

REVIEW ARTICLE

Immunotherapy in bone and soft-tissue tumors: Current advances and future directions

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Abstract

Immunotherapy has emerged as a transformative strategy for treating bone and soft-tissue sarcomas, a class of rare, heterogeneous malignancies originating from mesenchymal tissues; however, significant challenges remain. This narrative review summarizes recent advances in sarcoma immunotherapy, covering molecular mechanisms, tumor microenvironment (TME) characteristics, and treatment responses specific to major subtypes such as osteosarcoma, liposarcoma, and synovial sarcoma. Notably, despite being a distinct myeloid neoplasm rather than a sarcoma, systemic mastocytosis is included in this study to identify common therapeutic targets through cross-disease comparisons (e.g., kinase-driven pathways and mechanisms regulating the immunosuppressive TME). Clinical data indicate that single-agent immune checkpoint inhibitors (ICIs) produce limited objective response rates in advanced sarcomas (approximately 16.7%), with significant efficacy disparities across subtypes, ranging from high response rates in alveolar soft part sarcomas to minimal responses in osteosarcomas. Key resistance mechanisms include a suppressive TME dominated by myeloid-derived suppressor cells, low tumor mutational burden, and antigenic heterogeneity. Combination strategies such as ICIs with radiotherapy, tyrosine kinase inhibitors, or anti-angiogenic agents significantly improve outcomes. Emerging cell therapies such as chimeric antigen receptor T-cell, T-cell receptor-engineered, and tumor-infiltrating lymphocyte therapies, combined with neoantigen vaccines and nanotechnology-driven delivery systems, demonstrate potential in reshaping the TME and overcoming immune escape. Biomarkers, including programmed death-ligand 1 expression, tertiary lymphoid structures, and immune gene profiles, hold prognostic value but require further validation. Future research should prioritize tissue-specific trial designs, combined TME remodeling regimens, and biomarker-guided personalized therapies to effectively convert “cold” sarcomas into immunotherapy-responsive malignancies.

Keywords: Bone and soft-tissue tumor; Combination immunotherapy; Tumor microenvironment

1. Introduction

Bone and soft-tissue sarcomas are a rare and highly heterogeneous group of malignancies originating from mesenchymal tissue, accounting for <1% of adult malignant tumors.¹⁻³ Although traditional treatments such as surgery, chemotherapy, and radiotherapy have made progress in local control, the prognosis for patients with advanced or metastatic disease remains poor, with a 5-year survival rate of <20%.⁴ Treating these malignancies remains challenging, primarily due to their marked molecular heterogeneity, complex tumor microenvironment (TME), and the lack of effective targeted therapeutic strategies.^{5,6}

In recent years, breakthroughs in immunotherapy for solid tumors have brought new opportunities for the treatment of bone and soft-tissue sarcomas. However, the inherent “cold” immune microenvironment characteristics of sarcomas, such as low levels of tumor-infiltrating lymphocytes (TILs) and the absence of specific biomarkers, significantly limit the efficacy of immunotherapy.^{7,8} Notably, studies have confirmed that specific sarcoma subtypes—such as alveolar soft part sarcoma (ASPS) and undifferentiated pleomorphic sarcoma (UPS)—show a high response rate to immune checkpoint inhibitors (ICIs).^{9,10} In addition, treatment strategies combining anti-angiogenic drugs or tyrosine kinase inhibitors (TKIs) can significantly enhance the response to immunotherapy.^{4,11}

The core value of immunotherapy lies in activating the host immune system to target and eliminate tumor cells, thereby overcoming the limitations of traditional treatments.^{4,12} Clinical studies have shown that programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors and cytotoxic T-lymphocyte-associated protein 4 inhibitors have the potential to prolong progression-free survival (PFS) and overall survival in patients.¹³ Emerging immunotherapies such as adoptive cell therapy and TIL therapy also show broad clinical application prospects.¹¹

In summary, the biological complexity and treatment challenges associated with bone and soft-tissue sarcomas highlight the necessity of developing immunotherapy. By elucidating the regulatory mechanisms of the tumor immune microenvironment and integrating personalized treatment strategies, new therapeutic avenues can be developed for patients with these difficult-to-treat tumors.¹⁴

To identify relevant literature for this narrative review, a comprehensive search was conducted in the electronic databases PubMed (<https://www.ncbi.nlm.nih.gov/>) and Web of Science (<https://www.webofscience.com>). The search focused on articles published primarily between 2015 and September 2025 to capture the most recent

advances. Key search terms included: “immunotherapy,” “bone tumor,” “soft-tissue tumor,” “sarcoma,” “immune checkpoint inhibitor,” “CAR-T,” “tumor-infiltrating lymphocytes,” and “cancer vaccine.” These terms were combined using Boolean operators (e.g., [immunotherapy] AND [sarcoma OR “bone tumor”]). The search was limited to studies published in English. Additional relevant publications were identified by manually screening the reference lists of key articles and recent reviews.

2. Immunological microenvironment characteristics of bone and soft-tissue sarcomas

2.1. Immunosuppressive mechanisms in the TME

The TME of bone and soft-tissue sarcomas exhibits significant immunosuppressive characteristics, which are the primary cause of poor immunotherapy outcomes.¹⁵ Research indicates that the sarcoma TME is enriched with suppressive immune cell populations, including dysfunctional T cells and immunologically suppressive macrophages, while lacking effector T cells.¹⁶ In osteosarcoma, this immunosuppressive microenvironment is characterized by low immune effector cell activity and hyperactivation of immunosuppressive cells.¹⁷ Tumor-associated macrophages (TAMs) further exacerbate the immunosuppressive state by expressing PD-L1 and altering their chemokine expression profiles.¹⁸ In addition, stromal components such as cancer-associated fibroblasts also participate in the construction of this complex immunosuppressive network.¹⁹ This immunosuppressive microenvironment constitutes a significant barrier to the efficacy of current immunotherapies, including ICIs and tumor vaccines.²⁰

2.2. Immunological characteristic differences among subtypes

Significant immunological heterogeneity exists among different subtypes of bone and soft-tissue sarcomas. Studies have shown that ICIs demonstrate efficacy only in specific subtypes such as UPS, ASPS, and leiomyosarcoma.²¹ Flow cytometry analysis indicates that tumor tissues from patients with dedifferentiated liposarcoma (DDLPS) exhibit significantly higher infiltration of cluster of differentiation (CD) 3⁺, CD8⁺, CD19⁺, and CD11c⁺ immune cells compared to patients with well-differentiated liposarcoma.²² Based on immune-feature classification, sarcomas can be divided into three immune subtypes with unique TMEs.²³ In Ewing sarcoma, the TME exhibits unique metabolic reprogramming and functional specialization. Single-cell RNA sequencing analysis revealed differences in immune cell metabolic reprogramming and functional

specialization in bone tumors, including osteosarcoma, Ewing sarcoma, and osteoblastoma.²⁴ In addition, there are significant differences in the immune composition between soft-tissue sarcomas and bone metastases.¹⁶

2.3. Predictive biomarkers for immunotherapy response

Current research has identified multiple biomarkers and risk scores associated with prognosis and immunotherapy response in soft-tissue sarcomas.²² Tumor mutational burden (TMB) is considered one of the key indicators for predicting immunotherapy response.²¹ Tertiary lymphoid structures (TLS), as an important component of the tumor immune microenvironment, provide significant insights into patient prognosis and immunotherapy response.²⁵ Immune escape markers such as PD-L1 and CD80 may be associated with metastasis in soft-tissue sarcomas.²³ Immune-related genes play a key role in sarcoma development and the construction of the tumor immune microenvironment, and may have prognostic and predictive value.²⁶ In osteosarcoma, identifying highly sensitive immune microenvironment characteristic markers has become a research focus.²⁷ Recent studies have also found that the preadrenergic signaling pathway may influence immunotherapy efficacy, and the beta-blocker propranolol can significantly enhance the efficacy of anti-CTLA-4 therapy.²⁸ These findings provide valuable insights for developing more precise biomarker systems.

3. Immunotherapy in selected tumor types: Sarcomas and systemic mastocytosis (SM)

3.1. Osteosarcoma

3.1.1. Molecular mechanisms of osteosarcoma

Osteosarcoma is the most common primary malignant bone tumor, primarily affecting adolescents and young adults aged 10–24 years.^{29,30} The second peak of incidence occurs in individuals aged 60 years and older, often associated with secondary bone lesions, such as Paget's disease.^{31,32} The TME of osteosarcoma plays a key role in disease progression, primarily composed of T lymphocytes, macrophages, B lymphocytes, and mast cells. Tumor cells regulate the M1/M2 macrophage balance, activate PD-1/PD-L1 signaling, thereby establishing an immunotolerant environment and promoting tumor growth and drug resistance. Mesenchymal stem cells also participate in the immune escape process, further enhancing immunotolerance.^{2,33}

Common genetic mutations in osteosarcoma include the *TP53* and retinoblastoma (*RB1*) genes, which play pivotal roles in the development and progression of the disease (Figure 1). Studies indicate that 62% of

osteosarcoma samples harbor alterations in *TP53*, *RB1*, or mouse double minute 2 homolog (*MDM2*) genes.³⁴ Germline and somatic mutations in the *TP53* gene are closely associated with osteosarcoma development, with fusion genes resulting from *TP53* promoter translocations representing a recurrent molecular event in this tumor.³⁵ Regarding the *RB1* pathway, approximately five cases of osteosarcoma simultaneously exhibiting *RB1* alterations and *TP53* mutations have been identified.³⁶ In addition, *MDM2* gene amplification (2–3-fold increase in copy number) is observed in approximately 19% of osteosarcoma cases. This amplification may suppress p53 function by enhancing *MDM2*–p53 binding.³⁷ Studies in Chinese patient cohorts have also identified frequent mutations in genes such as *NCOR1*, *LRP1B*, *ATRX*, and *TFE3*.³⁸

The pathogenesis of osteosarcoma involves abnormalities in the expression of multiple genes and dysregulation of signaling pathways. Phospholipase C β 4 is highly expressed in tumor tissues and is significantly associated with reduced patient survival rates.³⁹ The expression levels of chemokines (e.g., CCL5, CCL8) and their receptors (e.g., CCR4, CCR5) are closely related to prognosis. These factors influence tumor growth and metastasis by regulating signaling pathways such as Toll-like receptors (TLR), the mitogen-activated protein kinase (MAPK) family, and nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B).^{1,40}

Abnormal activation or inhibition of signaling pathways such as Wnt/ β -catenin, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR), MAPK, Notch, NF- κ B, and Hippo is closely associated with the occurrence and development of osteosarcoma.^{41–43} Among these, the Wnt/ β -catenin pathway drives cell proliferation and metastasis, while the PI3K/Akt/mTOR pathway mediates cell survival and drug resistance.^{42,43} The key effector molecules of the Hippo pathway, yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ), regulate cell proliferation and migration.⁴⁴

Long non-coding RNAs and microRNAs (miRNAs) are important regulators of osteosarcoma biology. For example, long non-coding RNA *MALAT1* regulates tumor proliferation and metastasis by modulating multiple signaling pathways and miRNAs.^{45,46} miRNA-21, miRNA-34a, and miRNA-143, among others, influence disease progression and drug resistance by targeting key genes.^{41,47} These non-coding RNAs possess both potential as diagnostic markers and therapeutic targets.⁴¹

3.1.2. Immunotherapy for osteosarcoma

ICIs represent a core strategy in the field of osteosarcoma immunotherapy. Preclinical models have shown that PD-1/

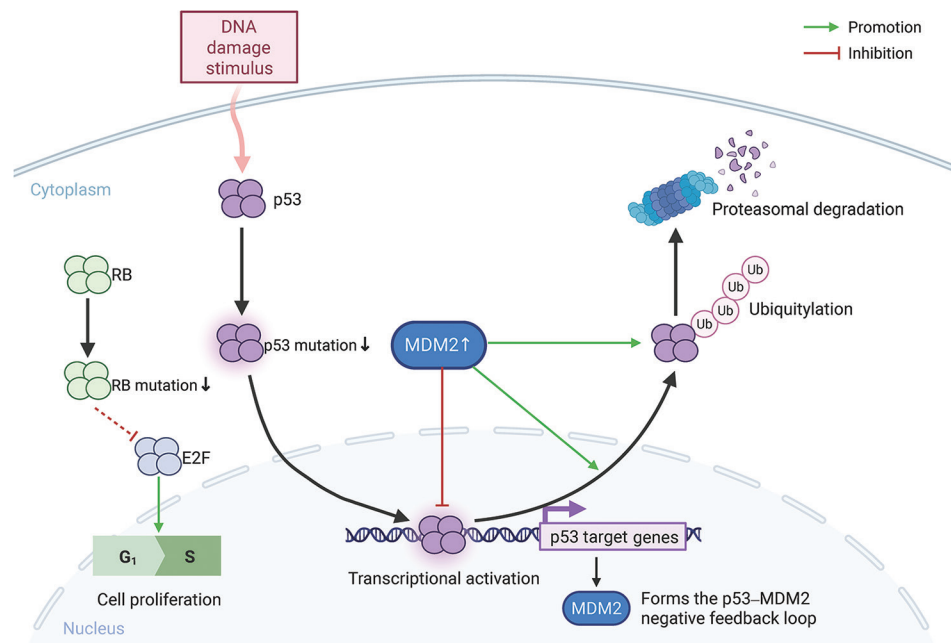


Figure 1. Genetic mutations in osteosarcoma. Mutations in the *TP53* gene cause loss of function, preventing DNA damage from being repaired and allowing tumor cells to escape apoptosis. The *RB* gene mutation causes E2F inactivation, leading to failure of cell cycle checkpoints. Cells transition aberrantly from the G1 phase to the S phase, resulting in abnormal division and proliferation of tumor cells. Created in BioRender. Fang, (2026). <https://BioRender.com/0sjik88>.

Abbreviations: E2F: E2 promoter-binding factor; MDM2: Mouse double minute 2 homolog; RB: Retinoblastoma.

PD-L1 and cytotoxic T-lymphocyte-associated protein 4 inhibitors demonstrate significant efficacy in various tumors, but their efficacy remains relatively limited in osteosarcoma.⁴⁸ As shown in Table 1, retrospective studies have confirmed that the objective response rate (ORR) of osteosarcoma patients to ICIs is ≤5%, significantly lower than that of other sarcoma subtypes, which may be attributed to the tumor's low immunogenicity and immunosuppressive microenvironment.^{34,49,50} It is important to note that ICI therapy may induce severe side effects, such as immune-related adverse events.⁵¹ Current research focuses on exploring combination therapy strategies, such as carbon ion radiotherapy combined with ICIs, which has been shown to significantly inhibit lung metastasis in animal models.

