Bone niche-driven antitumor immune failure in osteosarcoma: Mechanisms and therapeutic implications (Review)

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Abstract. Osteosarcoma (OS) remains a clinically challenging primary malignant bone tumor that occurs predominantly in children, adolescents and young adults. Despite standard multimodal therapy, recurrent, metastatic and chemotherapy-refractory disease continues to have poor outcomes, and pulmonary recurrence remains a dominant cause of mortality. Tumor cell-intrinsic alterations, including genomic instability, clonal heterogeneity, stem-like plasticity and chemoresistance, explain important aspects of disease aggressiveness; however, they do not fully account for the limited responses to immune checkpoint blockade or engineered cellular therapies, nor for the high frequency of lung relapse after apparently adequate local control. The current review presents an evidence-graded bone niche-driven framework of layered antitumor immune failure in OS. In this model, the skeletal niche is not treated as a passive anatomical background but as a spatial and temporal organizer of immune-cell trafficking, myeloid remodeling, treatment-induced repair programs, systemic niche communication and pulmonary immune surveillance. Bone niche remodeling and myeloid-cell enrichment constitute the most mature mechanistic anchors, whereas pulmonary niche conditioning, efferocytosis, extracellular vesicle (EV)-mediated bone-lung signaling, and physical or metabolic stress adaptation are presented as emerging or hypothesis-generating modules. To prevent conceptual overextension, direct OS evidence is separated from contextual tumor-biology evidence and aligned with each claim, along with its current gap and a falsifiable validation route. Translationally, the framework supports a timed sequence of niche reprogramming, immune activation, and pulmonary niche maintenance, to be tested through perioperative window studies, paired primary-tumor and lung-metastasis cohorts, functional perturbation experiments, spatial immune profiling, circulating EV/chemokine monitoring and predefined pulmonary recurrence endpoints.

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Abbreviations: OS, osteosarcoma; TME, tumor microenvironment; TAM, tumor-associated macrophage; EV, extracellular vesicle; ECM, extracellular matrix; MSC, mesenchymal stromal cell; gMDSC, granulocytic myeloid-derived suppressor cell; NK, natural killer; CAR, chimeric antigen receptor; MHC, major histocompatibility complex; PD-L1, programmed death-ligand 1; B7-H3, B7 homolog 3; TGF-β, transforming growth factor-β; RANKL, receptor activator of nuclear factor κB ligand; CCL5, C-C motif chemokine ligand 5; CXCL10, C-X-C motif chemokine ligand 10; Gas6, growth arrest-specific 6; MerTK/MERTK, MER proto-oncogene tyrosine kinase; AXL, AXL receptor tyrosine kinase

Key words: OS, bone niche, layered antitumor immune failure, tumor immune microenvironment, pulmonary recurrence

Contents

1. Introduction

Osteosarcoma (OS) remains the most common primary malignant bone tumor in children, adolescents and young adults (1). Standard treatment consists of neoadjuvant chemotherapy, complete surgical resection and postoperative chemotherapy (2). However, outcomes remain poor in recurrent, metastatic or chemotherapy-refractory disease (2). Pulmonary metastasis and recurrence remain the principal causes of OS-related mortality (1,2). OS has shown a limited response to immunotherapies that have revolutionized the treatment of other solid tumors (for example, anti-programmed cell death protein 1 immune checkpoint inhibitors have revolutionized the treatment of melanoma and non-small cell lung cancer) suggesting that therapeutic failure is multifactorial rather than attributable to a single biological defect (3,4).

Traditional explanations have emphasized tumor cell-intrinsic mechanisms, such as genomic instability and clonal evolution (5). These mechanisms are interconnected, but they do not fully account for several long-standing clinical observations (6). Immune-cell infiltration is evident in a subset of OS tumors; however, its presence does not necessarily translate into durable tumor clearance (7,8). Similarly, technically successful local control does not assure freedom from pulmonary recurrence (1,2). Despite employing different mechanisms, immune checkpoint blockades, engineered cellular therapies and combination strategies often yield modest and inconsistent clinical benefits (3,6,9,10). Thus, tumor cell-intrinsic biology explains an important component of OS aggressiveness but has limited explanatory scope when considered in isolation (9).

