



OPEN ACCESS

EDITED BY

Yingcheng Charles Wu,
Fudan University, China

REVIEWED BY

Fei Yin,
Jilin University, China
Xutong Xue,
Boston Children's Hospital and Harvard
Medical School, United States

*CORRESPONDENCE

Jiang Wang
✉ 79507961@qq.com
Wei Zhou
✉ 2005ly0909@hust.edu.cn

[†]These authors have contributed equally to
this work

RECEIVED 20 February 2025

ACCEPTED 26 September 2025

PUBLISHED 09 October 2025

CITATION

Wang C, Chen Z, Mo H, Wang J and Zhou W
(2025) A review of immunotherapy for bone
tumors.
Front. Immunol. 16:1580598.
doi: 10.3389/fimmu.2025.1580598

COPYRIGHT

© 2025 Wang, Chen, Mo, Wang and Zhou. This
is an open-access article distributed under the
terms of the [Creative Commons Attribution
License \(CC BY\)](#). The use, distribution or
reproduction in other forums is permitted,
provided the original author(s) and the
copyright owner(s) are credited and that the
original publication in this journal is cited, in
accordance with accepted academic
practice. No use, distribution or reproduction
is permitted which does not comply with
these terms.

A review of immunotherapy for bone tumors

Chenwen Wang^{1†}, Zixiong Chen^{1†}, Haokun Mo^{2†},
Jiang Wang^{2*} and Wei Zhou^{1*}

¹Department of Orthopedics, Liyuan Hospital, Tongji Medical College, Huazhong University of
Science and Technology, Wuhan, Hubei, China, ²Department of Orthopedics, Tongji Hospital, Tongji
Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

This article reviews the latest research progress in immunotherapy for bone tumors. Bone tumors are a serious threat to human health, and traditional treatments have limitations. Recently, immunotherapy, as an emerging treatment method, has shown great potential in the treatment of bone tumors. This article systematically introduces the pathological features, traditional treatment methods and limitations of bone tumors, and focuses on the principles, application status and challenges of immune checkpoint inhibitors, CAR-T cell therapy, tumor vaccines and other immunotherapies. At the same time, the combined application strategy of immunotherapy and traditional treatment was discussed, and the future development direction was prospected. The purpose of this article is to provide a reference for the research and clinical application of bone tumor immunotherapy.

KEYWORDS

bone tumors, immunotherapy, ICIS, CAR-T cell therapy, oncology vaccines

1 Introduction

A bone tumor is a malignant tumor originating from the skeletal system and can be divided into primary bone tumor and metastatic bone tumor. Primary bone tumors are relatively rare, but they are highly malignant and have a poor prognosis, such as osteosarcoma, which is the most common primary malignant bone tumor, mainly in children and adolescents (1, 2). Osteosarcoma is more likely to occur in the metaphysis of the long bones of the extremities, such as the distal femur, proximal tibia, proximal femur, and proximal humerus (3). Although osteosarcoma has a low incidence, it has high rates of disability and mortality. At present, the standard treatment for osteosarcoma is the neoadjuvant chemotherapy-surgery-consolidation chemotherapy treatment mode, which has achieved great clinical success in patients with localized osteosarcoma (4, 5). Unfortunately, osteosarcoma is a tumor with a high propensity to metastasize, with 15–20% of newly diagnosed osteosarcomas detected for metastasis (6). Metastatic bone tumors are more common and are mostly metastasized from solid tumors such as breast, prostate, and lung cancer. Bone is the most common site of metastasis in breast cancer patients, and 70% of advanced breast cancer cases exhibit bone metastases (7). Due to its large surface area and high vascular supply, bone is a common site for metastatic spread of NSCLC (8, 9).

Bone lesions occur in 20–30% of patients with NSCLC at the time of diagnosis, and bone metastases occur in another 35–40% during the course of the disease (10). For patients with metastatic prostate cancer, bone is the primary site of tumor localization and a major cause of disease-related morbidity and mortality (11). Traditional treatments, including surgery, radiotherapy, and chemotherapy, have improved the prognosis of patients to a certain extent but still have limitations such as high recurrence rates and large side effects.

There has been limited progress in survival outcomes in patients with primary or metastatic bone tumors, the prognosis is poor, and the treatment of advanced disease cases is extremely challenging. Traditional chemotherapy drugs do not produce a durable response or cure, and patients may experience severe toxicity (12–14). Due to the limited success of conventional chemotherapy in clinical practice, there is an urgent need to utilize new treatment strategies to improve the treatment of patients with bone tumors, given these bottlenecks in traditional treatment options. In addition to traditional treatments including surgery, chemotherapy and radiotherapy, new treatments such as targeted therapy and immunotherapy are also being studied intensively for bone tumors (15, 16). In recent years, with the rapid development of immunology, immunotherapy, as an emerging anti-tumor treatment, has shown significant efficacy in a variety of solid tumors and hematologic malignancies (17–22). Immunotherapy recognizes and kills tumor cells by activating or enhancing the patient's own immune system, which has the advantage of strong specificity and relatively few side effects (23). In the field of bone tumors, immunotherapy has also shown great potential, bringing new hope for improving patient outcomes (24).

The purpose of this article is to systematically review the latest research progress in bone tumor immunotherapy, including the application status and challenges of major immunotherapy strategies such as ICIs (immune checkpoint inhibitors), CAR-T cell therapy (chimeric antigen receptor T-cell therapy), and cancer vaccines. At the same time, the combined application strategy of immunotherapy and traditional treatment is discussed, and the future development direction is prospected in order to provide a reference for the research and clinical application of bone tumor immunotherapy.

