated above, immunogenic cytotoxic drugs such as anthracyclines play a crucial role, inducing specific cellular responses beyond traditional apoptotic pathways and rendering tumor cell death immunogenic. Wilky et al. conducted a phase 2 study combining doxorubicin with zalifrelimab (CTLA-4 inhibitor) and balstilimab (PD-1 inhibitor) in advanced STS [8]. The study aimed to improve 6-months PFS compared to historical doxorubicin. Among thirty enrolled patients with various STS types, four (12%) experienced grade 3/4 immune-related adverse events, including colitis, pancreatitis, diabetic ketoacidosis, hypertriglyceridemia, and hypothyroidism. Despite acceptable safety, the 6-month non-progression rate (NPR) was 46.4% (95% CI 28–66), falling short of the study's objective of 63%. Martin-Broto et al. reported the efficacy and safety data of a combination of nivolumab with the doxorubicin/dacarbazine chemotherapy regimen [9]. Like the rationale reported by Wilky et al., this study included thirty-six patients with advanced leiomyosarcomas. Safety was acceptable, with 15% of patients experiencing grade 3/4 neutropenia. Nine patients achieved an objective response, six had stable disease, and one had progressive disease. The mPFS was 8.7 months (95% CI 7.9–9.3).

Beyond cytotoxic drugs, radiation therapy has also shown promise in impacting the tumor microenvironment and enhancing immune responses by releasing tumor antigens. In a limited series of 11 patients with STS, neoadjuvant radiation therapy led to a substantial rise in the overall immune cell infiltration within tumors across various histologic subtypes [44]. A significant elevation was noted in the proportion of monocytes and macrophages, specifically M2 macrophages, along with an increased presence of B cells and CD4+T cells. Several studies investigating radiotherapy-immunotherapy regimens are currently underway in advanced STS and summarized in Table 3.

Oncolytic viruses represent another potential approach that has shown significant immune-stimulating potential in preclinical settings. Hatta et al. demonstrated the potential of oncolytic viral therapy, specifically utilizing the third generation of HSV T-01, as a promising alternative to chemotherapy for refractory sarcomas [45]. In vitro and in vivo experiments in this study revealed the significant cytotoxic effects and replication capacity of T-01 in both rhabdomyosarcomas (RMS) and leiomyosarcomas (LMS). T-01 effectively suppressed tumor growth in subcutaneous tumor models of LMS and RMS, highlighting its immune-stimulating effects and potential as a novel therapeutic approach for cold sarcomas. The METROMAJX study investigated the systemic impact of JX-594, an oncolytic virus, in 15 patients with advanced STS, revealing an upregulation of antitumor immune response-related cytokines [46]. Although the clinical activity was low, the results of this study pave the way for innovative approaches to be evaluated in patients with advanced STS. The combination of oncolytic virus with immune checkpoint inhibition may represent one of them, as illustrated by the reported results of a single-center, phase II trial that investigated the combination of talimogene laherparepvec (T-VEC), an oncolytic immunotherapy derived from a modified human herpes simplex virus type 1, with pembrolizumab in patients with advanced STS [47]. T-VEC was administered intratumorally, with 20 patients enrolled in the trial. Most of them had locally advanced disease, and objective responses were observed in 30% of patients across five different histological subtypes. In the second part of the METROMAJX study, the response rate was lower. However, sequential biopsies revealed that intra-tumoral injection of JX-594 was capable of reshaping the microenvironment in TLS-negative sarcomas, thereby sensitizing them to PDL1 inhibition [48]. Several other studies investigating oncolytic viral therapies are currently underway and summarized in Table 4. Antiangiogenic therapy, by