In the field of cell therapy, B10 chimeric antigen receptor T cells (CAR-T) targeting the tumor stem cell marker DNAJB8 have demonstrated anti-osteosarcoma activity in preclinical studies.⁵⁷ CAR-T therapy uses engineered T cells to specifically recognize and kill tumor cells. While it has achieved breakthroughs in hematological tumors, its application in osteosarcoma remains in the exploratory stage.⁵⁸ Modified natural killer cell and macrophage therapies enhance efficacy by boosting immune cell activity, but tumor heterogeneity and complex microenvironments limit their widespread application.^{58,59}

The immunosuppressive microenvironment of osteosarcoma is a core factor in treatment failure, characterized by extensive infiltration of M2-type macrophages and insufficient immune cell infiltration, leading to low response rates.¹⁷ Targeting the reprogramming of TAMs to a proinflammatory M1 phenotype (e.g., using nanodrugs or cytokine regulation) can enhance anti-tumor immunity.⁶⁰ Bioactive molecule delivery systems based on nanomaterials (e.g., Mg²⁺ combined with anti-PD-L1 antibodies) can simultaneously induce tumor cell death and promote bone regeneration.⁶¹ Nanoplatfoms targeting mitochondrial autophagy can also enhance immune cell activity.⁶²

Given the limitations of monotherapy, combination strategies have become a research focus: ICIs combined with chemotherapy drugs (e.g., curcumin) exhibit synergistic antitumor effects in animal models,⁶³ whereas ICIs combined with radiotherapy (e.g., carbon ion radiotherapy) can significantly inhibit lung metastasis.⁶⁴ These multi-target combination regimens hold promise for overcoming the limitations of monotherapy and improving clinical efficacy.

3.2. Liposarcoma

3.2.1. Molecular mechanisms of liposarcoma

Liposarcoma is a rare malignant tumor of adipocyte origin. According to the World Health Organization classification

Table 1. Summary of selected clinical studies on immunotherapy for sarcoma

Sarcoma subtype	Immunotherapy/regimen	n (evaluable)	Objective response rate (%)	Median progression-free survival	Median overall survival	Main reference
Kaposi sarcoma	Immunotherapy cohort, as reported by Lee <i>et al.</i> ⁴⁹	6	66.7	-	-	Lee <i>et al.</i> ⁴⁹
ASPS	Axitinib+pembrolizumab (Phase II)	33 (12 ASPS)	≈54.5 (ASPS subgroup)	3-month progression-free survival rate: 72.7%	-	Wilky <i>et al.</i> ⁵²
Alveolar soft part sarcoma	Immunotherapy cohort, as reported by Lee <i>et al.</i> ⁴⁹	4	50	-	-	Lee <i>et al.</i> ⁴⁹
Undifferentiated pleomorphic sarcoma	SARC028: Pembrolizumab (anti-PD-1)	10	40	-	-	Tawbi <i>et al.</i> ³⁴
Undifferentiated pleomorphic sarcoma	Immunotherapy cohort, as reported by Lee <i>et al.</i> ⁴⁹	18	27.8	11.3 months	-	Lee <i>et al.</i> ⁴⁹
Angiosarcoma	Immunotherapy cohort, as reported by Lee <i>et al.</i> ⁴⁹	15	33.3	6.4 months	-	Lee <i>et al.</i> ⁴⁹
Angiosarcoma	SWOG S1609/DART: Nivolumab+ipilimumab	16–20	≈25	-	-	Wagner <i>et al.</i> ⁵³
Myxofibrosarcoma	Immunotherapy cohort, as reported by Lee <i>et al.</i> ⁴⁹	14	28.6	27.4 months	-	Lee <i>et al.</i> ⁴⁹
Chondrosarcoma	SARC028: Pembrolizumab	5	20 (1/5)	-	-	Tawbi <i>et al.</i> ³⁴
Dedifferentiated liposarcoma	SARC028: Pembrolizumab	10	20	-	-	Tawbi <i>et al.</i> ³⁴
Synovial sarcoma	SARC028: Pembrolizumab	10	10	-	-	Tawbi <i>et al.</i> ³⁴
Synovial sarcoma	Immunotherapy cohort, as reported by Lee <i>et al.</i> ⁴⁹	7	0	2.4 months	-	Lee <i>et al.</i> ⁴⁹
Liposarcoma	Immunotherapy cohort, as reported by Lee <i>et al.</i> ⁴⁹	27	3.7	4.2 months	-	Lee <i>et al.</i> ⁴⁹
Osteosarcoma	SARC028: Pembrolizumab	22+	≈5 (SARC028);	Very short	-	Tawbi <i>et al.</i> ³⁴
Osteosarcoma	IMMUNOSARC study (NCT03277924, Phase II): Nivolumab	38	5	3.8 months	11.9 months	Palmerini <i>et al.</i> ⁵⁴
Osteosarcoma	PROMO (Phase II)	12	0 (Phase II PROMO)	Not improved	-	Boye <i>et al.</i> ⁵⁰
Osteosarcoma	Immunotherapy cohort, as reported by Lee <i>et al.</i> ⁴⁹	6	0	4.0 months	-	Lee <i>et al.</i> ⁴⁹
Osteosarcoma (adjuvant)	Mifamurtide (LMTPE)+chemotherapy (INT0133)	662	Not applicable (adjuvant)	-	6 year overall survival improved (from 70% to 78%)	Meyers <i>et al.</i> ⁵⁵
Leiomyosarcoma	SARC028: Pembrolizumab	10	0 (SARC028)	Short median progression-free survival	-	Tawbi <i>et al.</i> ³⁴
Leiomyosarcoma	Alliance A091401: Nivolumab+ipilimumab	15 (nivolumab)/14 (nivolumab+ipilimumab)	Nivolumab: 5; nivolumab+ipilimumab: 16	-	-	D'Angelo <i>et al.</i> ⁵⁶

Abbreviation: ASPS: Alveolar soft part sarcoma.

criteria, it is primarily divided into four subtypes: atypical lipomatous tumor/well-differentiated liposarcoma, DDLPS, myxoid liposarcoma (MLPS), and pleomorphic liposarcoma (PLPS).⁶⁵ The molecular mechanisms of this tumor primarily involve amplification of the chromosome 12q13-q15 region, leading to overexpression of the *MDM2*

and cyclin-dependent kinase (*CDK4*) genes (Figure 2). p53 regulates the functions of macrophages, dendritic cells, natural killer cells, T cells, and B cells through secreted factors, contributing to immune surveillance and suppressing tumorigenesis.⁶⁶ The overexpression of *MDM2*, a key negative regulator of the p53 pathway, can inhibit the

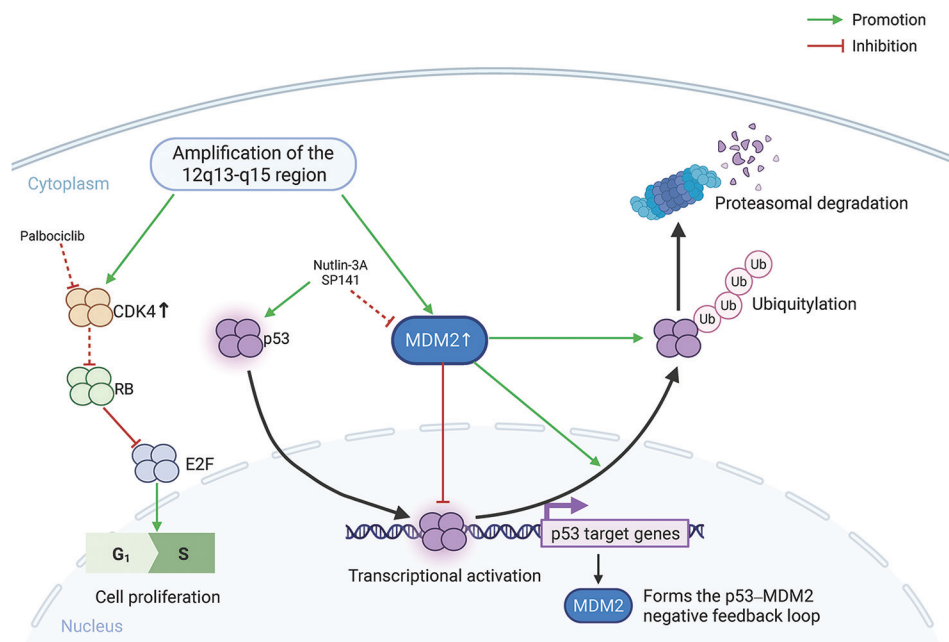


Figure 2. Molecular mechanisms of the development of liposarcoma. MDM2 overexpression leads to excessive degradation of the p53 protein, preventing cells with DNA damage from halting proliferation or undergoing apoptosis. CDK4 overexpression leads to excessive phosphorylation and inactivation of the RB protein, resulting in uncontrolled cell cycle progression and disordered cell division. Created in BioRender. Fang (2026). <https://BioRender.com/tyzw9va>.

Abbreviations: CDK4: Cyclin-dependent kinase 4; E2F: E2 promoter-binding factor; MDM2: Mouse double minute 2 homolog; RB: Retinoblastoma.

tumor-suppressing function of p53, thereby promoting tumor growth.⁶⁷ CDK4 drives tumor proliferation by regulating the cell cycle.⁶⁸ Genetic characteristics vary among subtypes: Both well-differentiated liposarcoma and DDLPS exhibit MDM2/CDK4 amplification, but DDLPS has a higher amplification rate and is associated with more complex genomic alterations.⁶⁹ MLPS is characterized by fused in sarcoma/DNA damage inducible transcript 3 gene fusion, whereas PLPS lacks specific molecular markers and exhibits more complex genetic alterations.⁷⁰ Notably, amplification in the 1p32 and 6q23 regions in DDLPS may be associated with its aggressive phenotype.⁷¹

3.2.2. Immunotherapy for liposarcoma

Based on the aforementioned molecular mechanisms, various targeted therapeutic strategies are currently under development. MDM2 and CDK4 are current research hotspots: MDM2 inhibitors (e.g., Nutlin-3A and SP141) demonstrate antitumor potential by restoring p53 function or inhibiting MDM2 metabolic activity.^{67,72} CDK4/6 inhibitors (e.g., palbociclib) have shown efficacy in clinical trials.⁷¹ T-cell therapy targeting the New York esophageal squamous cell carcinoma 1 antigen in MLPS (e.g., letetresgene autoleucel) has demonstrated clinical value in early studies, particularly in HLA-A*02:01-positive patients.⁷³ The microtubule inhibitor eribulin shows potential for achieving complete

remission in unresectable liposarcoma, with its mechanism potentially related to downregulating the phosphorylated-Akt signaling pathway.⁷⁴

3.3. Synovial sarcoma (SS)

3.3.1. Molecular mechanisms of SS

SS is a rare but highly aggressive soft-tissue sarcoma that primarily affects adolescents and young adults.⁷⁵ Its core molecular characteristic is the chromosomal translocation t(X;18)(p11;q11), which results in the fusion of the SS18 gene with the SSX gene (e.g., SSX1, SSX2, or SSX4) to form the SS18–SSX fusion protein. As an ATP-dependent chromatin remodeling complex, switch/sucrose non-fermentable (BAF) antagonizes the repressive effects of the polycomb repressive complex, thereby activating the expression of tumor suppressor genes.⁷⁶ The SS18–SSX fusion protein abnormally binds to the switch/sucrose non-fermentable chromatin remodeling complex, disrupting its chromatin structural and dynamic regulatory function, thereby driving tumorigenesis (Figure 3).⁷⁷ In addition, the SS18–SSX fusion protein interacts with the lysine demethylase 2B (KDM2B)–polycomb repressive complex 1.1, activating developmental-related genes silenced by polycomb proteins through KDM2B-mediated histone demethylation, thereby promoting cellular malignant transformation.⁷⁸

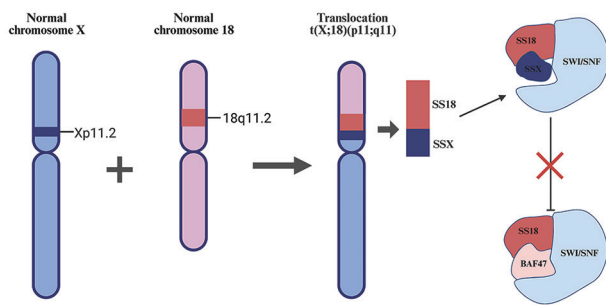


Figure 3. Formation of the SS18–SSX fusion protein. The SS18–SSX fusion protein disrupts proper assembly of the BAF chromatin remodeling complex, impairing activation of tumor suppressor gene expression. Created in BioRender. Fang, L. (2026). <https://BioRender.com/scjfa9u>. Abbreviation: SS: Synovial sarcoma.