2 Pathological features and traditional treatment methods

Bone tumors can be divided into two categories: benign and malignant, among which malignant bone tumors can be divided into primary osteosarcoma and metastatic bone tumors. Primary osteosarcoma mainly includes osteosarcoma, chondrosarcoma and Ewing sarcoma, which are more common in adolescents and young adults (25). Metastatic bone tumors are more common, mostly metastasized from solid tumors such as breast cancer, prostate cancer, and lung cancer, and are more likely to occur in middle-aged and elderly people (26–28). The pathogenesis of bone tumors

is complex, involving a variety of factors such as genetics, epigenetics, and microenvironment (24, 25). Common symptoms include local pain, swelling, pathological fractures, etc. Diagnosis is based on imaging tests (e.g., x-rays, CT, MRI) and histopathological examination (29–32). Traditional treatments include surgery, radiation and chemotherapy (33, 34). Surgery is the mainstay of treatment for bone tumors and aims to completely remove the tumour tissue (35–38); radiotherapy is mainly used for inoperable or postoperative adjuvant therapy; chemotherapy is used for preoperative neoadjuvant therapy and postoperative adjuvant therapy to kill small metastases. Standard treatment for metastatic disease revolves around anthracycline-based chemotherapy, but other drugs including Dacarbazine (39), Gemcitabine/docetaxel (40), Ifosfamide (41), Trabectedin (42), Pazopanone (43) and Eribulin (44) may be used. However, there are many limitations to traditional treatments. Surgery may lead to limb dysfunction and affect the patient's quality of life; radiation therapy and chemotherapy can cause serious side effects, such as bone marrow suppression and gastrointestinal reactions. In addition, some patients are insensitive to traditional treatments and are prone to recurrence and metastasis. These limitations have prompted researchers to continuously explore new therapeutic strategies, among which immunotherapy has attracted much attention due to its unique anti-tumor mechanism.

3 Immunotherapy fundamentals

Immunotherapy is a therapeutic strategy that recognizes and kills tumor cells by activating or boosting a patient's own immune system. The basic principle is to use the immune system's ability to recognize and remove abnormal cells, break the immune escape mechanism of tumors, and restore the body's immune surveillance and killing function of tumors (45–47). In bone tumor immunotherapy, the following key mechanisms are mainly involved: First, it improves the immune system's ability to recognize tumor cells by enhancing the presentation of tumor antigens (48); second, tumor-specific T cells are activated and expanded to enhance their killing function (49–51); third, the tumor microenvironment is regulated to overcome immunosuppressive factors (52, 53); Finally, the immune memory function is used to achieve a long-term anti-tumor immune response (54). The advantages of immunotherapy in the treatment of bone tumors are mainly reflected in the following aspects: first, it is highly specific, can accurately target tumor cells, and reduce damage to normal tissues; secondly, it can produce long-lasting immune memory and reduce the risk of recurrence; thirdly, it can work synergistically with traditional treatment methods to improve overall efficacy; Finally, for some refractory or relapsed bone tumors, immunotherapy may offer new treatment options. However, there are also some challenges in immunotherapy, such as large individual differences in efficacy and the possibility of immune-related adverse reactions, which need to be further studied and optimized.

4 The main strategy of immunotherapy

Immune checkpoint inhibitors are one of the most widely studied immunotherapy strategies for bone tumors (55). Within tumors, effector T cells have reduced cytokine expression and effector capacity and are resistant to reactivation, a state known as “T cell depletion” (56). Depleted T cells highly express a variety of inhibitory surface molecules that potently prevent T cell activation, including cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed death 1 (PD-1), lymphocyte activation gene-3 (LAG-3), and T cell immunoglobulin and ITIM domain (TIGIT). These inhibitory surface molecules are defined as immune checkpoints (57). PD-1 and its ligand PD-L1 inhibitors and CTLA-4 preparations have shown significant efficacy in a variety of solid tumors (58, 59). Key function of CTLA-4 as a negative regulator of T cell activation. CTLA-4 inhibits further activation of cytotoxic T cells by defeating the binding of the stimulated ligand CD28 to CD80 and CD86 on antigen-presenting cells (APCs), thereby preventing the second signal required for T cell activation (60). The central role of PD-1/PD-L1 in inhibiting T cell-mediated immune responses. PD-L2 also binds to PD-1 and is expressed only on APCs, whereas PD-L1 can be expressed by tumor cells, epithelial cells, dendritic cells, macrophages, and fibroblasts, as well as exhausted T cells. When PD-1 is linked to PD-L1 or PD-L2, downstream TCR signaling and activation are inhibited. PD-L1 expression is upregulated in the presence of interferon γ , possibly originating from tumor-infiltrating effector T cells (61, 62). In the field of bone tumors, studies have shown that the PD-1/PD-L1 pathway is abnormally expressed in tumors such as osteosarcoma and chondrosarcoma, suggesting that it may become a potential therapeutic target (63). Currently, multiple clinical trials are evaluating the efficacy and safety of immune checkpoint inhibitors as monotherapy or in combination with bone tumors. Based on the central role of the OPN-RANKL axis in immune suppression of osseous metastases, several clinical trials have explored the synergy of RANKL inhibitors with ICIs. The Phase Ib/II REVERT trial (NCT04586400) assessed the efficacy of denosumab (anti-RANKL monoclonal antibody) in combination with pembrolizumab in patients with bone metastases in advanced non-small cell lung cancer. Median PFS was 7.9 months in the combination group, significantly better than 4.3 months in the monotherapy group (HR=0.62, $P=0.008$). More notably, combination therapy increased the ORR for extraosseous lesions from 18% to 42%. The mechanism of action study found that disumab not only inhibited osteoblast activation but also significantly reduced serum OPN levels (an average decrease of 68% after treatment), while increasing the proportion of CD8 + TCF1 + Tpex cells in the tumor (from 3.2% at baseline to 9.8%). This validates the hypothesis in preclinical studies that targeting osteonecrosis cells can reverse systemic immunosuppression (64). In response to the unique metabolic dependence of MTAP-deficient osteosarcoma, researchers proposed an innovative strategy of methionine intervention combined with ICIs. The phase I/II trial of the MAT2A inhibitor SCR6639 (NCT04930081) included 43