Table 3 Clinical trial combining immunotherapy and radiation therapy

Trial NCT number	Immunotherapy agent	Mechanism of action	Radiation therapy modality	Phase	Setting	Current status
NCT05488366	Pembrolizumab	Anti PD-1	SBRT*	Phase 1	Advanced STS	Recruiting
NCT03338959	Pembrolizumab	Anti PD-1	External Beam Radiation Therapy	Phase 1/2	Localized or metastatic STS	Completed
NCT01347034	Autologous Dendritic Cells	-	External Beam Radiation Therapy	Phase 2	Localized STS	Completed
NCT03116529	Durvalumab Tremelimumab	Anti PD-L1 Anti CTLA4	External Beam Radiation Therapy	Phase1/2	Localized STS	Active not recruiting
NCT03463408	Nivolumab Ipilimumab	Anti PD-1 Anti CTLA4	External Beam Radiation Therapy	Phase 1	Localized STS	Active not recruiting
NCT06074692	Camrelizumab Fluzoparib	Anti PD-1 PARPi	SBRT	Phase 2	Advanced STS	Recruiting
NCT05774275	Sintilimab Doxorubicin or Liposomal Doxorubicin	Anti PD-1 Anthracycline or Liposomal Antraciclyne	External Beam Radiation Therapy	Phase 1b/2	Localized STS	Recruiting
NCT06128863	Pembrolizumab Eftilagimod alpha	Anti PD-1 Anti LAG-3	External Beam Radiation Therapy	Phase 2	UPS, myxofibrosarcoma, DDLPS, myxoid and round cell LPS, ES, angiosarcoma, soft tissue sarcoma not otherwise specified	Recruiting
NCT04420975	BO-112 Nivolumab	Double-stranded RNA (activating TLR3, RIG-1 and MDA-5) Anti PD-1	External Beam Radiation Therapy	Phase 1	UPS, myxofibrosarcoma, LMS, DDLPS, SS, MPNST, pleomorphic RMS	Active not recruiting
NCT03548428	Atezolizumab	Anti PD-L1	SBRT	Phase 2	Oligometastatic LMS, LPS, undifferentiated sarcomas	Recruiting
NCT04616248	CDX-301 CDX-1140 Poly-ICLC	Recombinant FLT3 ligand Anti CD40 Double stranded RNA (PRR ligand)	External Beam Radiation Therapy	Phase 1	Selected advanced solid tumors including STS	Recruiting
NCT03307616	Nivolumab Ipilimumab	Anti PD-1 Anti CTLA4	External Beam Radiation Therapy	Phase 2	Localized UPS and DDLPS	Active not recruiting
NCT02992912	Atezolizumab	Anti PD-L1	SBRT	Phase 2	Selected advanced solid tumors including STS	Unknown status
NCT04977453	GI-101	Bi-specific CD80-IgG4 Fc-IL2v fusion protein	External Beam Radiation Therapy	Phase 1/2	Selected advanced solid tumors including STS	Recruiting

**SBRT* stereotactic body radiation treatment

targeting tumor vasculature, may also reshape the microenvironment to enhance immune cell infiltration. Van Tine et al. recently reported the results of a randomized phase 2 study [11] investigating the activity of the VEGFR inhibitor cabozantinib combined with nivolumab and ipilimumab in a randomized phase 2 study versus cabozantinib alone. Sixty-nine patients were randomized to the combination arm, and 36 received cabozantinib monotherapy. The combination arm observed seven objective responses (11%), while the monotherapy arm had two (6%). The mPFS was 5.3 months (95% CI 4.1–11) for the combination and 3.5 months (95% CI 1.1–7.7) for monotherapy ($p=0.016$). The mOS was 22.6 months (95% CI 14.8-NA) for the combination and not reached (95% CI 9.6-NA) for monotherapy ($p=0.42$). Notably, among the 19 patients from the cabozantinib monotherapy arm who were allowed to crossover to the combination arm, seven showed tumor shrinkage, suggesting at least an additive effect of the combination of nivolumab and ipilimumab. These strategies collectively represent a multifaceted approach to enhancing tumor immunogenicity and improving responsiveness to immune checkpoint inhibitors. However, it is important to note that the majority of the recently reported or ongoing studies are single-arm and/or did not include analysis of sequential blood or tissue samples. Unfortunately, the absence of sequential tumor biopsies and randomization hinders drawing definitive conclusions regarding the influence of these combinations on the tumor microenvironment and their potential correlation with clinical benefits. Therefore, a paradigm shift in the design of immune-oncology trials in patients with STS is essential to enhance their scientific value and contribute to advancing knowledge in the field.

T cells are pivotal players in cell-mediated immunity, and the landscape of cancer treatment has witnessed