Recent advances in single-cell, spatial and multi-omics studies support a more tissue-specific interpretation of OS biology (11,12). OS arises within a complex skeletal microenvironment rather than at a generic tumor site (13). Mineralized matrix, marrow-derived cells, abnormal vasculature, stromal populations and immune signals may interact to regulate immune-cell trafficking, local immune suppression and pulmonary niche remodeling (14). This interpretation is supported by recent cellular atlases, tumor microenvironment studies and analyses of pulmonary metastases (11-15).

In the present review, layered antitumor immune failure refers to the progressive accumulation of defects in immune cell trafficking, antigen presentation, effector activation, cytotoxic elimination of tumor cells and pulmonary immune surveillance. This term is used as an organizational concept rather than as a replacement for established concepts such as immunosuppression, immune exclusion or immunologically cold tumors (8,16).

Layered antitumor immune failure differs from immune exclusion or an immunologically cold phenotype in that it emphasizes the spatial and temporal accumulation of defects across the primary bone niche, treatment-induced tissue repair programs, systemic niche communication and pulmonary immune surveillance. The term therefore describes not only insufficient immune activation, but also the misdirection of immune activity toward non-eradicating, repair-associated or metastasis-permissive programs. This concept explains the presence of measurable immune activity in OS, yet the failure of this cancer to succeed across the downstream checkpoints needed to achieve durable tumor elimination and prevent relapse.

The term 'bone niche-driven' is used in the present review in a qualified sense. This does not mean that the bone niche has been established as a universal or exclusive causal driver of immune failure in OS. Rather, it is an evidence-based framework through which the structural, cellular, stromal and metabolic features of the skeletal niche may orchestrate multiple levels of antitumor immune dysfunction.

Therefore, the present review tracks the biological progression of OS, rather than simply cataloguing immune abnormalities. The suggested sequence involves bone niche remodeling, myeloid cell predominance, tolerogenic processing of therapy-induced cell death, extracellular vesicle (EV)-mediated niche communication, physical and metabolic adaptation, and pulmonary niche conditioning. These modules are synthesized from OS-specific evidence and contextual tumor-biology literature (8,11-14,16-21), with relatively mature evidence distinguished from hypothesis-generating or extrapolated mechanisms.

First, the present review recharacterizes OS immune resistance as a bone niche-organized process rather than a simple catalogue of immune cell abnormalities or therapeutic targets. Second, the theory of layered antitumor immune failure explains the coexistence of immune infiltration, local tumor control and immune activation with the failure of cytotoxic clearance and the delayed recurrence of pulmonary tumors. Third, it clearly separates direct evidence of OS from indirect evidence inferred from other bone tumors or from general solid tumor biology, thus minimizing the risk of overinterpreting causality in poorly validated modules. Fourth, the proposed framework is operationalized through claim evidence gap mapping, a minimal validation package, and trial design scenarios that prioritize longitudinal sampling, spatial functional readouts and pulmonary recurrence endpoints.

An OS-specific rationale supports a bone niche-centered framework of immune failure (14-17). Unlike most soft-tissue malignancies, OS develops within a mineralized matrix, osteoid-producing tissue and an actively remodeling marrow compartment (14,16,17). These anatomical and biological features impose several disease-specific constraints. First, the mineralized matrix and osteoid-rich architecture may restrict immune-cell access and impair effective T cell-tumor cell contact (14,16,21). Second, the marrow compartment is naturally enriched with myeloid progenitors, macrophages, osteoclast-lineage cells and mesenchymal stromal cells (MSCs), thereby favoring myeloid-dominant immune regulation (14,16-18). Third, bone remodeling, tissue repair and inflammatory resolution are tightly coupled, allowing therapy-induced cell death to be processed through repair-associated or tolerogenic programs (18). Fourth, bone-derived stromal, vascular and EV signals may communicate with the circulation and pulmonary microenvironment (15,19,20). Finally, pulmonary recurrence requires not only disseminated tumor cells but also permissive immune and stromal conditions in the lung (15,19-21). Together, these features support the view that the bone niche functions as an organizing variable in OS immune failure, rather than merely serving as a passive site of tumor growth.