The SS18–SSX fusion protein regulates gene expression through multiple mechanisms: (i) it binds to the *TRPS1* gene locus to activate transcription, promoting tumor proliferation and metastasis;⁷⁹ and (ii) it inhibits the expression of the tumor suppressor gene *EGRI*, accelerating tumor progression.⁸⁰ This protein can also activate the Hippo pathway effector molecules YAP/TAZ: It regulates large tumor suppressor 1/Mps one binder through the insulin-like growth factor 2/insulin-like growth factor 1 receptor signaling loop, enhancing YAP/TAZ–TEA/ATTS domain transcriptional activity.⁸¹ Simultaneously, it inhibits apoptosis through the tyrosine kinase 2/signal transducer and activator of transcription (STAT) 3/B-cell lymphoma 2 signaling axis, enhancing tumor cell survival capacity.⁸²

3.3.2. Immunotherapy for SS

In the field of immunotherapy, retrospective analyses suggest that patients with PD-L1–positive SS have poorer outcomes but may be more sensitive to PD-1 inhibitor therapy.⁸³ To overcome single-agent resistance, combination strategies show promise: PD-1 inhibitors combined with anti-angiogenic agents (e.g., anlotinib) demonstrate significant antitumor activity in SS, particularly the ASPS subtype.⁸⁴ Radiotherapy can enhance the response to immunotherapy by upregulating PD-L1 expression.⁸⁵

Given that SS18–SSX drives tumorigenesis through epigenetic mechanisms, targeting related regulatory factors has become an important direction: Histone deacetylase inhibitors (e.g., romidepsin) can reverse SS18–SSX-mediated polycomb protein-dependent gene silencing and reactivate tumor suppressor gene expression.⁸⁰ Compounds targeting epigenetic regulatory factors such as KDM2B and WD repeat domain 5 also demonstrate antitumor potential.^{78,86} Targeting downstream signaling pathways, YAP/TAZ small-molecule inhibitors (e.g., verteporfin) effectively inhibit tumor cell growth.⁸¹

3.4. Ewing sarcoma

3.4.1. Molecular mechanisms and immunological features

Ewing sarcoma is characterized by chromosomal translocations that generate fusion proteins, most commonly the *EWSR1–FLI1* fusion gene, which serves as a diagnostic and therapeutic hallmark.⁸⁷ These fusion oncoproteins drive tumorigenesis by aberrantly regulating multiple signaling pathways, including PI3K/AKT and MAPK cascades, and key pathogenic molecules such as the eyes absent transcriptional coactivator and phosphatase 3 tyrosine phosphatase.⁸⁸ Immunologically, Ewing sarcoma typically presents as a “cold” TME, exhibiting minimal response to PD-1 inhibitor monotherapy due to low immune cell infiltration and adaptive immune resistance mechanisms.⁸⁹ The TME is further defined by unique immune cell subsets, including CD14⁺, CD16⁺ macrophage populations, and C-X-C motif chemokine ligand 10-driven chemokine pathways that modulate immune trafficking.⁹⁰ Single-cell analyses reveal complex immunosuppressive features, such as transcriptional heterogeneity and clonal evolution, which contribute to immune evasion and therapy resistance.⁹¹

3.4.2. Immunotherapy for Ewing sarcoma

Current immunotherapy strategies for Ewing sarcoma focus on targeting specific vulnerabilities identified through molecular profiling. These include:

- Targeting surface antigens: Interleukin-1 receptor accessory protein, a cell surface protein with minimal expression in normal tissues but critical roles in metastasis and anoikis resistance, represents a promising immunotherapeutic target.⁹²
- Modulating immune axes: The macrophage migration inhibitory factor/CD74 axis has been identified as a key regulator of T-cell activation and tumor growth, with inhibitory approaches showing potential to enhance antitumor immunity.⁹³
- Fusion protein degradation: Ubiquitin-specific peptidase 9 inhibitors (e.g., WP1130) promote the ablation of EWS–FLI1 fusion proteins, directly addressing the core oncogenic driver and synergizing with immune interventions.⁹⁴
- Combination cell therapies: T-cell receptor-engineered T cells (TCR-T) combined with Y-box binding protein 1–based oncolytic virotherapy have demonstrated improved survival in preclinical models, highlighting the potential of multimodal immunotherapeutic approaches.⁹⁵

However, these strategies face significant challenges, including intrinsic tumor heterogeneity, chemotherapy

resistance mechanisms mediated by pathways such as Janus kinase (JAK) 1/STAT6/growth arrest-specific 6/TAM signaling, and the need for improved preclinical models. Multi-kinase inhibitors like KC1036 show broad anti-angiogenic and growth-suppressive activity but require validation in immunotherapy combination regimens.^{96,97} Optimizing humanized orthotopic mouse models is essential for accurate efficacy evaluation, while proteomic studies continue to identify novel surface targets like ectonucleotide pyrophosphatase/phosphodiesterase 1 for future immunotherapeutic development.^{98,99} Overcoming these barriers will require integrated efforts focusing on TME reprogramming and biomarker-guided personalized strategies.

3.5. Chondrosarcoma

3.5.1. Molecular mechanisms and classification

Chondrosarcoma is a malignant bone tumor originating from chondrocytes, representing the second most common primary bone sarcoma after osteosarcoma.^{100,101} Its molecular pathogenesis is characterized by frequent isocitrate dehydrogenase (*IDH1/IDH2*) gene mutations, detected in approximately 50% of conventional cases, leading to accumulation of the oncometabolite D-2-hydroxyglutarate that dysregulates DNA methylation and epigenetic programming to promote tumorigenesis.^{102–105}

Key signaling pathways are constitutively activated, including the Hedgehog pathway, which drives tumor growth through glioma-associated transcription factors; the enhancer of zeste homolog 2/sulfatase 1/c-Met receptor tyrosine kinase axis, which mediates malignant progression; and YAP signaling, the enhancement of which is associated with *Trp53/Rb1* gene deficiencies that drive metastasis.^{106–108} The genetic mutation profile beyond IDH includes TP53 mutations in approximately 33.5% of patients and RB1 deletions in 8.7%, with co-deletion inducing spinal chondrosarcoma and pulmonary metastases.^{105,108} Molecular classification divides chondrosarcoma into conventional, dedifferentiated, and mesenchymal subtypes, with the dedifferentiated subtype exhibiting higher PD-L1 expression (45%) and more targetable mutations.¹⁰²

3.5.2. Immunotherapy for chondrosarcoma

Immunotherapy faces significant challenges due to the immunosuppressive TME, which is dominated by TAMs constituting up to 50% of tumor mass and exhibits low effector T cell infiltration, limiting the efficacy of ICIs.^{102,109,110} The low immunogenicity is evidenced by few cases with TMB >10 mutations/Mb and no instances of high microsatellite instability,¹⁰² while IDH mutation-induced epigenetic alterations (e.g., DNA/histone hypermethylation) further

suppress immune responses.^{111,112} Potential strategies to overcome resistance include epigenetic modulators like DNA methyltransferase inhibitors (e.g., decitabine) to reverse immunosuppression,¹¹² IDH inhibitors combined with checkpoint blockade,^{102,103} and multi-pathway targeting of Hedgehog–glioma-associated (e.g., GANT-61) or c-Met receptor tyrosine kinase axes.^{106,107,113} Differential response is notable, with the dedifferentiated subtype's higher PD-L1 positivity (45% vs. 10% in conventional chondrosarcoma) suggesting greater potential benefit from immunotherapy.¹⁰²

3.6. SM

3.6.1. Molecular mechanisms of SM

Although SM is classified as a myeloid neoplasm rather than a sarcoma, its immunotherapy advancements provide valuable insights into targeting kinase-driven pathways and immunosuppressive TME, which are relevant to sarcoma treatment. SM is a rare myeloid neoplasm characterized by clonal, neoplastic proliferation of mast cells and infiltration into one or more organ systems.¹¹⁴ The pathological manifestations of this disease are complex, encompassing multidimensional features such as morphological, molecular, genetic, and immunophenotypic characteristics.

The diagnosis of SM primarily relies on histological evidence, particularly the abnormal proliferation of mast cells in bone marrow biopsies.¹¹⁵ The World Health Organization and the International Consensus Classification system have established clear diagnostic criteria, including mast cell aggregation, morphological abnormalities, *KIT* D816V mutations, and abnormal expression of mast cell surface markers (e.g., CD25, CD2, and CD30). The bone marrow is the most commonly affected organ, where mast cells typically exhibit spindle-shaped, low-granular morphology and form dense aggregates.^{115,116}

The *KIT* D816V mutation (found in approximately 80% of SM patients) drives mast cell proliferation through constitutive kinase activation. This underpins targeted therapies such as avapritinib.^{116,117} The *KIT* D816V mutation directly activates the JAK/STAT pathway, which represents its core downstream mechanism. The constitutively activated *KIT* receptor triggers JAK kinases, which in turn phosphorylate STAT proteins, initiating a signal transduction cascade that regulates the expression of cell growth and anti-apoptotic genes¹¹⁸ (Figure 4). In addition, the molecular pathophysiology of SM involves other genetic and epigenetic alterations (e.g., DNA methyltransferase 3α and Runt-related transcription factor 1 mutations), which may play important roles in disease progression.^{119,120}

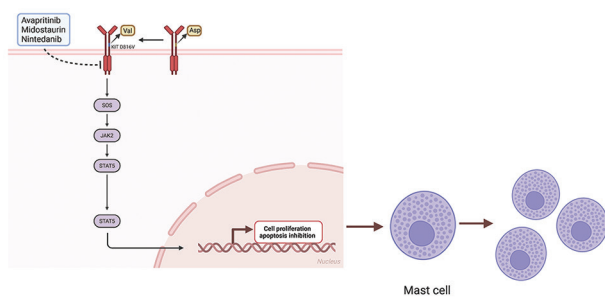


Figure 4. The *KIT* D816V mutation drives mast cell hyperplasia by constitutively activating the JAK/STAT signaling pathway. This pathogenic signaling can be inhibited by the tyrosine kinase inhibitors avapritinib, midostaurin, and nintedanib. Created in BioRender. Fang, L. (2026). <https://BioRender.com/447efcw>.

Abbreviations: Asp: Aspartate; JAK2: Janus kinase 2; SOS: Son of sevenless; STAT5: Signal transducer and activator of transcription 5; Val: Valine.

3.6.2. Treatment of SM

In recent years, targeted therapies have made significant progress in the treatment of SM, particularly TKIs targeting the *KIT* D816V mutation. Avapritinib, the first approved *KIT* D816V-specific inhibitor for advanced SM (AdvSM), holds significant therapeutic value for patients with rapidly progressing or TKI-resistant disease.^{121,122} This highly selective inhibitor demonstrates significant efficacy in AdvSM, with clinical trials showing an overall response rate of 75%, including 19% achieving complete remission, and significantly reducing serum tryptase levels (93%), bone marrow mast cell burden (88%), and *KIT* D816V variant allele frequency (60%).¹²³ In the Explorer and Pathfinder trials, avapritinib induced sustained remissions, with some patients successfully bridging to allogeneic hematopoietic stem cell transplantation.¹²⁴ It is important to note that the drug may cause cognitive impairment or intracranial hemorrhage, particularly in patients with severe thrombocytopenia, although overall tolerability is good.^{121,122}

Midostaurin is a multi-targeted kinase inhibitor approved by the Food and Drug Administration and the European Medicines Agency for the treatment of AdvSM, effectively inhibiting the *KIT* D816V mutation.^{114,125} This drug can reverse organ damage in AdvSM patients, reduce bone marrow mast cell burden and splenomegaly, achieving an overall response rate of 60%, including 45% major response.^{126,127} However, its complete response rate is relatively low, its efficacy has limited durability, and its inhibitory effect on the *KIT* D816V mutation is relatively weak, which may limit its clinical applicability.^{125,127}

Nintedanib is a multi-targeted TKI that inhibits vascular endothelial growth factor receptor, platelet-derived growth

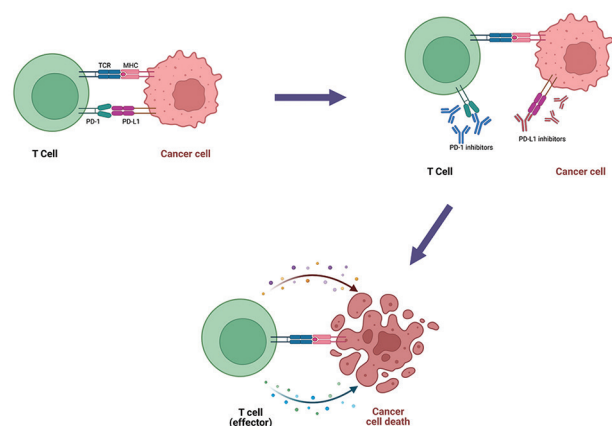


Figure 5. Immune checkpoint inhibitors for tumor treatment. PD-1/PD-L1 inhibitors restore T-cell-mediated cytotoxicity by blocking the interaction between PD-1 on T-cells and PD-L1 on tumor cells. Created in BioRender. Fang, L. (2026). <https://BioRender.com/qldm05v>.

Abbreviations: MCH: Major histocompatibility complex; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; TCR: T-cell receptor.

factor receptor, and fibroblast growth factor receptor.¹²⁸ Studies have shown that nintedanib has inhibitory activity against the *KIT* D816V mutation (*in vitro* experiments showed nanomolar IC₅₀ values) and can potentially inhibit mast cell proliferation. Preliminary data suggest it may be effective for patients with primary *KIT* D816V SM, but large-scale clinical trials are still needed to validate this.¹²⁹

4. Therapeutic approaches

4.1. Clinical research advances in ICLs

The PD-1/PD-L1 inhibitors function by blocking the interaction between PD-1 on T cells and PD-L1 on tumor cells, thereby reactivating T-cell-mediated antitumor immunity (Figure 5). PD-1/PD-L1 inhibitors have demonstrated clinical activity in the treatment of bone and soft-tissue sarcomas, although their efficacy varies significantly across different subtypes. Clinical studies by Lee *et al.*⁴⁹ confirm that monotherapy with PD-1/PD-L1 inhibitors produces favorable treatment responses in specific subtypes. Specifically, Kaposi sarcoma exhibited an ORR of 66.7%, followed by ASPS (50%), angiosarcoma (33.3%), myxofibrosarcoma (28.6%), and UPS (27.8%). However, the overall ORR remains relatively low, at approximately 16.7% in advanced sarcoma patients, with notably low ORRs in osteosarcoma, SS, and liposarcoma, as shown in Table 1.^{34,49,50} In osteosarcoma treatment, PD-1/PD-L1 inhibitors showed promising therapeutic potential when used in combination with other agents.^{130,131} However, clinical response to monotherapy remains limited, likely due to the heterogeneous and immunosuppressive nature of the sarcoma microenvironment.^{25,132}

Immunotherapy responses in bone and soft-tissue sarcomas exhibit significant histological subtype differences. Existing evidence indicates that subtypes such as ASPS and UPS demonstrate relatively favorable responses to ICIs. This variability may correlate with differences in TMB and immune microenvironment characteristics across subtypes. ASPS and UPS exhibit greater responsiveness to ICIs, potentially attributable to their unique TME composition. This includes richer infiltration of CD8⁺ T cells, M1 macrophages, and CD20⁺ B cells, creating an immunologically “hot” phenotype that favors ICI-mediated antitumor activation.¹³³

Neoantigen burden alone does not appear to fully explain immunotherapy responsiveness across sarcoma subtypes. UPS often exhibits low TMB, yet specific molecular alterations (e.g., high-copy number variations) may enhance neoantigen presentation or immune surveillance. Despite low TMB per se, these alterations may still contribute to responses to ICIs.¹³⁴ ASPS may compensate for a relatively low neoantigen load by generating a more antigenic microenvironment through biological features such as Xp11.2/TFE3 translocations.¹³⁵

Regarding immune exclusion mechanisms, ASPS and UPS exhibit fewer immune-evasion features, such as lower PD-L1 expression levels and reduced immune regulatory imbalances. Notably, ASPS also demonstrates particular sensitivity to immunotherapy due to its unique angiogenic characteristics and high lymphocytic infiltration.^{21,136} In contrast, other subtypes may enhance exclusion by increasing inhibitory molecules like vascular endothelial growth factor A or downregulating soluble receptors, thereby limiting ICI efficacy (Table 1).²³

In osteosarcoma, PD-1/PD-L1 expression patterns correlate with treatment response, although reliable predictive biomarkers remain unestablished.^{130,131} An immunological analysis across multiple sarcoma subtypes revealed significant heterogeneity in biomarker expression between subtypes, with no single biomarker universally predictive of immunotherapy response identified to date.¹³⁷ This histology-specific variability underscores the critical need for personalized immunotherapy strategies in sarcoma.^{138,139}