Table 4 Clinical trial testing oncolytic viral therapies

Trial NCT number	Oncolytic viral therapy	Mechanism of action	Phase	Setting	Current status
NCT05851456	R130	Recombinant oncolytic HSV1* containing the gene coding for anti-CD3 scFv/CD86/PD1/HSV2-US11	Phase 1	Advanced bone sarcoma and STS	Recruiting
NCT04065152	Talimogene laherparepvec (T-VEC)	Recombinant oncolytic HSV1 containing the gene coding for GM-CSF**	Phase 2	Kaposi sarcoma	Recruiting
NCT00503295	Reolysin	Oncolytic wild type reovirus	Phase 2	Selected advanced solid tumors including STS	Completed
NCT05361954	STI-1386	2nd generation recombinant oncolytic HSV1 expressing transgenes encoding an anti-PD-1 scFv-Fc, a TGFB receptor 2, and IL-12.	Phase1	Selected advanced solid tumors including STS	Not yet recruiting
NCT05602792	T3011	Recombinant oncolytic HSV1 expressing IL-12 and PD-1 antibody	Phase 1/2	Selected advanced solid tumors including STS	Recruiting
NCT04725331	BT-001	Oncolytic vaccinia virus containing genes encoding the 4-E03 human recombinant anti-hCTLA4 antibody and human GM-CSF	Phase 1/2	Selected advanced solid tumors including STS	Recruiting
NCT00931931	HSV1716	Oncolytic HSV1	Phase 1	Selected advanced solid tumors including STS	Completed
NCT05061537	Sasanlimab PF-07263689	Anti PD-1 Oncolytic vaccinia virus	Phase 1	Selected advanced solid tumors including STS	Terminated
NCT02714374	GL-ONC1	A triple modified attenuated oncolytic vaccinia virus	Phase 1	Selected advanced solid tumors including STS	Terminated
NCT02700230	MV-NIS	Oncolytic Measles Virus Encoding Thyroidal Sodium Iodide Symporter	Phase 1	MPNST in the context of neurofibromatosis type 1	Recruiting

*HSV1: herpes simplex virus type 1

**GM-CSF: granulocyte-macrophage colony-stimulating factor

notable advancements with the introduction of adoptive cell transfer (ACT) strategies, offering an alternative avenue in immunotherapy alongside immune checkpoint inhibition. Two prominent approaches in this realm are chimeric antigen receptor (CAR) T cell therapy and T cell receptor (TCR) T cell therapy, each unlocking new possibilities in the battle against malignant tumors.

In the spotlight is afami-cel, an autologous TCR T cell therapy specifically designed for HLA A*02–eligible patients with advanced solid tumors expressing the cancer testis antigen MAGE-A4. The ongoing SPEARHEAD-1 trial [NCT04044768] is actively assessing the efficacy and safety of afami-cel in individuals with advanced/metastatic synovial sarcomas (SS) or myxoid/round cell liposarcomas (LPS) [49].

The intricacies of this therapy unfold as autologous T cells are meticulously isolated and genetically engineered with a vector to express an affinity enhanced TCR, also known as a specific peptide enhanced affinity receptor T cell or SPEAR T cell. These modified T cells are primed to recognize and obliterate tumoral cells expressing the specific antigen MAGE-A4. Following this intricate process, the genetically enhanced T cells are expanded and reintroduced into the patient post-lymphodepletive chemotherapy.

Interim OS data from advanced SS patients treated with afami-cel paint an encouraging picture. The mOS reached 15.4 months (95% CI 10.9-NA), with 52% of patients censored at the data cutoff. The 12-month OS probability stood at 60%, while the 24-month OS probability reached 40%. Particularly noteworthy were the outcomes for the 17 patients with a RECIST response by independent review, where the median OS was not reached, and the 12-month and 24-month OS probabilities soared to 90% and 60%, respectively [50].

In the dynamic landscape of cancer therapeutics, afami-cel targeted approach, harnessing the power of genetically modified T cells against the specific antigen MAGE-A4, underscores the potential of ACT in addressing the complexities of advanced solid tumors such as SS and myxoid/round cell LPS. These results not only shed light on the promise of precision oncology but also pave the way for future advancements in personalized cancer treatments.

Targeted therapies

In navigating the complex landscape of sarcoma treatment, the emergence of targeted therapies offers a beacon of hope, especially for select subtypes. This precision-oriented approach tailors treatments to the unique molecular profiles of these cancers, promising improved outcomes. As we explore the transformative potential of targeted therapies in STS management, it's essential to acknowledge their selective impact, marking a new era of personalized care for specific subgroups within the sarcoma spectrum. While some strategies have been

substantiated by compelling clinical data, others remain at the preclinical stage with clinical validation still pending.

Targeted treatment strategies supported by clinical data

NTRK targeting in sarcomas

The study of NTRK fusions in sarcomas has become increasingly significant due to the therapeutic implications of targeting these genetic abnormalities with TRK inhibitors. NTRK fusions result from translocations involving one of the three neurotrophic receptor tyrosine kinase genes (NTRK1, NTRK2, NTRK3), leading to the expression of chimeric TRK proteins that have constitutive kinase activity. This aberrant activity promotes oncogenesis through various downstream signaling pathways, making NTRK fusions attractive targets for cancer therapy.