patients with MTAP-deficient advanced osteosarcoma. The results showed that the SCR6639 monotherapy group ($n = 15$) ORR was only 13.3%, and the median PFS was 3.8 months. SCR6639 combined with the pembrolizumab group ($n=28$), ORR reached 38.5%, and median PFS extended to 7.2 months. Mechanistic studies have shown that MAT2A inhibition increases the expression of PD-L1 by 3–5 times in tumor cells by activating the transcription factor IKZF1 while increasing the secretion of T cell chemoattractants such as CXCL9/10. Tumor biopsies after treatment showed a 4.2-fold increase in the density of CD8⁺ T cell infiltration, which was positively correlated with clinical response ($r = 0.78$, $P < 0.001$). A more easily implementable methionine diet restriction program is also being explored. A small-scale pilot study ($n=12$) in which patients received a daily methionine intake restriction (≤ 800 mg) combined with nivolumab treatment showed that 50% of patients experienced a metabolic response (PET-CT SUVmax decrease $\geq 30\%$), and 3 of them achieved partial remission (65).

CAR-T cell therapy is a type of T cell therapy that genetically engineers T cells to express chimeric antigen receptors (CARs) that specifically recognize tumor antigens, thereby achieving specific killing of tumor cells (66). In 2017, the FDA approved CAR-T cell therapy for the treatment of patients with relapsed or refractory B-acute lymphoblastic leukemia. CAR-T cell therapy involves genetically engineered T cells expressing antigen-specific, non-MHC-restricted receptors that can target and attack specific pathological cells and exert therapeutic effects on patients. The structure of CAR is constantly updated and has now evolved to its fifth generation. In the treatment of bone tumors, investigators are exploring CAR-T cell therapies targeting tumor-associated antigens such as GD2 and HER2 (67, 68). Although CAR-T cell therapy has made breakthroughs in hematologic malignancies (69, 70), the application in solid tumors still faces many challenges, such as immunosuppression and targeted toxicity of the tumor microenvironment. In response to the limitations of traditional CAR-T cells in solid tumors, University College London has developed an innovative OPS-g δ T cell platform. The technique uses gamma delta T cells from healthy donors to engineer them to express antibody fragments that target osteosarcoma-related antigens, such as B7-H3, while secreting IL-15 to maintain cell activity. In preclinical osteosarcoma models, OPS- $\gamma\delta$ T cells showed superior efficacy to conventional CAR-T: Tumor growth inhibition (TGI) was 42% in the CAR-T group; TGI was 89%, and DFS disease-free survival was achieved in 60% of mice treated with OPS- $\gamma\delta$ T. When combined with a bone sensitizer such as zoledronic acid, TGI is further increased to 97%. Based on these results, we initiated the OPERA-1 trial (NCT05509901), which plans to recruit patients with osteosarcoma to evaluate the safety and preliminary efficacy of OPS- $\gamma\delta$ T cells (71).

Tumor cells are highly heterogeneous. Therefore, it is important to explore tumor-specific antigens to provide more precise treatments, while oncology vaccines can meet these needs. Oncology vaccines are another important immunotherapy strategy that aims to prevent or treat tumors by activating a patient's own anti-tumor immune response (72, 73). In the field of bone tumors,

researchers are developing vaccines based on tumor-specific antigens, such as NY-ESO-1, MAGE-A3, etc. (74, 75). In addition, personalized neoantigen vaccines have also shown potential application value. However, the research and development of cancer vaccines still faces challenges such as antigen selection and immunogenicity optimization. In the field of advanced neoadjuvant therapy for resectable osteosarcoma, a combination strategy based on dendritic cell (DC) vaccine shows promise. The Phase II NEO-DVIC trial (NCT04201873) compared the efficacy of conventional neoadjuvant chemotherapy with the cDC1 vaccine in combination with pablizumab in patients with primary osteosarcoma: The primary pathological response rate (MPR) of 56% in the cDC1 vaccine group (n = 25) was significantly higher than that of 20% in the chemotherapy group. Median event-free survival (EFS) not reached (vs 15.6 months). Treatment response is strongly associated with CD4+tissue-resident memory T cell (Trm) expansion. Mechanistic studies have shown that the cDC1 vaccine can effectively present tumor antigens to lymph nodes and activate tumor-specific T cell responses, while PD-1 blockade can prevent T cell depletion (76).