4.2. Innovative breakthroughs in adoptive T-cell therapy

Chimeric antigen receptor T-cell therapy, as a groundbreaking immunotherapy strategy, has demonstrated remarkable efficacy in treating hematologic malignancies.^{140,141} However, in solid tumors such as bone and soft-tissue sarcomas, CAR-T therapy still faces numerous technical challenges, including limitations due

to low tumor antigen specificity, limited T-cell persistence, and complex TME.^{142,143} Preclinical studies in osteosarcoma indicate that CAR-T cells targeting the B7-H3 antigen can significantly enhance tumor homing capacity through expression of corresponding chemokine receptors.¹⁴⁴ In SS and rhabdomyosarcoma, CAR-T cells targeting the GD2 antigen (iCasp9.2A.GD2.CAR-CD28.4-1BBζ) have demonstrated preclinical therapeutic potential.¹⁴⁵ Current technological advances primarily focus on optimizing co-stimulatory domains (e.g., CD28, 4-1BB), introducing safety switch systems (e.g., iCasp9), and co-expressing chemokine receptors.^{142,145}

As one of the earliest developed autologous T-cell therapies, lifileucel received accelerated approval from the United States Food and Drug Administration in February 2024 for treating advanced melanoma, marking the first regulatory approval of a TIL product.¹⁴⁶ TIL therapy has also demonstrated promising clinical potential in solid tumors such as cervical cancer.^{147,148} In bone and soft-tissue sarcomas, TIL therapy utilizes populations of naive T cells isolated and expanded from tumor tissue, enabling recognition of multiple tumor antigens.^{149,150} Clinical studies indicate that TIL therapy not only directly kills tumor cells but also modulates the TME to exert therapeutic effects.¹⁵¹ However, its application in sarcomas is constrained by challenges, including limited availability of tumor tissue, the lengthy *in vitro* expansion cycle, and the immunosuppressive microenvironment.^{148,149} Current research focuses on optimizing TIL culture systems, combining with ICIs, and developing novel TIL selection methods.^{147,151}

TCR-T therapy offers advantages over CAR-T by recognizing intracellular antigens, providing novel therapeutic approaches for sarcoma treatment.^{141,152} TCR-T therapy targets sarcoma-associated antigens and neoantigens by isolating tumor-specific T cell clones or designing high-affinity T-cell receptors (TCRs).^{153,154} In solid tumors, TCR-T therapy has demonstrated complementary efficacy alongside TIL and CAR-T therapies.^{152,155} Current technical challenges include limited target antigen selection, risks of TCR cross-reactivity, and complex manufacturing processes.^{153,156} Recent translational research focuses on antigen-independent TCR screening technologies, multi-target TCR-T design, and optimizing T cell subset composition.^{153,154} In pediatric sarcomas such as osteosarcoma, combination strategies integrating TCR-T therapy with CAR-T therapy are under investigation.^{157,158}

4.3. Exploration of combined treatment strategies

The exploration of combined treatment strategies in bone and soft-tissue sarcomas often draws upon principles

and early clinical evidence established in more common solid tumors, such as non-small cell lung cancer and hepatocellular carcinoma. While these insights provide valuable rationales for testing similar combinations in sarcomas, it is critical to acknowledge that the distinct immunobiological features of sarcomas may lead to divergent responses.

The following sections discuss promising combined treatment strategies while highlighting the need for sarcoma-specific validation. Preclinical studies in various solid tumors indicate that radiotherapy enhances tumor immunogenicity by inducing immunogenic cell death, releasing tumor-associated antigens (TAAs), and damage-associated molecular patterns.¹⁵⁹ Multiple clinical studies in cancers such as non-small cell lung cancer demonstrate that patients receiving radiotherapy within 3 months before immunotherapy exhibit significantly prolonged PFS (median PFS = 10.0 months).¹⁶⁰ Although this supports the biological rationale, its direct applicability to sarcomas requires confirmation in dedicated trials. The combination of stereotactic body radiotherapy with ICIs has garnered particular attention, as this pairing enhances both local and systemic antitumor immune responses.¹⁶¹ However, inconsistent clinical outcomes suggest the need for further optimization of radiotherapy dose, fractionation schemes, and timing relative to immunotherapy.^{162,163}

Combination strategies of targeted therapy and immunotherapy offer novel treatment options for patients with bone and soft-tissue sarcomas. Clinical evidence indicates significant differences in response characteristics across treatment regimens: some patients respond poorly to chemotherapy and targeted therapy but respond favorably to immunotherapy.¹⁶⁴ Notably, in the adjuvant setting for melanoma, combining targeted therapy with immunotherapy may reduce pathological complete response rates, suggesting the need for careful evaluation of the long-term benefits of this combination.¹⁶⁵ At present, explored combination regimens include the pairing of anti-angiogenic targeted agents with ICIs, as well as the synergistic use of targeted drugs targeting specific signaling pathways alongside immunotherapy.^{166,167} However, targeted therapies may alter the TME and influence immunotherapy efficacy, necessitating further research to elucidate their mechanisms of interaction.¹⁶⁸

Multimodal combination therapy represents the latest advancement in immunotherapy for bone and soft-tissue sarcomas. Preclinical studies indicate that peroxisome proliferator-activated receptor α agonists exert dual effects in modulating the TME, potentially enhancing the efficacy of targeted therapy and radiotherapy; however,

their interactions with immunotherapy require further investigation.¹⁵⁸ At present, explored triple-combination regimens include the integration of stereotactic body radiotherapy, immunotherapy, and targeted therapy, with early α -fetoprotein changes potentially serving as a prognostic indicator for this treatment approach.¹⁶⁶ In addition, a triple-targeted combination of image-guided radiotherapy, targeted α therapy, and antibody-targeted interleukin-2 immunocytokine therapy has demonstrated potential advantages.¹⁶⁹ Optimizing these multimodal treatment regimens requires consideration of treatment sequencing, dose intensity, and personalized biomarker-guided strategies.^{144,170}

4.4. Progress in the development of therapeutic vaccines

4.4.1. Personalized design strategies for neoantigen vaccines

The development of therapeutic vaccines for sarcomas is still in its nascent stages. Consequently, current strategies and preclinical models are frequently extrapolated from advances in other malignancies where vaccine platforms have shown greater maturity, such as melanoma and pancreatic cancer. At present, two main forms of vaccines are being studied: dendritic cell vaccines pulsed with TAAs, including proteins, peptides, or tumor lysates, and protein or peptide adjuvant vaccines. These different immune mechanisms may yield distinct therapeutic effects, particularly in highly heterogeneous bone and soft-tissue sarcomas.^{138,171} Development of mRNA tumor vaccines for soft-tissue sarcomas has begun to explore potential tumor antigens and to stratify patients through immune subtype analysis, providing a basis for personalized treatment.¹⁷²

4.4.2. Cross-subtype application of TAA vaccines

Cancer vaccines composed of TAAs and adjuvants suppress tumor growth by inducing the proliferation of TAA-specific cytotoxic T lymphocytes. However, the therapeutic efficacy of such vaccines is highly dependent on the characteristics of the TME.¹⁷³ In sarcomas, the cross-subtype application of TAA vaccines faces significant challenges, primarily due to the pronounced heterogeneity of the sarcoma stromal microenvironment. Previous studies have explored mucin 1 glycopeptides as TAAs, combined with α -galactosyl ceramide adjuvants and gold nanoparticle carriers in vaccine designs, demonstrating tumor growth inhibition in animal models.¹⁷⁴ In addition, tumor-associated carbohydrate antigen vaccines, which encapsulate the TLR-9 agonist CpG oligodeoxynucleotide adjuvants in Tn antigen-modified liposomes, demonstrate strong binding affinity to anti-Tn-specific antibodies.¹⁴⁰

4.4.3. Immunostimulatory efficacy of vaccine-adjuvant combinations

Adjuvants play a key role in regulating and enhancing antigen-induced immune responses. In sarcoma vaccine development, *Brucella* luminescent synthase, a decameric protein with delivery and adjuvant properties, has been explored as an antigen delivery system.¹⁷⁵ Studies have shown that constructing vaccines by co-presenting α -galactosyl ceramide adjuvants with antigens on gold nanoparticles significantly enhances antitumor efficacy.¹⁷⁴ In addition, TLR4 ligands have demonstrated great potential as adjuvants for dendritic cell vaccines.¹⁷⁶ A novel three-in-one protein-conjugated vaccine strategy covalently linking a small-molecule TLR7 agonist adjuvant with the mucin 1 TAA offers a new approach to overcoming immune tolerance.¹⁷⁷ The combination of adenovirus-encoded adjuvant with adenovirus-encoded antigen vaccines has also been shown to enhance immune responses to tumor antigens.¹⁷⁸

5. Challenges and future directions

5.1. Current challenges

5.1.1. Suppressive tumor immune microenvironment and low immunogenicity in bone and soft-tissue sarcomas

The immunosuppressive TME of bone and soft-tissue sarcomas is a key factor limiting the efficacy of immunotherapy. The TME is rich in pro-tumor cells, such as myeloid-derived suppressor cells, and immunosuppressive mediators, which hinder the immune system's ability to effectively recognize and eliminate tumor cells.¹⁷ Such microenvironments significantly reduce treatment response rates, as exemplified by the low immunogenicity of the TME in osteosarcoma, which leads to poor efficacy of ICIs.¹⁷⁹ In soft-tissue sarcomas, the heterogeneity of the immune microenvironment also restricts immunotherapy efficacy to specific subtypes, such as non-adipocytic soft-tissue sarcomas.¹⁸⁰

Compounding the effects of the suppressive TME, bone and soft-tissue tumors frequently exhibit low immunogenicity and heterogeneous antigen expression. Tumor antigens are often inadequately expressed or lack sufficient specificity, thereby failing to elicit a robust antitumor immune response. Although certain TAAs—including cancer/testis antigens (CTAs) such as MAGE-A4, PRAME, and MAGE-A1—are highly expressed in subtypes such as UPS and osteosarcoma, making them potential targets, inter-subtype variability in their expression levels limits the broad applicability of immunotherapy.^{22,181} Insufficient antigen specificity also

leads to poor persistence and limited efficacy of targeted therapies such as CAR-T cell therapy.¹⁴²

5.1.2. Therapeutic resistance and low response rates

Sarcoma immunotherapy exhibits significant therapeutic resistance, with low response rates and short PFS in patients with metastatic or recurrent osteosarcoma.¹⁷⁹ The suboptimal efficacy of ICIs (e.g., PD-1/PD-L1 blockers) is associated with complex resistance mechanisms, including heterogeneous activation of the PD-1/PD-L1 signaling pathway and immune escape mechanisms.¹⁸² Although multi-kinase inhibitors (e.g., regorafenib) have demonstrated clinical benefits in non-adipocytic soft-tissue sarcomas and osteosarcomas, overall response rates remain inconsistent, and recurrence rates are high.¹⁸³

5.1.3. Disease heterogeneity and subtype-specific limitations

The immunobiological characteristics of sarcoma subtypes (e.g., osteosarcoma, SS, and UPS) vary substantially, leading to heterogeneous treatment responses. ICIs are effective for soft-tissue sarcoma subtypes with high PD-L1 expression, but demonstrate poor overall efficacy in osteosarcoma.^{90,179,184} High-risk clinical features, such as lung metastasis, further reduce treatment feasibility.¹⁸⁵

5.1.4. Challenges in clinical translation

Current immunotherapy strategies remain largely at the preclinical or early clinical trial stage, with a lack of large-scale, randomized clinical validation. CAR-T cell therapy and tumor vaccines show promise in osteosarcoma models but continue to face limitations, including limited *in vivo* persistence and treatment-related toxicities.¹⁴² Immunotherapy for soft-tissue sarcomas requires optimization of patient selection criteria to improve response rates.¹⁸⁰

5.2. Future research directions

5.2.1. Histotype-specific precision trial design

The significant disease heterogeneity of bone and soft-tissue sarcomas represents a core challenge in therapeutic development. Traditional “pan-sarcoma” clinical trial designs often obscure the substantial differences in treatment response across distinct histological subtypes, leading to potentially effective therapies being deemed ineffective in the overall population. Future drug development should focus on histotype-specific approaches, as exemplified by the successful application of regorafenib in non-adipocytic soft-tissue sarcoma, and move away from pan-sarcoma trial designs.¹⁸⁶ Molecular characteristics such as TLS density and specific gene fusions (e.g., *SS18-SSX*) can be used as stratification factors to improve trial population homogeneity.

5.2.2. Novel targets and TME reprogramming

The highly immunosuppressive TME in bone and soft-tissue sarcomas represents a major bottleneck that limits the efficacy of immunotherapy. To reverse this suppressive state, future research should focus on two parallel strategies: (i) identifying novel therapeutic targets using high-throughput technologies to enable precision intervention and (ii) developing synergistic therapies that directly reprogram the TME.

Bioinformatics analysis based on tumor genomics and the TME can identify novel immune targets (such as CTAs like MAGE-A4 and PRAME) and cell surface antigens, thereby guiding personalized immunotherapy strategies.^{181,187} Given subtype-specific differences in CTA expression profiles, the development of multi-antigen-targeted vaccines (e.g., MAGE-A4+PRAME) or bispecific antibodies holds promise. Combining patient-specific TME characteristics (e.g., PD-1/PD-L1 expression-based stratification) with customized treatment plans represents a core strategy for overcoming tumor heterogeneity.²²

Concurrently, research should focus on targeting inhibitory factors within the TME (e.g., transforming growth factor β) or combining TME modulators (e.g., cytokine-based therapies) to enhance immune cell infiltration and function. In osteosarcoma, there is an urgent need to develop strategies that regulate TAMs or restore T-cell function to reverse immunosuppression.¹⁷ In soft-tissue sarcomas, targeting abnormal interactions between tumor cells and stromal cells is essential to optimize therapeutic responses.¹⁷⁹ Collectively, these reprogramming strategies aim to transform “cold” tumors into “hot” tumors that are more responsive to immunotherapy, thereby unlocking the immune system’s full anticancer potential.