Recent clinical trials and studies have highlighted the efficacy of TRK inhibitors in tumors harboring NTRK fusions, showing significant clinical responses across a diverse set of tumor types, including sarcomas. For instance, the efficacy of larotrectinib and entrectinib, both TRK inhibitors, has been demonstrated in various cancers with NTRK fusions, leading to their approval for use in this context by regulatory bodies like the FDA [51, 52].

Larotrectinib has shown robust efficacy in sarcomas with NTRK gene fusions, with a reported overall response rate (ORR) of 58% in adult patients, and particularly high efficacy in infantile fibrosarcoma [14]. The median progression-free survival (PFS) reached 28.3 months, underscoring the durability of responses, and a 36-month overall survival (OS) rate was impressively high at 77%. This positions larotrectinib as a potent treatment option, especially for pediatric sarcoma patients where it has shown to alter disease course significantly.

Entrectinib provides a broader therapeutic benefit, given its ability to cross the blood-brain barrier, which is advantageous for patients with central nervous system (CNS) involvement. The updated efficacy data from an integrated analysis reveals an ORR of 57.7% in the NTRK fusion-positive sarcoma cohort, with a median duration of response (DoR) of 15.0 months and median OS of 18.7 months [15]. These results highlight entrectinib's ability to manage diverse sarcoma histologies effectively.

Both drugs have well-documented safety profiles with manageable side effects, making them suitable for long-term management of sarcoma patients harboring NTRK fusions. The choice between larotrectinib and entrectinib may be influenced by specific patient needs, including CNS involvement and previous treatments.

The compelling data from both therapeutic agents emphasize the necessity of routine genomic screening for NTRK fusions in sarcomas to tailor personalized treatment approaches that can significantly improve patient outcomes. This shift towards precision medicine in oncology not only enhances the efficacy of treatment regimens but also minimizes unnecessary exposure to less effective therapies.

EZH-2 inhibitors in epithelioid sarcoma

SMARCB1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1), also known as INI1 (integrase interactor 1), serves as a core subunit within the SWI/SNF ATP-dependent chromatin remodeling complex [53]. Functioning as a potent tumor suppressor gene, INI1 regulates diverse cellular processes, including differentiation and proliferation [54]. Genetic aberrations in INI1, identified in a subset of STS, present a potential therapeutic target.

Loss of INI1 function leads to the upregulation of EZH2, a crucial epigenetic regulator. This dysregulation results in the trimethylation of H3K27 on target genes, leading to their repression. Consequently, this cascade contributes to the activation of various oncogenic signaling pathways, including Sonic Hedgehog, Wnt/β-Catenin, and MYC [54].

The frequency of INI1 loss is notably high (50 to 80%) in epithelioid sarcoma (ES) and other sarcomas displaying epithelioid features, such as malignant peripheral nerve sheath tumors (MPNST) [55, 56].

Tazemetostat (EPZ-6438), a potent and highly selective EZH2 inhibitor, demonstrated promising results in a phase 1 trial evaluating its efficacy and tolerability in advanced solid tumors [57]. Notably, a patient with an INI1-negative malignant rhabdoid tumor exhibited a complete response lasting over 4 years. Subsequent inclusion of patients with similar genetic aberrations showed objective responses or prolonged stable disease, particularly in those with INI1- or SMARCA4-negative solid tumors. In INI1-negative tumors, a basket phase 2 study [16], notably in the epithelioid sarcoma cohort, revealed an ORR of 15% [95% CI 6.9–25.8], with a median follow-up of 59.9 weeks. The median duration of response was not reached, and the overall DCR was 26% [95% CI 15.5–38.5]. The mPFS was 23.7 weeks [95% CI 14.7–25.7], and the mOS was 82.4 weeks [95% CI 47.4-NA].

Tazemetostat stands as a paradigm of effective targeted therapy within a specific sarcoma sub-histotype, leading to an exceptional response and the accelerated approval of an epigenetic drug in January 2020 in the USA, specifically for the treatment of adults and adolescents with locally advanced or metastatic ES not eligible for complete resection.

Furthermore, this drug exhibits potential for combination treatment with ICIs. Noteworthy induction of CD8 T cells in an epithelioid sarcoma patient treated with tazemetostat has been reported [57]. Preclinical models

have highlighted the role of EZH2 in immunomodulation [58], and synergies between EZH2 inhibition and ICI efficacy have been demonstrated in various types of solid tumors [59, 60]. These findings lay the groundwork for clinical trials, such as the ongoing phase 2 trial CAIRE [NCT04705818], evaluating the combination of tazemetostat and durvalumab in different solid tumors, including STS and TLS-positive tumors.