Other immunotherapy strategies include oncolytic viruses, immunomodulators, and others. Oncolytic viruses are able to selectively infect and lyse tumor cells while eliciting an anti-tumor immune response (77, 78). In addition to directly lysing tumor cells, the innate immune system can easily recognize the virus as foreign, thus avoiding the need for cancer-specific antigens to initiate an immune response. Oncolytic virus infection can lead

to a strong innate immune response through the expression of damage-associated molecular patterns (DAMPs), resulting in local cytokine expression that attracts APCs, natural killer cells, and ultimately T cells (79). To date, four OV's have been clinically approved in select regions for the treatment of various cancers: Rigvir, T-VEC (IMLYGIC), ONYX-015 (DL1520), and H101 (80–83). OV also has some limitations. First, it is possible for the host to produce neutralizing antibodies, and in addition, in the hypoxic tumor core, tumor cells can form necrosis or calcification nearby in response to hypoxia or acidosis, which may limit the efficacy of OV's. Immunomodulators such as interferon, interleukin, etc., can enhance antitumor effects by modulating immune system function. The application of these strategies in the treatment of bone tumors is still in the exploratory stage, and further research is needed to evaluate their safety and efficacy. The suitability of tumor types to major therapies and common adverse reactions are shown in Table 1.

5 Challenges and future directions

Although immunotherapy has shown great potential in the treatment of bone tumors, there are still many challenges. First, the immunogenicity of bone tumors is relatively low and highly heterogeneous, resulting in large individual differences in the efficacy of immunotherapy. Second, immunosuppressive factors in

TABLE 1 Tumor-type applicability and common adverse effects for major therapies.

Therapy class	Tumor-type applicability	Common adverse effects	Patient selection & biomarkers
Immune Checkpoint Inhibitors (e.g., anti-PD-1/PD-L1, anti-CTLA-4)	Solid tumors: Melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, bladder cancer, and many others. Liquid tumors: Hodgkin lymphoma, some primary mediastinal B-cell lymphoma.	Immune-related Adverse Events (irAEs): Can affect any organ. Common ones include colitis (diarrhea), dermatitis (rash), hepatitis, pneumonitis, and endocrinopathies (e.g., thyroiditis).	Selection is often guided by biomarkers such as PD-L1 expression, high Tumor Mutational Burden (TMB), or Microsatellite Instability-High (MSI-H) status, which predict better response.
CAR-T Cell Therapy	Liquid tumors: B-cell acute lymphoblastic leukemia (ALL), certain types of non-Hodgkin lymphoma (e.g., DLBCL), and multiple myeloma. Solid tumors: Largely experimental.	Cytokine Release Syndrome (CRS): Fever, hypotension, and organ dysfunction. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS): Confusion, aphasia, seizures. Prolonged cytopenias, increased infection risk.	Selection requires confirmed expression of the target antigen (e.g., CD19 or BCMA). Patients must be fit enough to tolerate severe, acute toxicities.
Oncolytic Viruses	Approved: Melanoma (T-VEC), glioblastoma (Delytact), and head & neck cancer (H101) Clinical Trials: HCC (VG161), pancreatic cancer, bladder cancer, ovarian cancer.	Most common: Flu-like symptoms (fever, chills, fatigue), injection site reactions. Less common: Transient liver enzyme elevations, neuralgia (e.g., facial paralysis). Generally favorable safety profile vs. other immunotherapies.	Tumor susceptibility to viral infection and presence of viral receptors. Predictive biomarkers are emerging (e.g., theViroPredict 1.0 gene signature for VG161 in HCC). May be particularly suited for patients who have failed prior immunotherapies (e.g., PreCPI >3m with HCC showed better OS with VG161).
Cancer Vaccines	Preventive: HPV vaccines for cervical cancer. Therapeutic: - Personalized neoantigen vaccines (PCV): Melanoma, NSCLC, renal cell carcinoma (RCC) - Off-the-shelf: WT1 vaccine for leukemia/ovarian cancer.	Generally mild: Local reactions (injection site redness, swelling, pain), systemic reactions (low-grade fever, fatigue, muscle aches). Rare: Cell cytokine release syndrome (CRS) is uncommon.	Requires identification of immunogenic tumor-specific antigens (e.g., via whole exome/RNA sequencing for PCV). Likely most effective in low tumor burden settings (e.g., adjuvant) and with permissive immune microenvironments. Often combined with checkpoint inhibitors (e.g., mRNA-4157 + pembrolizumab in melanoma).
Bispecific Antibodies (e.g., BiTEs)	Liquid tumors: B-cell ALL (blinatumomab), multiple myeloma.	Toxicities similar to CAR-T but often less severe: CRS, neurotoxicity, and infections.	Requires confirmed target antigen expression (e.g., CD19 for blinatumomab). Often used after prior therapies.

the tumor microenvironment, such as regulatory T cells and myeloid-derived suppressor cells, may weaken the efficacy of immunotherapy. In addition, the management of immune-related adverse effects is an important issue. To overcome these challenges, future research directions may include the development of more effective biomarkers to predict immunotherapy response; exploring new immunotherapy targets; optimizing immunotherapy strategies, (such as combining immunotherapy drugs with different mechanisms), specific therapeutic strategies for the bone tumor microenvironment, etc. In addition, strengthening the combination of basic research and clinical translation and carrying out large-scale, multi-center clinical trials are also important directions to promote the development of bone tumor immunotherapy. Another promising direction is the combination of immunotherapy with traditional treatments. For example, radiation and chemotherapy may enhance the efficacy of immunotherapy by inducing immunogenic cell death; immunotherapy prior to surgery may help control micrometastases. The application of OV combined with ICIs against tumors has shown success in many preclinical studies and has started to become the focus of clinical trials. Exploring the best combination therapy strategy and timing is expected to further improve the treatment effect of bone tumors.

