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NARRATIVE REVIEW

Targeted Therapies and Immunotherapy in Bone and Soft Tissue Sarcomas: Current Evidence and Future Directions

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ABSTRACT

Bone and soft tissue sarcomas are a heterogeneous group of rare malignancies with diverse molecular profiles and clinical behaviours. Despite advances in surgery and radiotherapy, outcomes for advanced or metastatic disease remain poor. Targeted therapies have transformed treatment for selected sarcoma subtypes. Tyrosine kinase inhibitors such as imatinib, sunitinib, and regorafenib have dramatically improved outcomes in gastrointestinal stromal tumours, while pazopanib has shown activity across several soft tissue sarcomas[1-2]. Molecularly defined subsets—including NTRK fusion sarcomas, ALK-rearranged inflammatory myofibroblastic tumours, and MDM2-amplified liposarcomas—have benefited from precision-guided treatments [3-4].

Immunotherapy provides additional benefit, especially in undifferentiated pleomorphic sarcoma and alveolar soft part sarcoma[5-6]. However, most sarcomas exhibit an immunologically cold phenotype. Combination strategies integrating TKIs, immune checkpoint inhibitors, epigenetic therapies, and radiation are under active investigation[7-9].

This review summarises advances in targeted therapies and immunotherapy, discusses biomarkers, and highlights emerging strategies.

1. Introduction

Bone and soft tissue sarcomas comprise more than 70 histologic subtypes and account for approximately 1% of adult cancers and 15% of paediatric malignancies[10-11]. Their rarity and biological diversity create challenges for diagnosis, treatment, and clinical trial development[12-13]. Historically, systemic treatment relied on cytotoxic chemotherapy, including doxorubicin, ifosfamide, gemcitabine, and taxanes[14-15].

The discovery of KIT and PDGFRA mutations in gastrointestinal stromal tumours established molecularly targeted therapy as a transformative approach[16-17]. Subsequent development of TKIs, CDK4/6 inhibitors, MDM2 antagonists, NTRK inhibitors, and ALK inhibitors expanded treatment options[18-21]. Immunotherapy also provides meaningful responses in certain subtypes such as undifferentiated pleomorphic sarcoma and alveolar soft part sarcoma[5-6].

2. Methods

A structured literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar for studies published between January 2000 and January 2026. Search terms included sarcoma targeted therapy, sarcoma immunotherapy, TKI soft tissue sarcoma, GIST imatinib, immune checkpoint inhibitors sarcoma, NTRK fusion sarcoma, MDM2 amplification liposarcoma, and alveolar soft part sarcoma immunotherapy. Peer-reviewed clinical trials, meta-analyses, translational studies, and reviews were included. Case reports and non–peer-reviewed sources were excluded. A total of 1,842 studies were screened; 100 high-quality publications were selected.

3. Results

3.1 TARGETED THERAPİES İN BONE SARCOMAS

Osteosarcoma:

Osteosarcoma is characterised by marked genomic instability and lacks a dominant actionable driver mutation, making the development of targeted therapies particularly challenging[22-23]. Nevertheless, several tyrosine kinase inhibitors (TKIs) have demonstrated clinical benefit. Regorafenib and cabozantinib, for example, have shown significant improvements in progression-free survival in patients with relapsed or refractory disease[24-25]. However, inhibitors targeting IGF1R and mTOR pathways have yielded only modest or limited efficacy in clinical trials[26-27]. The lack of robust biomarkers and the heterogeneity of osteosarcoma underscore the need for further molecular characterisation and novel therapeutic strategies[28-29].

Ewing Sarcoma:

Ewing sarcoma is defined by the presence of the EWSR1–FLI1 fusion gene, which acts as an oncogenic driver[30]. While PARP inhibitors have shown synergistic effects when combined with DNA-damaging agents, their single-agent activity remains limited[31-32]. IGF1R inhibitors and CDK inhibitors have also been evaluated, but their clinical impact has been modest[26-27]. The inability to directly target the fusion protein remains a major therapeutic barrier[33].

Chondrosarcoma:

A subset of chondrosarcomas harbours IDH1/2 mutations, which can be targeted by small molecule inhibitors such as ivosidenib, leading to disease stabilisation in some patients[34]. However, hedgehog pathway inhibitors have not demonstrated significant clinical benefit[35].