Preclinical data have also suggested synergistic activity of EZH2 inhibition in combination with chemotherapy [61]. This combination has been demonstrated to be clinically safe, and a Phase 3 study is currently underway. This study aims to compare tazemetostat + doxorubicin against the current frontline standard treatment, single-agent doxorubicin + placebo, as a first-line treatment in locally advanced unresectable or metastatic ES [17].

MDM2 targeting in well-differentiated and dedifferentiated liposarcoma

In the intricate landscape of STS, the aberrant MDM2 (Mouse Double Minute 2) signaling pathway has become a focal point, particularly in LPS, constituting approximately 20% of STS cases. The well-differentiated (WDLPS) and dedifferentiated (DDLPS) subtypes of LPS, characterized by MDM2 amplification and wild-type TP53 gene status, present a compelling therapeutic target [62].

MDM2, acting as a negative regulator of the tumor suppressor protein p53, exerts its influence through a complex interplay involving the binding of MDM2 to the transcription activation domain of p53, ultimately leading to proteasomal degradation. Strategies to disrupt the MDM2-TP53 interaction have been pursued to restore p53 function, promoting apoptosis, cell cycle arrest, and DNA repair in MDM2-amplified, TP53 wild-type tumors [63].

Traditionally, MDM2-TP53 interaction antagonists, such as nutlins and spiro-oxindoles, have been explored [64, 65]. However, a new class of compounds, MDM2 degraders, has garnered attention for its distinct approach. MDM2 degraders, utilizing the PROTAC (PROteolysis TAgeting Chimeras) technology, go beyond mere inhibition of the MDM2-TP53 interaction [66]. Instead, they induce the degradation of the MDM2 protein itself, leading to a reduction in MDM2 levels within the cell. This dual mechanism of action not only decreases the inhibitory effect of MDM2 on p53 but also enhances p53 activity by reducing MDM2 levels.

Recent trials, such as the MANTRA phase 3 trial [19] assessing milademetan and the ongoing phase 2/3 trial Brightline-01 exploring BI907828 [18], underscore the complexity of therapeutic interventions in LPS. While the MANTRA trial did not meet its primary endpoint, ongoing investigations into BI907828 in DDLPS highlight the evolving landscape of targeted therapies.

Moreover, the pursuit of MDM2 inhibition extends beyond its classical role in apoptosis. Emerging evidence suggests that MDM2's oncogenic activities encompass broader transcriptional regulation programs, influencing amino acid metabolism, redox homeostasis, and the expression of stress response genes [67, 68]. The exploration of these additional facets holds promise for uncovering novel therapeutic opportunities and expanding our understanding of the intricate molecular landscape associated with MDM2 inhibition in sarcomas.

As the field progresses, the potential for MDM2 inhibitors, whether disrupting the MDM2-TP53 interaction or inducing MDM2 degradation, offers hope for improved outcomes in STS. The nuanced interplay between these inhibitors and the intricate molecular pathways within tumors remains an area of active research, with the goal of refining therapeutic strategies for a more targeted and effective approach in the diverse landscape of soft tissue sarcomas.

Inhibition of gamma-secretase as a therapeutic intervention

In the intricate landscape of tumor biology, the role of gamma-secretase emerges as a critical determinant, influencing cellular processes through the cleavage of various membrane proteins. Among its notable substrates there is the Notch receptor, a key player in cell differentiation, proliferation, and survival [69]. Dysregulation of the Notch signaling pathway, orchestrated by gamma-secretase, has been implicated in the initiation, progression, and metastasis of tumors.

Within this broader context, desmoid tumors, characterized by their local aggressiveness and unpredictable course, present unique challenges in terms of therapeutic interventions [70]. Traditionally, surgical and local treatments have been considered, yet the infiltrative growth of desmoid tumors in specific anatomical locations often necessitates alternative systemic approaches [70, 71].

Nirogacestat, a first-in-class gamma-secretase inhibitor, has recently emerged as a promising addition to the therapeutic arsenal for desmoid tumors. In the DeFi trial, a phase 3 study, [72] nirogacestat demonstrated a substantial improvement in PFS compared to placebo, signifying a paradigm shift in the management of this locally aggressive disease. The observed increase in the ORR in the treatment arm further underscores the clinical significance of gamma-secretase inhibition, with an ORR of 41% in the treatment arm versus 8% in the placebo arm ($p < 0.001$).

However, the safety profile of nirogacestat does include some concerns that are particularly relevant to this demographic. The drug has been associated with other side effects such as diarrhea, fatigue, nausea, and rash.