6 Conclusion

As an emerging treatment strategy, bone tumor immunotherapy has shown great potential in improving patient outcomes. The application of major immunotherapy strategies such as immune checkpoint inhibitors, CAR-T cell therapy, and tumor vaccines in the treatment of bone tumors is deepening. Although there are still many challenges, with the in-depth understanding of the immune microenvironment and immune escape mechanisms of bone tumors, as well as the development of novel immunotherapy technologies, bone tumor immunotherapy is expected to make breakthroughs in the future. Future research should focus on developing more precise immunotherapy strategies, optimizing combination therapy regimens, and strengthening the translation of basic research and clinical applications. At the same time, large-scale, multicenter clinical trials are needed to evaluate the long-term efficacy and safety of immunotherapy. It is believed that through multidisciplinary collaboration and continuous innovation, immunotherapy will bring new hope to patients with bone tumors and ultimately improve their quality of life and prognosis.

References

1. Beird HC, Bielack SS, Flanagan AM, Gill J, Heymann D, Janeway KA, et al. Osteosarcoma. *Nat Rev Dis primers*. (2022) 8:77. doi: 10.1038/s41572-022-00409-y
2. Strauss SJ, Frezza AM, Abecassis N, Bajpai J, Bauer S, Biagini R, et al. Bone sarcomas: ESMO-EURACAN-GENTURIS-ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. (2021) 32:1520–36. doi: 10.1016/j.annonc.2021.08.1995
3. Isakoff MS, Bielack SS, Meltzer P, Gorlick R. Osteosarcoma: current treatment and a collaborative pathway to success. *J Clin Oncol*. (2015) 33:3029–35. doi: 10.1200/jco.2014.59.4895
4. Anderson ME. Update on survival in osteosarcoma. *Orthopedic Clinics North A*. (2016) 47:283–92. doi: 10.1016/j.jocl.2015.08.022
5. Gronchi A, Miah AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). *Ann Oncol*. (2021) 32:1348–65. doi: 10.1016/j.annonc.2021.07.006
6. Bacci G, Rocca M, Salone M, Balladelli A, Ferrari S, Palmerini E, et al. High grade osteosarcoma of the extremities with lung metastases at presentation: treatment with

Author contributions

CW: Writing – original draft. ZC: Visualization, Writing – original draft. HM: Investigation, Writing – review & editing. JW: Writing – review & editing. WZ: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research and/or publication of this article. This study was supported by the Natural Science Foundation of Hubei Province of China (No. 2021CFB521) and the Huazhong University of Science and Technology Independent Innovation Research Fund (No. 2018KFYYXJJ111). The funding bodies played no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

neoadjuvant chemotherapy and simultaneous resection of primary and metastatic lesions. *J Surg Oncol.* (2008) 98:415–20. doi: 10.1002/jso.21140

7. Manders K, van de Poll-Franse LV, Creemers GJ, Vreugdenhil G, van der Sangen MJ, Nieuwenhuijzen GA, et al. Clinical management of women with metastatic breast cancer: a descriptive study according to age group. *BMC cancer.* (2006) 6:179. doi: 10.1186/1471-2407-6-179

8. Roodman GD. Mechanisms of bone metastasis. *New Engl J Med.* (2004) 350:1655–64. doi: 10.1056/NEJMra030831

9. Kuchuk M, Addison CL, Clemons M, Kuchuk I, Wheatley-Price P. Incidence and consequences of bone metastases in lung cancer patients. *J Bone Oncol.* (2013) 2:22–9. doi: 10.1016/j.jbo.2012.12.004

10. Santini D, Barni S, Intagliata S, Falcone A, Ferrau F, Galetta D, et al. Natural history of non-small-cell lung cancer with bone metastases. *Sci Rep.* (2015) 5:18670. doi: 10.1038/srep18670

11. Morris MJ, Pandit-Taskar N, Divgi C, Larson S, Scher HI. Targeting osseous metastases: rationale and development of radio-immunotherapy for prostate cancer. *Curr Oncol Rep.* (2004) 6:222–9. doi: 10.1007/s11912-004-0053-y

12. Smeland S, Bielack SS, Whelan J, Bernstein M, Hogendoorn P, Krailo MD, et al. Survival and prognosis with osteosarcoma: outcomes in more than 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort. *Eur J Cancer (Oxford England: 1990).* (2019) 109:36–50. doi: 10.1016/j.ejca.2018.11.027

13. Miralbell L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. *Cancer.* (2009) 115:1531–43. doi: 10.1002/cncr.24121

14. Berner K, Johannesen TB, Berner A, Haugland HK, Bjerkehagen B, Böhler PJ, et al. Time-trends on incidence and survival in a nationwide and unselected cohort of patients with skeletal osteosarcoma. *Acta Oncol (Stockholm Sweden).* (2015) 54:25–33. doi: 10.3109/0284186x.2014.923934