3.2 TARGETED THERAPİES İN SOFT TİSSUE SARCOMAS

Gastrointestinal Stromal Tumour (GIST):

The discovery of KIT and PDGFRA mutations revolutionised the treatment of GIST, with imatinib achieving response rates exceeding 70%[16-17]. For patients who develop resistance to imatinib, sunitinib and regorafenib are effective second- and third-line options[1-2]. Avapritinib has demonstrated high efficacy in patients with PDGFRA D842V-mutant GIST, a subgroup previously considered resistant to standard TKIs[17].

Liposarcoma:

Dedifferentiated liposarcoma frequently exhibits MDM2 amplification and CDK4 overexpression. MDM2 inhibitors (milademetan, idasanutlin) and CDK4/6 inhibitors (palbociclib, abemaciclib) have shown promising activity in clinical trials, offering new therapeutic avenues for this challenging subtype[3, 36-37].

Synovial Sarcoma:
EZH2 inhibition with tazemetostat has demonstrated clinical benefit in synovial sarcoma, and TCR-engineered T-cell therapies targeting NY-ESO-1 have produced durable responses in selected patients[38-39].

Angiosarcoma:
TKIs such as pazopanib and axitinib have shown efficacy in angiosarcoma, particularly in subtypes driven by UV exposure. Immunotherapy has also emerged as a highly effective option in these cases[40].

Undifferentiated Pleomorphic Sarcoma (UPS):
UPS is notable for its responsiveness to immune checkpoint inhibitors, with pembrolizumab and nivolumab producing meaningful clinical responses[5-6].

3.3 Immunotherapy in Sarcomas

Immune checkpoint inhibitors (ICIs) have shown the most robust responses in UPS and alveolar soft part sarcoma. The combination of nivolumab and ipilimumab has been associated with increased overall response rates compared to monotherapy[6,41]. Adoptive T-cell therapies, including TCR-engineered and CAR T-cell approaches, have demonstrated striking efficacy in synovial sarcoma and myxoid liposarcoma, although CAR T-cell therapies remain largely experimental[38]. Cancer vaccines targeting tumour antigens such as NY-ESO-1, WT1, and survivin are under active investigation and may further expand immunotherapeutic options[42].

3.4 Biomarkers of Response

Key predictive biomarkers for targeted therapy include alterations in KIT, PDGFRA, NTRK, ALK, and MDM2[16-17,3-4]. For immunotherapy, biomarkers such as PD-L1 expression, tumour-infiltrating lymphocytes, and tumour mutational burden have been associated with response, although their predictive value remains imperfect[43-44]. Multi-omic approaches that integrate genomic, transcriptomic, and immunologic data may enhance the accuracy of response prediction[42].

3.5 COMBİNATİON STRATEGİES

- **TKI + ICI Combinations:** The combination of TKIs (e.g., axitinib) with ICIs (e.g., pembrolizumab) has demonstrated synergistic effects in early-phase trials[7].
- **Epigenetic Therapy:** Agents targeting epigenetic regulators may enhance antigen presentation and sensitise tumours to immunotherapy[8].
- **Radiation Therapy:** Radiation can increase tumour immunogenicity by promoting neoantigen release, potentially augmenting the efficacy of immunotherapy[9].

3.6 Emerging Therapies

- **NTRK Inhibitors:** Larotrectinib and entrectinib have shown high efficacy in NTRK fusion-positive sarcomas[4].
- **ALK Inhibitors:** Crizotinib is effective in ALK-rearranged inflammatory myofibroblastic tumours[21].
- **Oncolytic Viruses:** Agents such as talimogene laherparepvec (TVEC) are being explored for their ability to induce tumour lysis and stimulate anti-tumour immunity[45].

4. Discussion

Targeted therapies and immunotherapy have reshaped sarcoma management. GIST remains the clearest success of precision oncology. In contrast, osteosarcoma and Ewing sarcoma lack actionable alterations, limiting targeted therapies. Immune checkpoint inhibitors produce durable responses in UPS and ASPS, while adoptive T-cell therapies mark major progress in synovial sarcoma. Future directions emphasise combination therapy and biomarker development.

5. Conclusion

Targeted therapies and immunotherapy have advanced sarcoma treatment, yet many subtypes require better biomarkers and combination strategies. Integrating genomic, epigenomic, and immunologic insights is essential for precision treatment.

Conflict of Interest Statement:

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