More serious risks include ovarian dysfunction, which can lead to menstrual irregularities and potential temporary infertility, and liver problems, which require regular monitoring. The decision to use nirogacestat involves weighing these risks against the benefits of effective tumor control. This balance is particularly important for young, active patients who may be concerned not only with the immediate health impact but also with long-term consequences such as fertility and the possibility of chronic conditions.

In conclusion, the role of gamma-secretase in tumor biology takes center stage, and its targeted inhibition, exemplified by nirogacestat, not only addresses the unique challenges posed by desmoid tumors but also contributes to our broader understanding of the intricate interplay between molecular pathways and tumorigenesis. This therapeutic advancement signifies a promising step forward, offering renewed hope for patients with the complexities of locally aggressive tumors.

Targeted treatment strategies supported by preclinical data

CDK9

Cyclin-dependent kinase 9 (CDK9) stands at the intersection of critical cellular processes, exerting a profound influence on transcriptional elongation. As a serine/threonine protein kinase, CDK9 orchestrates the phosphorylation and activation of RNA polymerase II subunit RPB1. This cascade of events culminates in the upregulation of pivotal oncogenic genes, such as myeloid cell leukemia-1 (MCL-1) and c-Myc [73]. In the intricate dance of cellular machinery, CDK9 emerges as a central conductor, governing the orchestration of gene expression crucial for cell cycle progression, anti-apoptotic mechanisms, and cellular proliferation.

Within the expansive realm of cancer biology, CDK9 has assumed a role of increasing prominence due to its multifaceted contributions to tumorigenesis. Its involvement in transcriptional regulation positions it as a key player in the uncontrolled cellular growth characteristic of cancer. Beyond merely facilitating transcription, CDK9 has been implicated in the dysregulation of vital pathways, offering a unique therapeutic opportunity [74, 75].

Sarcomas present a compelling battleground for CDK9-targeted interventions [76, 77]. KB-0742, a highly selective and orally bioavailable CDK9 inhibitor, has shown promising results in a Phase 1 trial involving patients with various advanced solid tumors. This drug, developed from a meticulous small molecule microarray screen targeting an oncogenic variant of the androgen receptor, is designed to disrupt critical oncogene transcription processes by influencing transcription factor activity. Updated data from the ongoing Phase I/II study (NCT04718675) have been presented, which include manageable safety profiles (MTD not reached), a 24-hour plasma half-life, linear pharmacokinetics, CDK9 target engagement in peripheral blood mononuclear cells (PBMCs), and tumor tissue from pre- and on-treatment biopsy samples [20]. As of January 4, 2024, 112 patients have been enrolled, receiving a median of three lines of prior therapy. The study has included a wide range of tumor types, with notable enrollments in soft tissue sarcoma (STS) and adenoid cystic carcinoma (ACC). Treatment-emergent adverse events occurring in more than 15% of patients include nausea, vomiting, anemia, fatigue, diarrhea, and constipation; none assessed as grade 4 or 5. The most common reason for treatment discontinuation was disease progression (54.5%). Within the STS group, transcription factor fusion (TFF) positive patients displayed a trend towards improved outcomes versus those without a TFF, with a disease control rate (DCR) of 42.8% versus 29.4%. Notable responses include one partial response in a TFF positive myxoid liposarcoma patient at 60 mg, highlighting the drug's potential in transcriptionally STS.

Hippo pathway

Epithelioid hemangioendothelioma (EHE) is a rare vascular sarcoma uniquely characterized by the WWTR1(TAZ)–CAMTA1 gene fusion, which occurs in approximately 90% of cases. This fusion gene results in the production of a transcriptional coactivator TAZ, an end effector of the Hippo pathway, linked with CAMTA1, a calmodulin-binding transcription activator. This fusion leads to a constitutively active form of TAZ, driving the tumorigenesis process in EHE. The Hippo pathway, critical for regulating organ size and tissue homeostasis, typically restricts the proliferation and promotes apoptosis through the inactivation of YAP/TAZ by phosphorylation. However, in EHE, this regulation is circumvented, allowing uncontrolled TAZ activity.

Recent insights into the Hippo pathway's role in cancer reveal that dysregulation of this pathway, particularly the YAP/TAZ components, promotes aggressive tumor behaviors [78, 79] (Fig. 2). In EHE, the TAZ–CAMTA1 fusion hijacks the typical regulatory mechanisms, enabling continuous activity of TAZ that contributes directly to oncogenesis. This makes EHE a pertinent model for understanding YAP/TAZ-mediated carcinogenesis, which could extend to other cancers exhibiting similar pathway dysregulations.