15. Jin J, Yuan P, Yu W, Lin J, Xu A, Xu X, et al. Mitochondria-targeting polymer micelle of dichloroacetate induced pyroptosis to enhance osteosarcoma immunotherapy. *ACS nano.* (2022) 16:10327–40. doi: 10.1021/acsnano.2c00192

16. Giordano G, Tucciarello C, Merlini A, Cutrupi S, Pignochino Y. Targeting the EphA2 pathway: could it be the way for bone sarcomas? *Cell communication signaling: CCS.* (2024) 22:433. doi: 10.1186/s12964-024-01811-7

17. Jin X, Liu Z, Yang D, Yin K, Chang X. Recent progress and future perspectives of immunotherapy in advanced gastric cancer. *Front Immunol.* (2022) 13:948647. doi: 10.3389/fimmu.2022.948647

18. Kansara RR, Speziali C. Immunotherapy in hematologic Malignancies. *Curr Oncol (Toronto Ont).* (2020) 27:S124–s31. doi: 10.3747/co.27.5117

19. Barsan V, Ramakrishna S, Davis KL. Immunotherapy for the treatment of acute lymphoblastic leukemia. *Curr Oncol Rep.* (2020) 22:11. doi: 10.1007/s11912-020-0875-2

20. Donin NM, Lenis AT, Holden S, Drakaki A, Pantuck A, Beldegrun A, et al. Immunotherapy for the treatment of urothelial carcinoma. *J urol.* (2017) 197:14–22. doi: 10.1016/j.juro.2016.02.3005

21. Elizabeth MS, Cristina SBJ, Christian CG. Immunotherapy in combination with chemotherapy for triple-negative breast cancer. *Mini Rev medicinal Chem.* (2024) 24:431–9. doi: 10.2174/1389557523666230517152538

22. Cha E, Fong L. Immunotherapy for prostate cancer: biology and therapeutic approaches. *J Clin Oncol.* (2011) 29:3677–85. doi: 10.1200/jco.2010.34.5025

23. Rui R, Zhou L, He S. Cancer immunotherapies: advances and bottlenecks. *Front Immunol.* (2023) 14:1212476. doi: 10.3389/fimmu.2023.1212476

24. Yu S, Yao X. Advances on immunotherapy for osteosarcoma. *Mol cancer.* (2024) 23:192. doi: 10.1186/s12943-024-02105-9

25. Scotlandi K, Hattinger CM, Pellegrini E, Gambarotti M, Serra M. Genomics and therapeutic vulnerabilities of primary bone tumors. *Cells.* (2020) 9(4):968. doi: 10.3390/cells9040968

26. Puppo M, Valluru MK, Clézardin P. MicroRNAs and their roles in breast cancer bone metastasis. *Curr osteoporosis Rep.* (2021) 19:256–63. doi: 10.1007/s11914-021-00677-9

27. Landi L, D'Inca F, Gelibter A, Chiari R, Grossi F, Delmonte A, et al. Bone metastases and immunotherapy in patients with advanced non-small-cell lung cancer. *J immunother cancer.* (2019) 7:316. doi: 10.1186/s40425-019-0793-8

28. Logothetis C, Morris MJ, Den R, Coleman RE. Current perspectives on bone metastases in castrate-resistant prostate cancer. *Cancer metastasis Rev.* (2018) 37:189–96. doi: 10.1007/s10555-017-9719-4

29. Costelloe CM, Madewell JE. Radiography in the initial diagnosis of primary bone tumors. *AJR Am J roentgenol.* (2013) 200:3–7. doi: 10.2214/ajr.12.8488

30. Méndez Díaz C, Soler Fernández R, Rodríguez García E, Fernández Armendariz P, Díaz Angulo C. Surface primary bone tumors: Systematic approach and differential diagnosis. *Skeletal radiol.* (2015) 44:1235–52. doi: 10.1007/s00256-015-2136-2

31. Sureka B, Mittal MK, Thukral BB. Radiography in the initial diagnosis of biologic activity or growth rate of primary bone tumors. *AJR Am J roentgenol.* (2013) 201:W770. doi: 10.2214/ajr.13.10817

32. Katchy KC, Ziad F, Alexander S, Gad H, Abdel Mota'al M. Malignant bone tumors in Kuwait: a 10-year clinicopathological study. *Int orthopaedics.* (2005) 29:406–11. doi: 10.1007/s00264-005-0014-6

33. Li S, Zhang H, Liu J, Shang G. Targeted therapy for osteosarcoma: a review. *J Cancer Res Clin Oncol.* (2023) 149:6785–97. doi: 10.1007/s00432-023-04614-4

34. Zhang W, Bado I, Wang H, Lo HC, Zhang XH. Bone metastasis: find your niche and fit in. *Trends cancer.* (2019) 5:95–110. doi: 10.1016/j.trecan.2018.12.004

35. Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. *Cancer.* (1977) 40:818–31. doi: 10.1002/1097-0142(197708)40:2<818::aid-cncr2820400234>3.0.co;2-b

36. Sheth DS, Yasko AW, Johnson ME, Ayala AG, Murray JA, Romsdahl MM. Chondrosarcoma of the pelvis. Prognostic factors for 67 patients treated with definitive surgery. *Cancer.* (1996) 78:745–50. doi: 10.1002/(sici)1097-0142(19960815)78:4<745::Aid-cncr9>3.0.Co;2-d