5.2.3. Optimization of combination therapies

Monotherapy with immunotherapy often demonstrates limited efficacy in bone and soft-tissue sarcomas due to primary or acquired resistance. The mechanisms underlying this resistance involve multiple factors, including heterogeneous expression of immune checkpoint molecules, infiltration of immunosuppressive cells, and defects in antigen presentation. To overcome these limitations, combination therapy strategies based on synergistic mechanisms have emerged as a central approach. In osteosarcoma, given its highly immunosuppressive microenvironment, a recommended strategy involves combining CAR-T cell therapy with immune checkpoint blockade to overcome resistance.¹⁶² This approach aims to alleviate T-cell suppression through ICIs, thereby enhancing the *in vivo* persistence and cytotoxic activity of CAR-T cells. In soft-tissue sarcomas,

targeting specific resistance mechanisms, such as activated signaling pathways or epigenetic modifications, with corresponding targeted agents has been demonstrated to significantly improve treatment response rates.¹⁸⁸

5.2.4. Biomarker development and predictive modeling

The successful translation of effective immunotherapy strategies into clinical practice hinges on the ability to accurately identify patients’ special antigens or biomarkers. Therefore, establishing a biomarker system based on multidimensional genomic and TME features is essential for achieving precise prediction of immunotherapy response. For instance, large-scale databases such as The Cancer Genome Atlas can be leveraged to identify potential therapeutic targets or prognostic markers (e.g., specific gene expression profiles) in soft-tissue sarcomas.^{22,189} In parallel, in osteosarcoma, TME-related markers—such as the infiltration of specific immune cell lineages—have been developed for patient stratification and treatment response monitoring.¹⁷

To achieve in-depth analysis of massive multidimensional datasets, artificial intelligence (AI) and machine learning technologies are playing an increasingly vital role. AI-driven stratification strategies integrate genomics, transcriptomics, pathological imaging (radiomics), and clinical information to construct highly accurate predictive models. This integrated analysis helps uncover novel therapeutic targets and enables early prediction of long-term efficacy through dynamic biomarkers (e.g., circulating tumor DNA clearance rate), thereby providing a basis for timely treatment adjustment. Ultimately, this advances immunotherapy for bone and soft-tissue sarcomas toward a truly personalized era.

6. Discussion

This review highlights the marked histological subtype-specific efficacy of immunotherapy in bone and soft-tissue sarcomas. As presented in Table 1, ICIs have achieved breakthrough efficacy in subtypes such as ASPS and UPS, with ORRs reaching approximately 40%, yet demonstrate minimal efficacy in osteosarcoma, SS, and liposarcoma.^{90,137} This dichotomy stems from fundamental differences in TMB, antigen presentation machinery, and immune cell infiltration patterns across subtypes.^{138,190} Emerging evidence from sarcoma clinical trials suggests the potential of combination therapies to significantly enhance efficacy. For instance, a phase II study in soft-tissue sarcoma by Liu *et al.*⁸⁴ reported that the combination of the PD-L1 inhibitor TQB2450 with the anti-angiogenic agent anlotinib yielded promising activity, with clinical benefit that compared favorably with historical outcomes reported in prior checkpoint inhibitor trials.¹³⁷ This underscores

the potential of such strategies while illustrating the need for histotype-specific validation, as responses can vary significantly.¹⁹¹

The primary impediments to broader success are deeply rooted in the TME. First, the dominance of myeloid-derived suppressor cells and M2-polarized TAMs establishes a powerfully immunosuppressive milieu, secreting factors like transforming growth factor β and interleukin-10 that impair cytotoxic T-cell function.^{17,48} Second, a critical lack of effective antigen targets plagues these malignancies. Sarcomas generally possess a low TMB, limiting neoantigen generation, while the expression of CTAs like MAGE-A4 and PRAME is heterogeneous and not ubiquitous.^{181,189} This antigenic paucity undermines strategies dependent on T-cell recognition, including CAR-T therapy and cancer vaccines.¹⁴² Third, extensive stromal fibrosis and a dense extracellular matrix create a physical barrier that excludes immune cells from the tumor core, while also contributing to drug resistance.¹⁹ These barriers are not independent; they form a synergistic alliance that promotes immune evasion and limits drug penetration.

To address these limitations, future research must pivot toward innovative combination strategies and cutting-edge technologies. The limited efficacy of ICI monotherapy, as depicted in [Figure 5](#), necessitates rational combinations that simultaneously target multiple resistance pathways. Notably, the combination of ICIs with anti-angiogenic agents like anlotinib has demonstrated synergistic effects, potentially by normalizing dysfunctional tumor vasculature and enhancing T-cell infiltration.¹³⁷

Beyond pharmacologic combinations, emerging technological frontiers offer transformative potential. Nanotechnology provides a versatile platform for TME reprogramming; for instance, nano-delivery systems carrying Mg^{2+} and anti-PD-L1 antibodies have shown promise in osteosarcoma models by simultaneously inducing immunogenic cell death and promoting bone regeneration.⁶¹ The application of AI and machine learning is increasingly demonstrating utility in deciphering sarcoma heterogeneity. For example, a recent bioinformatics study leveraging The Cancer Genome Atlas sarcoma data employed machine learning to construct an m6A-related metabolic classification system with distinct prognostic value.¹⁴ Similarly, radiomics analyses of sarcomas are exploring AI-based models to predict treatment response and patient outcomes.¹⁸⁹ These early applications highlight the potential of AI to move beyond single biomarkers and integrate multi-omics data for improved patient stratification in future sarcoma trials. By integrating multi-omics data (e.g., genomics, transcriptomics) with radiomics and clinical outcomes, AI can identify predictive

biomarkers, define novel immune subtypes, and guide personalized treatment selection, moving beyond the inadequacy of single biomarkers like PD-L1.^{22,189}

Furthermore, spatial transcriptomics can map the precise topological relationships between immune cells and tumor cells within the TME, revealing spatial patterns of immune exclusion and identifying new stromal targets.²⁴ These technologies will be instrumental in developing the next generation of biomarker-driven, histotype-tailored clinical trials, which are essential for avoiding the failures of past “pan-sarcoma” study designs.¹⁸⁶ In the realm of cell therapy, overcoming the suppressive TME is paramount. Strategies such as engineering CAR-T cells to express chemokine receptors matching the tumor’s chemokine profile (e.g., B7-H3-targeted CAR-T cells) can improve homing to immunosuppressive sites.^{144,157} Similarly, combining CAR-T or TCR-T therapy with ICI blockade may be necessary to reverse T-cell exhaustion and enhance persistence within the sarcoma TME.¹⁶²

7. Conclusion: Summary and future perspectives

Immunotherapy has introduced a paradigm shift in the management of bone and soft-tissue sarcomas, yet its promising potential remains constrained by significant histotype-specific limitations. The path forward hinges on a concerted, multidisciplinary effort to address the core biological barriers, including myeloid cell-dominated immunosuppression, antigen scarcity, and stromal fibrosis, that characterize the “cold” sarcoma TME. The future of sarcoma treatment lies not in seeking a universal magic bullet, but in leveraging advanced technologies like nanotechnology for targeted drug delivery and immune modulation, AI for data-driven patient stratification, and spatial biology for deep TME profiling. By prioritizing histology-driven clinical trials and fostering collaboration across oncology, immunology, bioengineering, and computational biology, the field can move toward the ultimate goal of converting immunologically inert sarcomas into therapy-responsive malignancies, thereby delivering durable and transformative outcomes for patients.

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Conflict of interest

The authors declare that they have no competing interests.

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References

- Wang G, Li J, Bojmar L, *et al.* Tumour extracellular vesicles and particles induce liver metabolic dysfunction. *Nature*. 2023;618(7964):374–382.
doi: 10.1038/s41586-023-06114-4
- Liu Z, Yang Y, Fang H, *et al.* Single-cell and spatial analyses reveal the effect of VSIG₄*S100A10* TAMs on the immunosuppression of glioblastoma and anti-PD-1 immunotherapy. *Int J Biol Macromol*. 2025;308(Pt 3):142415.
doi: 10.1016/j.ijbiomac.2025.142415
- Xie C, Wu J, Yang H, *et al.* GSCs differentiation model-informed nanotherapy: Dual-functional brain-targeting liposomes with iRGD modification for co-delivery of osimertinib and bortezomib to combat radioresistant glioblastoma. *Cell Death Dis*. 2025;16(1):738.
doi: 10.1038/s41419-025-08083-0
- Liu Z, Weitao Y, Cui K, *et al.* The outcomes and treatment strategies in metastatic soft tissue sarcoma treated with immunotherapy-based therapy: A three-center study. *Front Immunol*. 2025;16:1504117.
doi: 10.3389/fimmu.2025.1504117
- Spalato-Ceruso M, Ghazzi NE, Italiano A. New strategies in soft tissue sarcoma treatment. *J Hematol Oncol*. 2024;17(1):76.
doi: 10.1186/s13045-024-01580-3
- Mavroeidis L, Napolitano A, Huang P, Jones RL. Novel therapeutics in soft tissue sarcoma. *Cancers (Basel)*. 2024;17(1):10.
doi: 10.3390/cancers17010010
- Yang J, Lu X, Cai Q, *et al.* Loss of TACC2 impairs chemokine CCL3 and CCL4 expression and reduces response to anti-PD-1 therapy in soft tissue sarcoma. *Mol Cancer*. 2025;24(1):158.
doi: 10.1186/s12943-025-02354-2
- Kret ZS, Sweder RJ, Pollock R, Tinoco G. Potential mechanisms for immunotherapy resistance in adult soft-tissue sarcoma. *Target Oncol*. 2025;20(3):485–502.
doi: 10.1007/s11523-025-01145-5
- Cao Y, Wang W, Xu H, *et al.* Efficacy of immune checkpoint inhibitors in the treatment of soft tissue sarcoma: A systematic review and meta-analysis of clinical trials. *Int Immunopharmacol*. 2025;148:114070.
doi: 10.1016/j.intimp.2025.114070
- Saerens M, Brusselaers N, Rottey S, Decruyenaere A, Creytens D, Lapeire L. Immune checkpoint inhibitors in treatment of soft-tissue sarcoma: A systematic review and meta-analysis. *Eur J Cancer*. 2021;152:165–182.
doi: 10.1016/j.ejca.2021.04.034
- Liu Z, Xu J, Liu M, Hu W, Xu N, Zhu D. Efficacy and safety of angiogenesis inhibitors plus immune checkpoint inhibitors in advanced soft tissue sarcoma: A real-world, single-center study. *Sci Rep*. 2023;13(1):3385.
doi: 10.1038/s41598-023-30412-6
- Yu S, Yao X. Advances on immunotherapy for osteosarcoma. *Mol Cancer*. 2024;23(1):192.
doi: 10.1186/s12943-024-02105-9
- Thanindratarn P, Dean DC, Nelson SD, Hornicek FJ, Duan Z. Advances in immune checkpoint inhibitors for bone sarcoma therapy. *J Bone Oncol*. 2019;15:100221.
doi: 10.1016/j.jbo.2019.100221
- Huang ZD, Fu YC, Liu SY, *et al.* m6A-related metabolism molecular classification with distinct prognosis and immunotherapy response in soft tissue sarcoma. *Front Immunol*. 2022;13:895465.
doi: 10.3389/fimmu.2022.895465
- Luo M, Hong H, Yang Y, *et al.* The role of melanoma-derived exosomes in metastasis: Challenges and opportunities. *Tumor Discov*. 2025;4(2):4–19.
doi: 10.36922/td.7108
- Siddiqui BA, Chapin BF, Jindal S, *et al.* Immune and pathologic responses in patients with localized prostate cancer who received daratumumab (anti-CD38) or edicotinib (CSF-1R inhibitor). *J Immunother Cancer*. 2023;11(3):e006262.
doi: 10.1136/jitc-2022-006262
- Lian H, Zhang J, Hou S, *et al.* Immunotherapy of

- osteosarcoma based on immune microenvironment modulation. *Front Immunol.* 2024;15:1498060.
doi: 10.3389/fimmu.2024.1498060
18. Liu S, Gao W, Ning Y, *et al.* Cardiovascular toxicity with PD-1/PD-L1 inhibitors in cancer patients: A systematic review and meta-analysis. *Front Immunol.* 2022;13:908173.
doi: 10.3389/fimmu.2022.908173
19. Song D, Hou S, Ma N, Yan B, Gao J. Efficacy and safety of PD-1/PD-L1 and CTLA-4 immune checkpoint inhibitors in the treatment of advanced colorectal cancer: A systematic review and meta-analysis. *Front Immunol.* 2024;15:1485303.
doi: 10.3389/fimmu.2024.1485303
20. Liu K, Zan P, Li Z, *et al.* Engineering bimetallic polyphenol for mild photothermal osteosarcoma therapy and immune microenvironment remodeling by activating pyroptosis and cGAS-STING pathway. *Adv Healthc Mater.* 2024;13(22):e2400623.
doi: 10.1002/adhm.202400623
21. Li Y, Liu Y, Qu Y, *et al.* Case report: Two cases of soft-tissue sarcomas: High TMB as a potential predictive biomarker for anlotinib combined with toripalimab therapy. *Front Immunol.* 2022;13:832593.
doi: 10.3389/fimmu.2022.832593
22. Wang XX, Liu YP, Lu Y, *et al.* Identifying specific TLS-associated genes as potential biomarkers for predicting prognosis and evaluating the efficacy of immunotherapy in soft tissue sarcoma. *Front Immunol.* 2024;15:1372692.
doi: 10.3389/fimmu.2024.1372692
23. Tang S, Wang Y, Luo R, *et al.* Proteomic characterization identifies clinically relevant subgroups of soft tissue sarcoma. *Nat Commun.* 2024;15(1):1381.
doi: 10.1038/s41467-024-45306-y
24. Chen J, Cui N, He SH, Xia CY, Li WQ. Single-cell transcriptomics reveals metabolic remodeling and functional specialization in the immune microenvironment of bone tumors. *J Transl Med.* 2025;23(1):554.
doi: 10.1186/s12967-025-06346-0
25. Yiong CS, Lin TP, Lim VY, Toh TB, Yang VS. Biomarkers for immune checkpoint inhibition in sarcomas - are we close to clinical implementation? *Biomark Res.* 2023;11(1):75.
doi: 10.1186/s40364-023-00513-5
26. Recine F, Vanni S, Bongiovanni A, *et al.* Clinical and translational implications of immunotherapy in sarcomas. *Front Immunol.* 2024;15:1378398.
doi: 10.3389/fimmu.2024.1378398
27. Wu A, Yang ZK, Kong P, *et al.* Exploring osteosarcoma based on the tumor microenvironment. *Front Immunol.* 2024;15:1423194.
doi: 10.3389/fimmu.2024.1423194
28. Fjæstad KY, Rømer AMA, Goitea V, *et al.* Blockade of beta-adrenergic receptors reduces cancer growth and enhances the response to anti-CTLA4 therapy by modulating the tumor microenvironment. *Oncogene.* 2022;41(9):1364-1375.
doi: 10.1038/s41388-021-02170-0
29. Beird HC, Bielack SS, Flanagan AM, *et al.* Osteosarcoma. *Nat Rev Dis Primers.* 2022;8(1):77.
doi: 10.1038/s41572-022-00409-y
30. Cole S, Gianferante DM, Zhu B, Mirabello L. Osteosarcoma: A surveillance, epidemiology, and end results program-based analysis from 1975 to 2017. *Cancer.* 2022;128(11):2107-2118.
doi: 10.1002/cncr.34163
31. Tempelaere C, Biau D, Babinet A, Anract P. Osteosarcoma after the age of fifty: A clinicopathological study. *Eur J Surg Oncol.* 2019;45(7):1288-1292.
doi: 10.1016/j.ejso.2019.04.010
32. Savage SA, Mirabello L. Using epidemiology and genomics to understand osteosarcoma etiology. *Sarcoma.* 2011;2011:548151.
doi: 10.1155/2011/548151
33. Heymann MF, Lézot F, Heymann D. The contribution of immune infiltrates and the local microenvironment in the pathogenesis of osteosarcoma. *Cell Immunol.* 2019;343:103711.
doi: 10.1016/j.cellimm.2017.10.011
34. Tawbi HA, Burgess M, Bolejack V, *et al.* Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): A multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol.* 2017;18(11):1493-1501.
doi: 10.1016/s1470-2045(17)30624-1
35. Wu R, Horimoto Y, Oshi M, *et al.* Emerging measurements for tumor-infiltrating lymphocytes in breast cancer. *Jpn J Clin Oncol.* 2024;54(6):620-629.
doi: 10.1093/jjco/hyae033
36. Miller CW, Aslo A, Won A, Tan M, Lampkin B, Koeffler HP. Alterations of the p53, Rb and MDM2 genes in osteosarcoma. *J Cancer Res Clin Oncol.* 1996;122(9):559-565.
doi: 10.1007/bf01213553
37. Arellano DL, Juárez P, Verdugo-Meza A, *et al.* Bone microenvironment-suppressed T cells increase osteoclast formation and osteolytic bone metastases in mice. *J Bone Miner Res.* 2022;37(8):1446-1463.
doi: 10.1002/jbmr.4615
38. Liu W, Cheng H, Huang Z, *et al.* The correlation between clinical outcomes and genomic analysis with high risk factors for the progression of osteosarcoma. *Mol Oncol.* 2024;18(4):939-955.