Given the pivotal role of the TAZ–CAMTA1 fusion in EHE pathogenesis, targeted therapies that specifically inhibit this fusion protein or its downstream effects present a promising therapeutic avenue. Phase 1 clinical trials are currently exploring inhibitors that target TEAD, a transcription factor that interacts with YAP/TAZ, aiming to curtail the oncogenic activity of the fusion protein

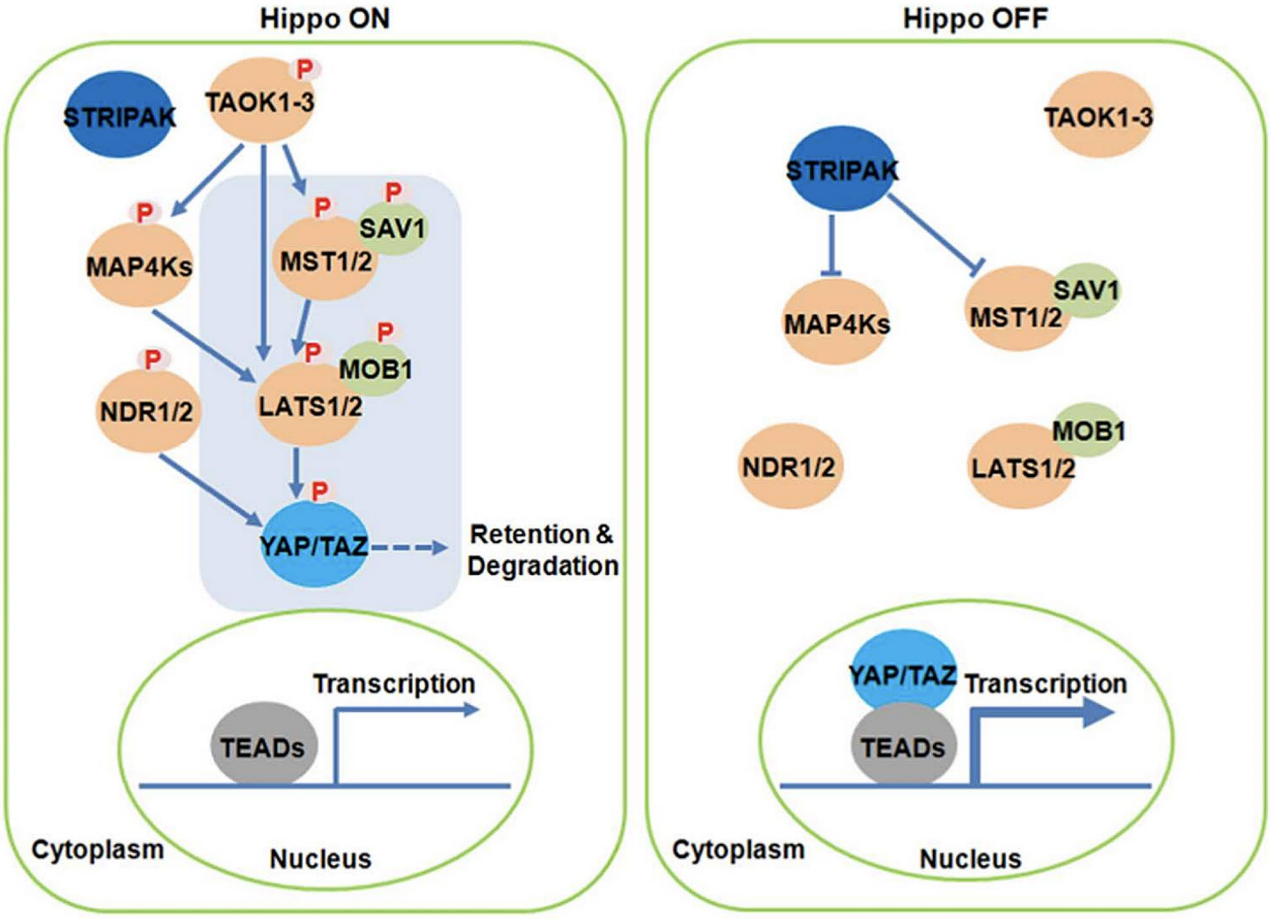

Fig. 2 Hippo pathway. Hippo pathway is regulated by various stimuli such as mechanical stress, G-protein coupled receptor signalling pathways, and cellular energy status. Activation of kinases leads to phosphorylation of transcriptional co-activators yes-associated protein 1 (YAP1) and transcriptional coactivator with PDZ-binding motif (TAZ) resulting their cytoplasmic retention and degradation. Thus, active physiological signalling of the Hippo pathway rather controls cell growth than stimulates it. When the Hippo signalling pathway is inactive, YAP1 and TAZ are non-phosphorylated and located in nucleus, where they interact and activate TEAD transcription factors (TEAD1-4). This YAP1/TAZ-TEAD complex drives expression of genes promoting cell proliferation and stem cell/progenitor cell self-renewal, and inhibiting apoptosis leading to organ growth, tissue regeneration, and tumorigenesis

[80]. These trials are crucial as they explore the potential of directly disrupting the protein-protein interactions at the core of TAZ-driven transcriptional activation.