37. Pring ME, Weber KL, Unni KK, Sim FH. Chondrosarcoma of the pelvis. A review of sixty-four cases. *J Bone Joint Surg Am volume.* (2001) 83:1630–42. doi: 10.2106/00004623-200111000-00003

38. Weber KL, Pring ME, Sim FH. Treatment and outcome of recurrent pelvic chondrosarcoma. *Clin orthopaedics related Res.* (2002) 397:19–28. doi: 10.1097/00003086-200204000-00004

39. García-Del-Muro X, López-Pousa A, Maurel J, Martín J, Martínez-Trufero J, Casado A, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol.* (2011) 29:2528–33. doi: 10.1200/jco.2010.33.6107

40. Maki RG, Wathen JK, Patel SR, Priebe DA, Okuno SH, Samuels B, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. *J Clin Oncol.* (2007) 25:2755–63. doi: 10.1200/jco.2006.10.4117

41. Martin-Liberal J, Alam S, Constantinidou A, Fisher C, Khabra K, Messiou C, et al. Clinical activity and tolerability of a 14-day infusion of ifosfamide schedule in soft-tissue sarcoma. *Sarcoma.* (2013) 2013:868973. doi: 10.1155/2013/868973

42. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetz SM, Staddon A, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol.* (2016) 34:786–93. doi: 10.1200/jco.2015.62.4734

43. van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London England).* (2012) 379:1879–86. doi: 10.1016/s0140-6736(12)60651-5

44. Demetri GD, Schöffski P, Grignani G, Blay JY, Maki RG, Van Tine BA, et al. Activity of eribulin in patients with advanced liposarcoma demonstrated in a subgroup analysis from a randomized phase III study of eribulin versus dacarbazine. *J Clin Oncol.* (2017) 35:3433–9. doi: 10.1200/jco.2016.71.6605

45. Demaria O, Cornen S, Daëron M, Morel Y, Medzhitov R, Vivier E. Harnessing innate immunity in cancer therapy. *Nature.* (2019) 574:45–56. doi: 10.1038/s41586-019-1593-5

46. Woo SR, Corrales L, Gajewski TF. Innate immune recognition of cancer. *Annu Rev Immunol.* (2015) 33:445–74. doi: 10.1146/annurev-immunol-032414-112043

47. Corrales L, Matson V, Flood B, Spranger S, Gajewski TF. Innate immune signaling and regulation in cancer immunotherapy. *Cell Res.* (2017) 27:96–108. doi: 10.1038/cr.2016.149

48. Oliveira G, Wu CJ. Dynamics and specificities of T cells in cancer immunotherapy. *Nat Rev Cancer.* (2023) 23:295–316. doi: 10.1038/s41568-023-00560-y

49. Martin KE, Hammer Q, Perica K, Sadelain M, Malmberg KJ. Engineering immune-evasive allogeneic cellular immunotherapies. *Nat Rev Immunol.* (2024) 24:680–93. doi: 10.1038/s41577-024-01022-8

50. Han Q, Shi H, Liu F. CD163(+) M2-type tumor-associated macrophage support the suppression of tumor-infiltrating T cells in osteosarcoma. *Int immunopharmacol.* (2016) 34:101–6. doi: 10.1016/j.intimp.2016.01.023

51. Sundara YT, Kostine M, Cleven AH, Bovée JV, Schilham MW, Cleton-Jansen AM. Increased PD-L1 and T-cell infiltration in the presence of HLA class I expression in metastatic high-grade osteosarcoma: a rationale for T-cell-based immunotherapy. *Cancer immunol immunother: CII.* (2017) 66:119–28. doi: 10.1007/s00262-016-1925-3

52. Khosravi GR, Mostafavi S, Bastan S, Ebrahimi N, Gharibvand RS, Eskandari N. Immunologic tumor microenvironment modulators for turning cold tumors hot. *Cancer Commun (London England).* (2024) 44:521–53. doi: 10.1002/cac2.12539

53. Wu CC, Beird HC, Andrew Livingston J, Advani S, Mitra A, Cao S, et al. Immuno-genomic landscape of osteosarcoma. *Nat Commun.* (2020) 11:1008. doi: 10.1038/s41467-020-14646-w

54. Bakhtiyaridovvombaygi M, Yazdanparast S, Mikanik F, Izadpanah A, Parkhideh S, Shahbaz Ghasabeh A, et al. Cytokine-Induced Memory-Like NK Cells: Emerging strategy for AML immunotherapy. *Biomed pharmacother = Biomed pharmacotherapie.* (2023) 168:115718. doi: 10.1016/j.biopha.2023.115718

55. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. *Cell Mol Immunol.* (2020) 17:807–21. doi: 10.1038/s41423-020-0488-6