- doi: 10.1002/1878-0261.13526
39. Liu G, Fang Y, Li J, Chen Z. Anoikis-related PLCB4 is linked to immunotherapy response in osteosarcoma. *Discov Oncol*. 2025;16(1):226.
doi: 10.1007/s12672-025-01970-0
40. Zhang Z, Liu C, Liang T, *et al*. Establishment of immune prognostic signature and analysis of prospective molecular mechanisms in childhood osteosarcoma patients. *Medicine (Baltimore)*. 2020;99(46):e23251.
doi: 10.1097/md.00000000000023251
41. Kushlinskii NE, Fridman MV, Braga EA. Molecular mechanisms and microRNAs in osteosarcoma pathogenesis. *Biochemistry (Mosc)*. 2016;81(4):315-328.
doi: 10.1134/s0006297916040027
42. Dana PM, Sadoughi F, Asemi Z, Yousefi B. Molecular signaling pathways as potential therapeutic targets in osteosarcoma. *Curr Med Chem*. 2022;29(25):4436-4444.
doi: 10.2174/0929867329666220209110009
43. Ji Z, Shen J, Lan Y, Yi Q, Liu H. Targeting signaling pathways in osteosarcoma: Mechanisms and clinical studies. *MedComm (2020)*. 2023;4(4):e308.
doi: 10.1002/mco2.308
44. Kovar H, Bierbaumer L, Radic-Sarikas B. The YAP/TAZ pathway in osteogenesis and bone sarcoma pathogenesis. *Cells*. 2020;9(4):972.
doi: 10.3390/cells9040972
45. Han J, Shen X. Long noncoding RNAs in osteosarcoma via various signaling pathways. *J Clin Lab Anal*. 2020;34(6):e23317.
doi: 10.1002/jcla.23317
46. Farzaneh M, Najafi S, Anbiyae O, Azizidoost S, Khoshnam SE. LncRNA MALAT1-related signaling pathways in osteosarcoma. *Clin Transl Oncol*. 2023;25(1):21-32.
doi: 10.1007/s12094-022-02876-x
47. Doghish AS, Hegazy M, Ismail A, *et al*. A spotlight on the interplay of signaling pathways and the role of miRNAs in osteosarcoma pathogenesis and therapeutic resistance. *Pathol Res Pract*. 2023;245:154442.
doi: 10.1016/j.prp.2023.154442
48. Sholevar CJ, Liu NM, Mukarrama T, Kim J, Lawrence J, Canter RJ. Myeloid cells in the immunosuppressive microenvironment as immunotargets in osteosarcoma. *Immunotargets Ther*. 2025;14:247-258.
doi: 10.2147/itt.s485672
49. Lee AQ, Hao C, Pan M, Ganjoo KN, Bui NQ. Histologic and immunologic factors associated with response to immune checkpoint inhibitors in advanced sarcoma. *Clin Cancer Res*. 2025;31(4):678-684.
doi: 10.1158/1078-0432.ccr-24-3485
50. Boye K, Longhi A, Guren T, *et al*. Pembrolizumab in advanced osteosarcoma: Results of a single-arm, open-label, phase 2 trial. *Cancer Immunol Immunother*. 2021;70(9):2617-2624.
doi: 10.1007/s00262-021-02876-w
51. Zhang Z, Tan X, Jiang Z, Wang H, Yuan H. Immune checkpoint inhibitors in osteosarcoma: A hopeful and challenging future. *Front Pharmacol*. 2022;13:1031527.
doi: 10.3389/fphar.2022.1031527
52. Wilky BA, Trucco MM, Subhawong TK, *et al*. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: A single-centre, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20(6):837-848.
doi: 10.1016/s1470-2045(19)30153-6
53. Wagner MJ, Othus M, Patel SP, *et al*. Multicenter phase II trial (SWOG S1609, cohort 51) of ipilimumab and nivolumab in metastatic or unresectable angiosarcoma: A substudy of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART). *J Immunother Cancer*. 2021;9(8):e002990.
doi: 10.1136/jitc-2021-002990
54. Palmerini E, Lopez Pousa A, Grignani G, *et al*. Nivolumab and sunitinib in patients with advanced bone sarcomas: A multicenter, single-arm, phase 2 trial. *Cancer*. 2025;131(1):e35628.
doi: 10.1002/cnrc.35628
55. Meyers PA, Schwartz CL, Krailo MD, *et al*. Osteosarcoma: The addition of muramyl tripeptide to chemotherapy improves overall survival--a report from the Children's Oncology Group. *J Clin Oncol*. 2008;26(4):633-638.
doi: 10.1200/jco.2008.14.0095
56. D'Angelo SP, Mahoney MR, Van Tine BA, *et al*. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): Two open-label, non-comparative, randomised, phase 2 trials. *Lancet Oncol*. 2018;19(3):416-426.
doi: 10.1016/s1470-2045(18)30006-8
57. Watanabe Y, Tsukahara T, Murata K, *et al*. Development of CAR-T cells specifically targeting cancer stem cell antigen DNAJB8 against solid tumours. *Br J Cancer*. 2023;128(5):886-895.
doi: 10.1038/s41416-022-02100-1
58. Park JA, Cheung NKV. Promise and challenges of T cell immunotherapy for osteosarcoma. *Int J Mol Sci*. 2023;24(15):12520.
doi: 10.3390/ijms241512520
59. Sun C, Li S, Ding J. Biomaterials-boosted immunotherapy for osteosarcoma. *Adv Healthc Mater*. 2024;13(23):e2400864.
doi: 10.1002/adhm.202400864
60. Gao Y, Wang Z, Jin X, *et al*. Enhanced osteosarcoma

- immunotherapy via CaCO_3 nanoparticles: Remodeling tumor acidic and immune microenvironment for photodynamic therapy. *Adv Healthc Mater.* 2024;13(23):e2400538.
doi: 10.1002/adhm.202400538
61. Chu X, Mi B, Xiong Y, *et al.* Bioactive nanocomposite hydrogel enhances postoperative immunotherapy and bone reconstruction for osteosarcoma treatment. *Biomaterials.* 2025;312:122714.
doi: 10.1016/j.biomaterials.2024.122714
62. Lu S, Yang Y, Song Z, *et al.* Dual functional nanoplateforms potentiate osteosarcoma immunotherapy via microenvironment modulation. *Natl Sci Rev.* 2025;12(3):nwaf002.
doi: 10.1093/nsr/nwaf002
63. Ratti C, Botti L, Cancila V, *et al.* Trabectedin overrides osteosarcoma differentiative block and reprograms the tumor immune environment enabling effective combination with immune checkpoint inhibitors. *Clin Cancer Res.* 2017;23(17):5149-5161.
doi: 10.1158/1078-0432.ccr-16-3186
64. Helm A, Tinganelli W, Simoniello P, *et al.* Reduction of lung metastases in a mouse osteosarcoma model treated with carbon ions and immune checkpoint inhibitors. *Int J Radiat Oncol Biol Phys.* 2021;109(2):594-602.
doi: 10.1016/j.ijrobp.2020.09.041
65. Anju MS, Chandramohan K, Bhargavan RV, Somanathan T, Subhadradevi L. An overview on liposarcoma subtypes: Genetic alterations and recent advances in therapeutic strategies. *J Mol Histol.* 2024;55(3):227-240.
doi: 10.1007/s10735-024-10195-4
66. Shi D, Jiang P. A different facet of p53 function: Regulation of immunity and inflammation during tumor development. *Front Cell Dev Biol.* 2021;9:762651.
doi: 10.3389/fcell.2021.762651
67. Cissé MY, Pyrdziak S, Firmin N, *et al.* Targeting MDM_2 -dependent serine metabolism as a therapeutic strategy for liposarcoma. *Sci Transl Med.* 2020;12(547):eaay2163.
doi: 10.1126/scitranslmed.aay2163
68. Yu H, Pei D, Chen L, Zhou X, Zhu H. Identification of key genes and molecular mechanisms associated with dedifferentiated liposarcoma based on bioinformatic methods. *Onco Targets Ther.* 2017;10:3017-27.
doi: 10.2147/ott.s132071
69. Horvai AE, DeVries S, Roy R, O'Donnell RJ, Waldman F. Similarity in genetic alterations between paired well-differentiated and dedifferentiated components of dedifferentiated liposarcoma. *Mod Pathol.* 2009;22(11):1477-1488.
doi: 10.1038/modpathol.2009.119
70. Baranov E, Black MA, Fletcher CDM, Charville GW, Hornick JL. Nuclear expression of DDIT₃ distinguishes high-grade myxoid liposarcoma from other round cell sarcomas. *Mod Pathol.* 2021;34(7):1367-1372.
doi: 10.1038/s41379-021-00782-1
71. Zhou MY, Bui NQ, Charville GW, Ganjoo KN, Pan M. Treatment of de-differentiated liposarcoma in the era of immunotherapy. *Int J Mol Sci.* 2023;24(11):9571.
doi: 10.3390/ijms24119571
72. Yang Y, Liu Z, Wei Y, *et al.* Single-cell multi-omics analysis reveals candidate therapeutic drugs and key transcription factor specifically for the mesenchymal subtype of glioblastoma. *Cell Biosci.* 2024;14(1):151.
doi: 10.1186/s13578-024-01332-3
73. D'Angelo SP, Druta M, Van Tine BA, *et al.* Letetresgene autoleucel in advanced/metastatic myxoid/round cell liposarcoma. *J Clin Oncol.* 2025;43(15):1777-1788.
doi: 10.1200/jco-24-01466
74. Nakamura H, Takada K, Emori M, Hayasaka N, Sugita S. Complete response to eribulin in a patient with unresectable liposarcoma: A case report and implications of new biomarkers. *Intern Med.* 2022;61(23):3617-3621.
doi: 10.2169/internalmedicine.9423-22
75. Ren T, Zhou Z, Hong H, *et al.* Synovial sarcoma extracellular vesicles induce fatty liver. *Biophys Rep.* 2025;11(3):209-216.
doi: 10.52601/bpr.2024.240041
76. Weber CM, Hafner A, Kirkland JG, *et al.* mSWI/SNF promotes Polycomb repression both directly and through genome-wide redistribution. *Nat Struct Mol Biol.* 2021;28(6):501-511.
doi: 10.1038/s41594-021-00604-7
77. Ren C, Liu J, Hornicek FJ, Yue B, Duan Z. Advances of SS18-SSX fusion gene in synovial sarcoma: Emerging novel functions and therapeutic potentials. *Biochim Biophys Acta Rev Cancer.* 2024;1879(6):189215.
doi: 10.1016/j.bbcan.2024.189215
78. Banito A, Li X, Laporte AN, *et al.* The SS18-SSX oncoprotein hijacks KDM2B-PRC1.1 to drive synovial sarcoma. *Cancer Cell.* 2018;33(3):527-541.e8.
doi: 10.1016/j.ccell.2018.01.018
79. Cloutier JM, Ingram DR, Wani K, Lazar AJ, Wang WL. Frequent TRPS1 expression in synovial sarcoma is associated with SS18-SSX fusion oncoprotein activity. *Hum Pathol.* 2022;130:88-94.
doi: 10.1016/j.humpath.2022.09.006
80. Lubieniecka JM, De Bruijn DRH, Su L, *et al.* Histone deacetylase inhibitors reverse SS18-SSX-mediated polycomb silencing of the tumor suppressor early growth response 1 in