The strategic targeting of the Hippo pathway, particularly through interventions against the TAZ–CAMTA1 fusion, offers hope not only for treating EHE but potentially for managing other cancers where YAP/TAZ dysregulation plays a critical role. By understanding the specific interactions and transformations driven by the Hippo pathway in these contexts, new therapeutic strategies can be developed to mitigate the aggressive nature of these cancers, ultimately improving patient outcomes. Thus, the study of TAZ–CAMTA1 in EHE serves as a critical gateway to broader applications in cancer therapy, highlighting the importance of pathway-targeted treatments in modern oncology.

Conclusions

The incremental progress in the survival of soft tissue sarcoma (STS) patients is intricately tied to the challenges posed by the rarity and heterogeneity of these tumors. Clinical trials, often constrained by small sample sizes and intricate stratification criteria, yield varied survival outcomes. Despite these challenges, recent years have witnessed a significant effort within the scientific community to enhance clinical trial strategies and elevate patient outcomes.

Chemotherapy retains its pivotal role as the cornerstone of STS treatment, with emerging studies such as LMS-04 exploring novel combinations tailored to specific histotypes. Combinatorial approaches intertwining immunogenic chemotherapies with immune checkpoint inhibitors seek to overcome the perceived resistance of STS to immunotherapies. However, despite compelling rationale, the efficacy of immune-checkpoint inhibitors (ICIs) in STS appears modest, underscoring the need for

refined patient selection, potentially through novel predictive biomarkers such as TLS.

Histology-driven trials leveraging distinct molecular characteristics have emerged as a pivotal paradigm for crafting effective strategies. Targeted therapies, gaining prominence in specific STS subtypes, exhibit heightened response rates, highlighting the potential of tailored approaches.

In addition to histology-driven and biomarker-guided studies, the third critical dimension for successful trials resides in meticulous planning of translational ancillary studies. Unraveling the mechanisms of action and, crucially, the resistance mechanisms of novel drugs become paramount. These insights not only deepen our understanding but also pave the way for the discovery of valuable biomarkers, ushering in a new era of precision medicine for STS patients.

Abbreviations

STS	Soft tissue sarcomas
mPFS	Median progression-free survival
mOS	Median overall survival
HR	Hazard ratio
DCR	Disease control rate
ICI	Immune checkpoint inhibitor
ORR	Overall response rate
TME	Tumor microenvironment
SIC	Sarcomas immune classes
TLS	Tertiary lymphoid structure
NPR	Non-progression rate
RMS	Rhabdomyosarcomas
LMS	Leiomyosarcomas
ACT	Adoptive cell transfer
CAR	Chimeric antigen receptor
TCR	T cell receptor
SS	Synovial sarcomas
LPS	Liposarcomas
IMT	Inflammatory myofibroblastic tumor
ALK	Anaplastic lymphoma kinase
NGS	Next-generation sequencing
PDGFRB	Platelet-derived growth factor receptor beta
NTRK3	Neurotrophic tyrosine receptor kinase 3
SMARCB1	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1
INI1	Integrase interactor 1
PRC2	Polycomb repressive complex 2
ES	Epithelioid sarcomas
MPNST	Malignant peripheral nerve sheath tumor
WDLPS	Well-differentiated liposarcomas
DDLPS	Dedifferentiated liposarcomas
MDM2	Mouse double minute 2
PROTAC	Proteolysis targeting chimera
GISTs	Gastrointestinal stromal tumors
TKi	Tyrosine kinase inhibitors
ctDNA	Circulating tumor DNA
HLA	Human leukocyte antigen
MAGE-A4	Melanoma-associated antigen A4
SPEAR	Specific peptide enhanced affinity receptor
CDK9	Cyclin-dependent kinase 9
MCL-1	Myeloid cell leukemia-1
BAF	BRG1/BRM–associated factor
ncBAF	Non-canonical BAF
cBAF	Canonical BAF

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AI , NEG and MSP conducted the literature search, drafted, and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

Consent for publication

Not applicable.

Competing interests

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