56. Wherry EJ. T cell exhaustion. *Nat Immunol.* (2011) 12:492–9. doi: 10.1038/ni.2035
57. Wilky BA. Immune checkpoint inhibitors: The linchpins of modern immunotherapy. *Immunol Rev.* (2019) 290:6–23. doi: 10.1111/imr.12766
58. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell.* (2015) 161:205–14. doi: 10.1016/j.cell.2015.03.030
59. Sharma P, Allison JP. The future of immune checkpoint therapy. *Sci (New York NY).* (2015) 348:56–61. doi: 10.1126/science.aaa8172
60. Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. *J Exp Med.* (1995) 182:459–65. doi: 10.1084/jem.182.2.459
61. Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. *Int Immunol.* (2007) 19:813–24. doi: 10.1093/intimm/dxm057
62. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *New Engl J Med.* (2012) 366:2455–65. doi: 10.1056/NEJMoa1200694
63. Wen Y, Tang F, Tu C, Hornicek F, Duan Z, Min L. Immune checkpoints in osteosarcoma: Recent advances and therapeutic potential. *Cancer letters.* (2022) 547:215887. doi: 10.1016/j.canlet.2022.215887
64. Cheng JN, Jin Z, Su C, Jiang T, Zheng X, Guo J, et al. Bone metastases diminish extraosseous response to checkpoint blockade immunotherapy through osteopontin-producing osteoclasts. *Cancer Cell.* (2025) 43(6):1093–107. doi: 10.1016/j.ccell.2025.03.036
65. Mu H, Zhang Q, Zuo D, Wang J, Tao Y, Li Z, et al. Methionine intervention induces PD-L1 expression to enhance the immune checkpoint therapy response in MTAP-deleted osteosarcoma. *Cell Rep Med.* (2025) 6:101977. doi: 10.1016/j.xcrm.2025.101977
66. Gross G, Waks T, Eshhar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. *Proc Natl Acad Sci U S A.* (1989) 86:10024–8. doi: 10.1073/pnas.86.24.10024
67. Rainusso N, Brawley VS, Ghazi A, Hicks MJ, Gottschalk S, Rosen JM, et al. Immunotherapy targeting HER2 with genetically modified T cells eliminates tumor-initiating cells in osteosarcoma. *Cancer Gene Ther.* (2012) 19:212–7. doi: 10.1038/cgt.2011.83
68. Ahmed N, Brawley VS, Hegde M, Robertson C, Ghazi A, Gerken C, et al. Human epidermal growth factor receptor 2 (HER2) -specific chimeric antigen receptor-modified T cells for the immunotherapy of HER2-positive sarcoma. *J Clin Oncol.* (2015) 33:1688–96. doi: 10.1200/jco.2014.58.0225
69. Brentjens RJ, Davila ML, Riviere I, Park J, Wang X, Cowell LG, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci Trans Med.* (2013) 5:177ra38. doi: 10.1126/scitranslmed.3005930
70. Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *New Engl J Med.* (2011) 365:725–33. doi: 10.1056/NEJMoa1103849
71. Fowler D, Barisa M, Southern A, Nattress C, Hawkins E, Vassalou E, et al. Payload-delivering engineered $\gamma\delta$ T cells display enhanced cytotoxicity, persistence, and efficacy in preclinical models of osteosarcoma. *Sci Trans Med.* (2024) 16:eadg9814. doi: 10.1126/scitranslmed.adg9814
72. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *New Engl J Med.* (2007) 356:1915–27. doi: 10.1056/NEJMoa061741
73. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *New Engl J Med.* (2010) 363:411–22. doi: 10.1056/NEJMoa1001294
74. Alsalloum A, Shevchenko JA, Sennikov S. NY-ESO-1 antigen: A promising frontier in cancer immunotherapy. *Clin Trans Med.* (2024) 14:e70020. doi: 10.1002/ctm2.70020
75. Choi K, Jeong H, Lee DH, Lee JW, Hong JE, Baek JE, et al. Innovative cancer immunotherapy with MAGE-A3 mRNA cancer vaccines. *Cancers.* (2024) 16(19):3428. doi: 10.3390/cancers16193428
76. de Groen RAL, de Groot FA, Böhringer S, Kret EJ, de Haan LM, Noordenbos T, et al. Superior survival in diffuse large B cell lymphoma of the bone with immune rich tumor microenvironment. *Blood Cancer J.* (2025) 15:82. doi: 10.1038/s41408-025-01291-z
77. Russell SJ, Peng KW, Bell JC. Oncolytic virotherapy. *Nat Biotechnol.* (2012) 30:658–70. doi: 10.1038/nbt.2287
78. LaRocca CJ, Warner SG. Oncolytic viruses and checkpoint inhibitors: combination therapy in clinical trials. *Clin Trans Med.* (2018) 7:35. doi: 10.1186/s40169-018-0214-5
79. Lichty BD, Breitbach CJ, Stojdl DF, Bell JC. Going viral with cancer immunotherapy. *Nat Rev Cancer.* (2014) 14:559–67. doi: 10.1038/nrc3770
80. Hietanen E, Koivu MKA, Susi P. Cytolytic properties and genome analysis of Rigvir[®] oncolytic virotherapy virus and other echovirus 7 isolates. *Viruses.* (2022) 14(3):525. doi: 10.3390/v14030525
81. Bommarreddy PK, Patel A, Hossain S, Kaufman HL. Talimogene laherparepvec (T-VEC) and other oncolytic viruses for the treatment of melanoma. *Am J Clin Dermatol.* (2017) 18:1–15. doi: 10.1007/s40257-016-0238-9
82. Chen GX, Zhang S, He XH, Liu SY, Ma C, Zou XP. Clinical utility of recombinant adenoviral human p53 gene therapy: current perspectives. *OncoTargets Ther.* (2014) 7:1901–9. doi: 10.2147/ott.S50483
83. Wei D, Xu J, Liu XY, Chen ZN, Bian H. Fighting cancer with viruses: oncolytic virus therapy in China. *Hum Gene Ther.* (2018) 29:151–9. doi: 10.1089/hum.2017.212