- synovial sarcoma. *Cancer Res.* 2008;68(11):4303-4310.
doi: 10.1158/0008-5472.can-08-0092
81. Isfort I, Cyra M, Elges S, *et al.* SS18-SSX-dependent YAP/TAZ signaling in synovial sarcoma. *Clin Cancer Res.* 2019;25(12):3718-3731.
doi: 10.1158/1078-0432.ccr-17-3553
82. Qin W, Peng C, Yang X, *et al.* SS18-SSX drives TYK₂ expression to activate STAT3/Bcl2 axis, facilitating apoptosis evasion and advancing synovial sarcoma progression. *Cell Biol Toxicol.* 2024;41(1):8.
doi: 10.1007/s10565-024-09952-8
83. Nowicki TS, Akiyama R, Huang RR, *et al.* Infiltration of CD8 T cells and expression of PD-1 and PD-L1 in synovial sarcoma. *Cancer Immunol Res.* 2017;5(2):118-126.
doi: 10.1158/2326-6066.cir-16-0148
84. Liu J, Gao T, Tan Z, *et al.* Phase II study of TQB2450, a novel PD-L1 antibody, in combination with anlotinib in patients with locally advanced or metastatic soft tissue sarcoma. *Clin Cancer Res.* 2022;28(16):3473-3479.
doi: 10.1158/1078-0432.ccr-22-0871
85. Patel KR, Martinez A, Stahl JM, *et al.* Increase in PD-L1 expression after pre-operative radiotherapy for soft tissue sarcoma. *Oncoimmunology.* 2018;7(7):e1442168.
doi:10.1080/2162402x.2018.1442168
86. Yu Y, Yu X, Pan B, *et al.* Pharmacologic degradation of WDR5 suppresses oncogenic activities of SS18:SSX and provides a therapeutic of synovial sarcoma. *Sci Adv.* 2025;11(17):eads7876.
doi: 10.1126/sciadv.ads7876
87. Sole A, Grosset   S, Heintz   M, *et al.* Unraveling ewing sarcoma tumorigenesis originating from patient-derived mesenchymal stem cells. *Cancer Res.* 2021;81(19):4994-5006.
doi: 10.1158/0008-5472.can-20-3837
88. Jia K, Cao L, Yu Y, *et al.* Signaling pathways and targeted therapies in Ewing sarcoma. *Pharmacol Ther.* 2025;266:108765.
doi: 10.1016/j.pharmthera.2024.108765
89. Daley JD, Mukherjee E, Ferraro D, *et al.* SARC0₂₈ samples reveal an interplay between TGF-  , IFN signaling, and Low HLA Class I expression as contributors to ewing sarcoma checkpoint blockade resistance. *Clin Cancer Res.* 2025;31(17):3805-3816.
doi: 10.1158/1078-0432.ccr-24-3882
90. Cillo AR, Mukherjee E, Bailey NG, *et al.* Ewing sarcoma and osteosarcoma have distinct immune signatures and intercellular communication networks. *Clin Cancer Res.* 2022;28(22):4968-4982.
doi: 10.1158/1078-0432.ccr-22-1471
91. Goodspeed A, Bodlak A, Duffy AB, *et al.* Single-cell RNA sequencing of Ewing sarcoma tumors demonstrates transcriptional heterogeneity and clonal evolution. *Clin Cancer Res.* 2025;31(10):2010-2023.
doi: 10.1158/1078-0432.ccr-24-2040
92. Zhang HF, Hughes CS, Li W, *et al.* Proteomic screens for suppressors of anoikis identify IL1RAP as a promising surface target in Ewing sarcoma. *Cancer Discov.* 2021;11(11):2884-2903.
doi: 10.1158/2159-8290.cd-20-1690
93. He F, Xu J, Zeng F, *et al.* Integrative analysis of Ewing's sarcoma reveals that the MIF-CD74 axis is a target for immunotherapy. *Cell Commun Signal.* 2025;23(1):23.
doi: 10.1186/s12964-024-02020-y
94. Wang S, Huo X, Yang Y, Mo Y, Kollipara RK, Kittler R. Ablation of EWS-FLI1 by USP9X inhibition suppresses cancer cell growth in Ewing sarcoma. *Cancer Lett.* 2023;552:215984.
doi: 10.1016/j.canlet.2022.215984
95. Schober SJ, Thiede M, Gassmann H, *et al.* TCR-transgenic T cells and YB-1-based oncolytic virotherapy improve survival in a preclinical Ewing sarcoma xenograft mouse model. *Front Immunol.* 2024;15:1330868.
doi: 10.3389/fimmu.2024.1330868
96. Yu L, Deng Y, Wang X, *et al.* Co-targeting JAK1/STAT6/GAS6/TAM signaling improves chemotherapy efficacy in Ewing sarcoma. *Nat Commun.* 2024;15(1):5292.
doi: 10.1038/s41467-024-49667-2
97. Ou X, Gao G, Ma Q, *et al.* KC1036, a multi-kinase inhibitor with anti-angiogenic activity, can effectively suppress the tumor growth of Ewing sarcoma. *Angiogenesis.* 2025;28(4):50.
doi: 10.1007/s10456-025-10008-6
98. Luo W, Hoang H, Liao Y, Pan J, Ayello J, Cairo MS. A humanized orthotopic mouse model for preclinical evaluation of immunotherapy in Ewing sarcoma. *Front Immunol.* 2023;14:1277987.
doi: 10.3389/fimmu.2023.1277987
99. Mooney B, Negri GL, Shyp T, *et al.* Surface and global proteome analyses identify ENPP1 and other surface proteins as actionable immunotherapeutic targets in Ewing sarcoma. *Clin Cancer Res.* 2024;30(5):1022-1037.
doi: 10.1158/1078-0432.ccr-23-2187
100. Yin H, Jiang D, Li Y, *et al.* KDELR1 regulates chondrosarcoma drug resistance and malignant behavior through Intergrin-Hippo-YAP1 axis. *Cell Death Dis.* 2024;15(12):928.
doi: 10.1038/s41419-024-07264-7
101. Ingangi V, De Chiara A, Ferrara G, *et al.* Emerging

- treatments targeting the tumor microenvironment for advanced chondrosarcoma. *Cells*. 2024;13(11):977.
doi: 10.3390/cells13110977
102. Wagner MJ, Pimenta EM, Sweeney NW, *et al*. Genomic characterization of chondrosarcoma reveals potential therapeutic targets. *JCO Precis Oncol*. 2025;9:e2400592.
doi: 10.1200/PO-24-00592
103. Rey V, Tornín J, Alba-Linares JJ, *et al*. A personalized medicine approach identifies enasidenib as an efficient treatment for IDH2 mutant chondrosarcoma. *EBioMedicine*. 2024;102:105090.
doi: 10.1016/j.ebiom.2024.105090
104. Meijer DM, Venneker S, Ameline B, *et al*. An integrated clinical genomic and transcriptomic subgrouping of central chondrosarcoma. *Mod Pathol*. 2025;38(12):100894.
doi: 10.1016/j.modpat.2025.100894
105. Denu RA, Yang RK, Lazar AJ, *et al*. Clinico-genomic profiling of conventional and dedifferentiated chondrosarcomas reveals TP53 mutation to be associated with worse outcomes. *Clin Cancer Res*. 2023;29(23):4844-4852.
doi: 10.1158/1078-0432.CCR-23-1703
106. Sun Y, Fang Q, Liu W, Liu Y, Zhang C. GANT-61 induces cell cycle resting and autophagy by down-regulating RNAP III signal pathway and tRNA-Gly-CCC synthesis to combat chondrosarcoma. *Cell Death Dis*. 2023;14(7):461.
doi: 10.1038/s41419-023-05926-6
107. Lin ZS, Chung CC, Liu YC, *et al*. EZH2/hSULF1 axis mediates receptor tyrosine kinase signaling to shape cartilage tumor progression. *Elife*. 2023;12:e79432.
doi: 10.7554/eLife.79432
108. Li Y, Yang S, Liu Y, Yang S. Mice with Trp53 and Rb1 deficiency in chondrocytes spontaneously develop chondrosarcoma via overactivation of YAP signaling. *Cell Death Dis*. 2022;13(6):570.
doi: 10.1038/s41419-022-04916-4
109. Quoniou R, Moreau E, Cachin F, *et al*. Chondrosarcoma co-culture 3D model-an insight to evaluate drugs acting on TAMs. *ACS Biomater Sci Eng*. 2024;10(9):5832-5843.
doi: 10.1021/acsbiomaterials.4c00625
110. Li B, Li G, Yan X, *et al*. Fresh tissue multi-omics profiling reveals immune classification and suggests immunotherapy candidates for conventional chondrosarcoma. *Clin Cancer Res*. 2021;27(23):6543-6558.
doi: 10.1158/1078-0432.CCR-21-1893
111. Sheikh TN, Chen X, Xu X, *et al*. Growth inhibition and induction of innate immune signaling of chondrosarcomas with epigenetic inhibitors. *Mol Cancer Ther*. 2021;20(12):2362-2371.
doi: 10.1158/1535-7163.MCT-21-0066
112. Shimada E, Matsumoto Y, Nakagawa M, *et al*. Methylation-mediated silencing of protein kinase C zeta induces apoptosis avoidance through ATM/CHK2 inactivation in dedifferentiated chondrosarcoma. *Br J Cancer*. 2022;126(9):1289-1300.
doi: 10.1038/s41416-021-01695-1
113. Zhou Z, Guan B, Xia H, Zheng R, Xu B. Particle radiotherapy in the era of radioimmunotherapy. *Cancer Lett*. 2023;567:216268.
doi: 10.1016/j.canlet.2023.216268
114. Li Z. New insights into the pathogenesis of systemic mastocytosis. *Int J Mol Sci*. 2021;22(9):4900.
doi: 10.3390/ijms22094900
115. Crupi F, Sordi B, Vanderwert F, *et al*. Histopathology and molecular genetics in systemic mastocytosis: Implications for clinical management. *Int J Mol Sci*. 2022;23(15):8772.
doi: 10.3390/ijms23158772
116. Sotlar K, George TI, Kluin P, *et al*. Standards of pathology in the diagnosis of systemic mastocytosis: Recommendations of the EU-US cooperative group. *J Allergy Clin Immunol Pract*. 2022;10(8):1986-1998.e2.
doi: 10.1016/j.jaip.2022.05.036
117. Coltoff A, Mascarenhas J. Relevant updates in systemic mastocytosis. *Leuk Res*. 2019;81:10-18.
doi: 10.1016/j.leukres.2019.04.001
118. Makeeva A, Stivala S, Ratti E, *et al*. Fedratinib and gandotinib induce apoptosis and enhance the efficacy of tyrosine kinase inhibitors in human mast cells. *Am J Cancer Res*. 2025;15(1):84-98.
doi: 10.62347/TYTU4465
119. Decruyenaere P, Mazure D, Moors I, *et al*. Systemic mastocytosis with myeloid sarcoma and B-CLL: Molecular and clonal heterogeneity in a rare case of SM-AHN with review of literature. *Acta Clin Belg*. 2023;78(1):58-66.
doi: 10.1080/17843286.2022.2033919
120. Górska A, Jabłońska E, Reszka E, *et al*. DNA methylation profile in patients with indolent systemic mastocytosis. *Clin Transl Allergy*. 2021;11(9):e12074.
doi: 10.1002/clt2.12074
121. Bose P, Verstovsek S. Avapritinib for systemic mastocytosis. *Expert Rev Hematol*. 2021;14(8):687-696.
doi: 10.1080/17474086.2021.1959315
122. Below S, Michaelis LC. Avapritinib in the treatment of systemic mastocytosis: An update. *Curr Hematol Malig Rep*. 2021;16(5):464-472.
doi: 10.1007/s11899-021-00650-4

123. Gotlib J, Reiter A, Radia DH, *et al.* Efficacy and safety of avapritinib in advanced systemic mastocytosis: Interim analysis of the phase 2 PATHFINDER trial. *Nat Med.* 2021;27(12):2192-2199.
doi: 10.1038/s41591-021-01539-8
124. Sriskandarajah P, McLornan DP, Oni C, *et al.* Advanced systemic mastocytosis with associated haematological neoplasm: Treatment with avapritinib can facilitate successful bridge to allogeneic haematopoietic cell transplant. *Curr Res Transl Med.* 2023;71(3):103398.
doi: 10.1016/j.retram.2023.103398
125. Kayser S, Levis MJ, Schlenk RF. Midostaurin treatment in FLT3-mutated acute myeloid leukemia and systemic mastocytosis. *Expert Rev Clin Pharmacol.* 2017;10(11):1177-1189.
doi: 10.1080/17512433.2017.1387051
126. Chandesris MO, Damaj G, Lortholary O, Hermine O. Clinical potential of midostaurin in advanced systemic mastocytosis. *Blood Lymphat Cancer.* 2017;7:25-35.
doi: 10.2147/BLCTT.S87186
127. Baird JH, Gotlib J. Clinical validation of KIT inhibition in advanced systemic mastocytosis. *Curr Hematol Malig Rep.* 2018;13(5):407-416.
doi: 10.1007/s11899-018-0469-3
128. Toledo MAS, Gatz M, Sontag S, *et al.* Nintedanib targets KIT D816V neoplastic cells derived from induced pluripotent stem cells of systemic mastocytosis. *Blood.* 2021;137(15):2070-2084.
doi: 10.1182/blood.2019004509
129. Degenfeld-Schonburg L, Gamperl S, Stefanzi G, *et al.* Antineoplastic efficacy profiles of avapritinib and nintedanib in KIT D816V+ systemic mastocytosis: A preclinical study. *Am J Cancer Res.* 2023;13(2):355-378.
130. Wen Y, Tang F, Tu C, Hornicek F, Duan Z, Min L. Immune checkpoints in osteosarcoma: Recent advances and therapeutic potential. *Cancer Lett.* 2022;547:215887.
doi: 10.1016/j.canlet.2022.215887
131. Park JA, Cheung NKV. GD2 or HER2 targeting T cell engaging bispecific antibodies to treat osteosarcoma. *J Hematol Oncol.* 2020;13(1):172.
doi: 10.1186/s13045-020-01012-y
132. Ligon JA, Choi W, Cojocaru G, *et al.* Pathways of immune exclusion in metastatic osteosarcoma are associated with inferior patient outcomes. *J Immunother Cancer.* 2021;9(5):e001772.
doi: 10.1136/jitc-2020-001772
133. Roulleaux Dugage M, Nassif EF, Italiano A, Bahleda R. Improving immunotherapy efficacy in soft-tissue sarcomas: A biomarker driven and histotype tailored review. *Front Immunol.* 2021;12:775761.
doi: 10.3389/fimmu.2021.775761
134. Cheung LS, Chen L, Oke TF, *et al.* Anti-PD-1 elicits regression of undifferentiated pleomorphic sarcomas with UV-mutation signatures. *J Immunother Cancer.* 2021;9(6):e002345.
doi: 10.1136/jitc-2021-002345
135. Nishikawa T, Kakunaga S, Tamura K, *et al.* Efficacy and safety of nivolumab monotherapy in patients with unresectable clear cell sarcoma and alveolar soft part sarcoma (OSCAR Trial/NCCH1510). *Cancer.* 2024;130(22):3836-3844.
doi: 10.1002/cncr.35483
136. Feng K, Zhang X, Li J, *et al.* Neoantigens combined with *in situ* cancer vaccination induce personalized immunity and reshape the tumor microenvironment. *Nat Commun.* 2025;16(1):5074.
doi: 10.1038/s41467-025-60448-3
137. Zhu MMT, Shenasa E, Nielsen TO. Sarcomas: Immune biomarker expression and checkpoint inhibitor trials. *Cancer Treat Rev.* 2020;91:102115.
doi: 10.1016/j.ctrv.2020.102115
138. Huang H, Fan Y, Zhang S, Bai X, Wang X, Shan F. Emerging immunotherapy and tumor microenvironment for advanced sarcoma: A comprehensive review. *Front Immunol.* 2025;16:1507870.
doi: 10.3389/fimmu.2025.1507870
139. Birdi HK, Jirovec A, Cortés-Kaplan S, *et al.* Immunotherapy for sarcomas: New frontiers and unveiled opportunities. *J Immunother Cancer.* 2021;9(2):e001580.
doi: 10.1136/jitc-2020-001580
140. Wang J, Chen Q, Shan Q, Liang T, Forde P, Zheng L. Clinical development of immuno-oncology therapeutics. *Cancer Lett.* 2025;617:217616.
doi: 10.1016/j.canlet.2025.217616
141. Zhang Y, Liu Z, Wei W, Li Y. TCR engineered T cells for solid tumor immunotherapy. *Exp Hematol Oncol.* 2022;11(1):38.
doi: 10.1186/s40164-022-00291-0
142. Li S, Zhang H, Shang G. Current status and future challenges of CAR-T cell therapy for osteosarcoma. *Front Immunol.* 2023;14:1290762.
doi: 10.3389/fimmu.2023.1290762
143. Niu X, Zhang P, Dai L, *et al.* Flagellin engineering enhances CAR-T cell function by reshaping tumor microenvironment in solid tumors. *J Immunother Cancer.* 2025;13(4):e010237.
doi: 10.1136/jitc-2024-010237
144. Kroeze SGC, Pavic M, Stellamans K, *et al.* Metastases-

- directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: Systematic review and consensus recommendations by the EORTC-ESTRO OligoCare consortium. *Lancet Oncol.* 2023;24(3):e121-e132.
doi: 10.1016/S1470-2045(22)00752-5
145. Zhou H, Song T. Conversion therapy and maintenance therapy for primary hepatocellular carcinoma. *Biosci Trends.* 2021;15(3):155-160.
doi: 10.5582/bst.2021.01091
146. Tsai KK, Komanduri KV. Tumor-infiltrating lymphocyte therapy for the treatment of metastatic melanoma. *Am J Clin Dermatol.* 2025;26(5):733-745.
doi: 10.1007/s40257-025-00957-5
147. Yu L, Lanqing G, Huang Z, *et al.* T cell immunotherapy for cervical cancer: Challenges and opportunities. *Front Immunol.* 2023;14:1105265.
doi: 10.3389/fimmu.2023.1105265
148. Liu S, Jiang W, Sheng J, Wang L, Cui M. Adoptive cell therapy for cancer: Combination strategies and biomarkers. *Front Immunol.* 2025;16:1603792.
doi: 10.3389/fimmu.2025.1603792
149. Kirtane K, Elmariah H, Chung CH, Abate-Daga D. Adoptive cellular therapy in solid tumor malignancies: Review of the literature and challenges ahead. *J Immunother Cancer.* 2021;9(7):e002723.
doi: 10.1136/jitc-2021-002723
150. Zhang L, Ding J, Li HY, Wang ZH, Wu J. Immunotherapy for advanced hepatocellular carcinoma, where are we? *Biochim Biophys Acta Rev Cancer.* 2020;1874(2):188441.
doi: 10.1016/j.bbcan.2020.188441
151. Pherez-Farah A, Boncompagni G, Chudnovskiy A, Pasqual G. The bidirectional interplay between T cell-based immunotherapies and the tumor microenvironment. *Cancer Immunol Res.* 2025;13(4):463-475.
doi: 10.1158/2326-6066.CIR-24-0857
152. Wei F, Cheng XX, Xue JZ, Xue SA. Emerging strategies in TCR-engineered T cells. *Front Immunol.* 2022;13:850358.
doi: 10.3389/fimmu.2022.850358
153. Lennerz V, Doppler C, Fatho M, *et al.* T-cell receptors identified by a personalized antigen-agnostic screening approach target shared neoantigen KRAS Q61H. *Front Immunol.* 2025;16:1509855.
doi: 10.3389/fimmu.2025.1509855
154. Wolf SP, Anastasopoulou V, Drousch K, *et al.* One CD4+TCR and one CD8+TCR targeting autochthonous neoantigens are essential and sufficient for tumor eradication. *Clin Cancer Res.* 2024;30(8):1642-1654.
doi: 10.1158/1078-0432.CCR-23-2905
155. Dougé A, El Ghazzi N, Lemal R, Rouzaire P. Adoptive T cell therapy in solid tumors: State-of-the art, current challenges, and upcoming improvements. *Mol Cancer Ther.* 2024;23(3):272-284.
doi: 10.1158/1535-7163.MCT-23-0310
156. Das S, Valton J, Duchateau P, Poirot L. Stromal depletion by TALEN-edited universal hypoinmunogenic FAP-CAR T cells enables infiltration and anti-tumor cytotoxicity of tumor antigen-targeted CAR-T immunotherapy. *Front Immunol.* 2023;14:1172681.
doi: 10.3389/fimmu.2023.1172681
157. Lake JA, Woods E, Hoffmeyer E, *et al.* Directing B7-H3 chimeric antigen receptor T cell homing through IL-8 induces potent antitumor activity against pediatric sarcoma. *J Immunother Cancer.* 2024;12(7):e009221.
doi: 10.1136/jitc-2024-009221
158. Qian Z, Chen L, Liu J, Jiang Y, Zhang Y. The emerging role of PPAR-alpha in breast cancer. *Biomed Pharmacother.* 2023;161:114420.
doi: 10.1016/j.biopha.2023.114420
159. Dyer BA, Feng CH, Eskander R, *et al.* Current status of clinical trials for cervical and uterine cancer using immunotherapy combined with radiation. *Int J Radiat Oncol Biol Phys.* 2021;109(2):396-412.
doi: 10.1016/j.ijrobp.2020.09.016
160. Xu S, Xu X, Zhu H. Pre-immunotherapy radiotherapy enhanced the efficacy of multi-line sintilimab in unresectable advanced esophageal squamous cell carcinoma. *Front Immunol.* 2023;14:960339.
doi: 10.3389/fimmu.2023.960339
161. Huang D, Lynch C, Pitroda SP, Weichselbaum RR. Facts and hopes in radioimmunotherapy of oligometastatic disease. *Clin Cancer Res.* 2025;31(13):2556-2564.
doi: 10.1158/1078-0432.CCR-24-2522
162. Chen C, Xie L, Ren T, Huang Y, Xu J, Guo W. Immunotherapy for osteosarcoma: Fundamental mechanism, rationale, and recent breakthroughs. *Cancer Lett.* 2021;500:1-10.
doi: 10.1016/j.canlet.2020.12.024
163. Giordano G, Tucciarello C, Merlini A, Cutrupi S, Pignochino Y. Targeting the EphA2 pathway: Could it be the way for bone sarcomas? *Cell Commun Signal.* 2024;22(1):433.
doi: 10.1186/s12964-024-01811-7
164. Li F, Wang S, Wang Y, *et al.* Multi-omics analysis unravels the underlying mechanisms of poor prognosis and differential therapeutic responses of solid predominant lung adenocarcinoma. *Front Immunol.* 2023;14:1101649.
doi: 10.3389/fimmu.2023.1101649
165. Hou W, Yi C, Zhu H. Predictive biomarkers of colon cancer

- immunotherapy: Present and future. *Front Immunol.* 2022;13:1032314.
doi: 10.3389/fimmu.2022.1032314
166. Zhang T, Li W, Chen Q, *et al.* Prognostic significance of early alpha fetoprotein and des-gamma carboxy prothrombin responses in unresectable hepatocellular carcinoma patients undergoing triple combination therapy. *Front Immunol.* 2024;15:1508028.
doi: 10.3389/fimmu.2024.1508028
167. Indini A, Massi D, Pirro M, *et al.* Targeting inflamed and non-inflamed melanomas: Biological background and clinical challenges. *Semin Cancer Biol.* 2022;86(Pt 2):477-490.
doi: 10.1016/j.semcancer.2022.06.005
168. Zhu S, Zhang T, Zheng L, *et al.* Combination strategies to maximize the benefits of cancer immunotherapy. *J Hematol Oncol.* 2021;14(1):156.
doi: 10.1186/s13045-021-01164-5
169. Insa A, Martín-Martorell P, Di Liello R, *et al.* Which treatment after first line therapy in NSCLC patients without genetic alterations in the era of immunotherapy? *Crit Rev Oncol Hematol.* 2022;169:103538.
doi: 10.1016/j.critrevonc.2021.103538
170. Han Z, Chen G, Wang D. Emerging immunotherapies in osteosarcoma: From checkpoint blockade to cellular therapies. *Front Immunol.* 2025;16:1579822.
doi: 10.3389/fimmu.2025.1579822
171. Zhang R, Yuan F, Shu Y, *et al.* Personalized neoantigen-pulsed dendritic cell vaccines show superior immunogenicity to neoantigen-adjuvant vaccines in mouse tumor models. *Cancer Immunol Immunother.* 2020;69(1):135-145.
doi: 10.1007/s00262-019-02448-z
172. Wu C, Duan Y, Gong S, Osterhoff G, Kallendrusch S, Schopow N. Identification of tumor antigens and immune subtypes for the development of mRNA vaccines and individualized immunotherapy in soft tissue sarcoma. *Cancers (Basel).* 2022;14(2):448.
doi: 10.3390/cancers14020448
173. Yoshida S, Shime H, Matsumoto M, Kasahara M, Seya T. Anti-oxidative amino acid L-ergothioneine modulates the tumor microenvironment to facilitate adjuvant vaccine immunotherapy. *Front Immunol.* 2019;10:671.
doi: 10.3389/fimmu.2019.00671
174. Liu Y, Wang Z, Yu F, *et al.* The adjuvant of α -galactosylceramide presented by gold nanoparticles enhances antitumor immune responses of MUC1 antigen-based tumor vaccines. *Int J Nanomedicine.* 2021;16:403-420.
doi: 10.2147/IJN.S273883
175. Yang J, Zhang J, Yan P, *et al.* Asymmetric assembly and self-adjuvanted antigen delivery platform for improved antigen uptake and antitumor effect. *Bioconj Chem.* 2023;34(5):856-865.
doi: 10.1021/acs.bioconjchem.3c00060
176. Park HJ, Jang GY, Kim YS, *et al.* A novel TLR4 binding protein, 40S ribosomal protein S3, has potential utility as an adjuvant in a dendritic cell-based vaccine. *J Immunother Cancer.* 2019;7(1):60.
doi: 10.1186/s40425-019-0539-7
177. Du JJ, Wang CW, Xu WB, *et al.* Multifunctional protein conjugates with built-in adjuvant (adjuvant-protein-antigen) as cancer vaccines boost potent immune responses. *iScience.* 2020;23(3):100935.
doi: 10.1016/j.isci.2020.100935
178. D'Alise AM, Nocchi L, Garzia I, *et al.* Adenovirus encoded adjuvant (AdEnA) anti-CTLA-4, a novel strategy to improve adenovirus based vaccines against infectious diseases and cancer. *Front Immunol.* 2023;14:1156714.
doi: 10.3389/fimmu.2023.1156714
179. Panagi M, Pilavaki P, Constantinidou A, Stylianopoulos T. Immunotherapy in soft tissue and bone sarcoma: Unraveling the barriers to effectiveness. *Theranostics.* 2022;12(14):6106-6129.
doi: 10.7150/thno.72800
180. Seong G, D'Angelo SP. New therapeutics for soft tissue sarcomas: Overview of current immunotherapy and future directions of soft tissue sarcomas. *Front Oncol.* 2023;13:1150765.
doi: 10.3389/fonc.2023.1150765
181. Chen A, Qiu Y, Yen YT, *et al.* Expression of cancer-testis antigens MAGE-A1, MAGE-A4, NY-ESO-1 and PRAME in bone and soft tissue sarcomas: The experience from a single center in China. *Cancer Med.* 2025;14(7):e70750.
doi: 10.1002/cam4.70750
182. Hashimoto K, Nishimura S, Goto K. PD1/PDL1 immune checkpoint in bone and soft tissue tumors (review). *Mol Clin Oncol.* 2025;22(4):31.
doi: 10.3892/mco.2025.2826
183. Blay JY, Duffaud F, George S, Maki RG, Penel N. Regorafenib for the treatment of sarcoma. *Curr Treat Options Oncol.* 2022;23(11):1477-1502.
doi: 10.1007/s11864-022-00990-0
184. Yang Y, Liu Z, Wang Z, *et al.* Large-scale bulk and single-cell RNA sequencing combined with machine learning reveals glioblastoma-associated neutrophil heterogeneity and establishes a VEGFA+ neutrophil prognostic model. *Biol Direct.* 2025;20(1):45.
doi: 10.1186/s13062-025-00640-z

185. Omura A, Kimura T, Tanaka R, *et al.* Surgical indication of pulmonary metastasis arising from osteosarcoma or soft tissue sarcoma. *Gen Thorac Cardiovasc Surg.* 2022;70(3):273-279.
doi: 10.1007/s11748-021-01726-x
186. Cren PY, Lebellec L, Ryckewaert T, Penel N. Anti-angiogenic agents in management of sarcoma patients: Overview of published trials. *Front Oncol.* 2020;10:594445.
doi: 10.3389/fonc.2020.594445
187. Liu W, Xie X, Qi Y, Wu J. Exploration of immune-related gene expression in osteosarcoma and association with outcomes. *JAMA Netw Open.* 2021;4(8):e2119132.
doi: 10.1001/jamanetworkopen.2021.19132
188. Morinaga S, Han Q, Mizuta K, *et al.* Recombinant methioninase increases eribulin efficacy 16-fold in highly eribulin-resistant HT1080 fibrosarcoma cells, demonstrating potential to overcome the clinical challenge of drug-resistant soft-tissue sarcoma. *Anticancer Res.* 2024;44(9):3777-3783.
doi: 10.21873/anticancer.17202
189. Li R, Yao F, Liu Y, *et al.* Mining TCGA to reveal immunotherapy-related genes for soft tissue sarcoma. *Medicine (Baltimore).* 2025;104(9):e41392.
doi: 10.1097/MD.00000000000041392
190. Dufresne A, Lindner LH, Striefler J, *et al.* The challenge of running trials in advanced angiosarcoma: A systematic review of the literature from EORTC/STBSG to guide the development of angiosarcoma-specific trials. *Eur J Cancer.* 2024;207:114188.
doi: 10.1016/j.ejca.2024.114188
191. Hepner A, Atkinson VG, Larkin J, *et al.* Re-induction ipilimumab following acquired resistance to combination ipilimumab and anti-PD-1 therapy. *Eur J Cancer.* 2021;153:213-222.
doi: 10.1016/j.ejca.2021.04.021