2. Search strategy and evidence classification

The present review is a mechanistic, problem-oriented narrative review; its reporting and organization were informed by established guidance for narrative reviews (22) and the SANRA quality framework (23). PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/), and Scopus (https://www.scopus.com/). were searched using combinations of 'osteosarcoma', 'bone niche', 'tumor immune microenvironment', 'macrophage', 'efferocytosis', 'extracellular vesicles', 'premetastatic niche', 'metabolic reprogramming' and 'immunotherapy resistance'. The last search was updated to April 2026. As the review aimed to develop and refine a mechanistic framework rather than to quantify pooled effects, no quantitative search protocol was preregistered. Mechanistic studies in English, and single-cell and spatial-omics studies, animal models, clinical specimens, translational therapy studies and high-quality reviews were prioritized. Detailed search strings and key inclusion criteria are provided in Table SI.

Since the aim was framework construction rather than quantitative synthesis, a meta-analysis or a formal risk-of-bias assessment was not performed. Candidate sources were first screened for topic relevance, and then re-evaluated for OS specificity, mechanistic support, functional or spatial validation, and translational value. At least two authors reviewed the key evidence domains, and evidence classification was finalized by consensus of the authors; disagreements were resolved by discussion. The reference list was restricted to sources that directly supported a mechanistic or translational claim within the text, tables or figure legends; broad background articles were used only to clarify mechanistic context not yet directly validated in OS.

Evidence from other bone tumors or broader solid tumor literature was treated as contextual rather than as OS-specific proof. Given that the objective was conceptual synthesis rather than systematic evidence aggregation, the resulting framework should be interpreted as an author-derived, evidence-weighted organizational tool rather than as a validated grading system.

For the purposes of the present review, mechanistic evidence was separated from grading and translational maturity staging. Mechanistic evidence was graded according to OS specificity, functional validation, spatial or longitudinal support, and translational relevance (Table I). Tier 1 comprised the relatively better-supported OS-specific mechanisms of bone niche remodeling (11-14,17,24-26) and myeloid-cell enrichment (8,11,13,27-31). Tier 2 comprised OS-supported but longitudinally or functionally incomplete mechanisms, including pulmonary premetastatic niche conditioning (15,19,20,32-34), efferocytosis-associated immune tolerance (18,35-37) and EV-mediated bone-lung communication (19,32,33,38-43). Tier 3 comprised mechanisms that remain largely associative, computational or extrapolated from broader tumor biology, including physical and metabolic immune adaptation (21,34,44-47). Translational maturity was staged separately as clinical, early translational, preclinical or conceptual (Table II).

The mechanistic synthesis was organized as a partially overlapping biological progression while preserving the evidence hierarchy. The sequence moves from the limitations of tumor cell-intrinsic explanations and the structural constraints of the primary bone niche to myeloid-cell remodeling, emerging efferocytosis and EV-mediated modules, metabolic adaptation, pulmonary niche conditioning and therapeutic implications. These modules should not be interpreted as a fixed unidirectional cascade; they may occur in parallel, overlap across disease stages or form feedback loops depending on treatment exposure and patient phenotype. For each module, the current strength of evidence, major uncertainties, priority validation strategies and falsifiable tests are indicated (Tables I and II).

3. Bone-niche constraints and myeloid remodeling

Limitations of tumor cell-intrinsic explanations. Tumor cell-intrinsic mechanisms are important but insufficient to explain the full pattern of therapeutic failure. Genomic instability contributes to tumor progression and treatment resistance (5), yet several persistent clinical observations remain incompletely explained (1,2,6). Immune infiltration may occur without durable tumor clearance (7,8), technically achievable local control may not prevent pulmonary recurrence (1,2), and immunotherapies directed at distinct proximal targets have generally produced limited and inconsistent clinical benefits (3,6,9,10).

This interpretation does not diminish the importance of tumor cell biology. Rather, it suggests that assigning explanatory primacy to tumor cell-intrinsic mechanisms alone may be insufficient to account for immune dysfunction and delayed pulmonary recurrence (4).

The skeletal niche may contribute earlier and more actively than implied by purely cancer cell-centric models (17,24). Rather than providing a detailed structural account in this section, the niche is used as an explanatory bridge: Immune infiltration can coexist with ineffective tumor clearance, local control can be followed by pulmonary recurrence and different immune-based therapies can encounter convergent microenvironmental constraints. These observations suggest that the relevant failure may involve not only malignant cell programs but also the spatial and cellular context in which antitumor immunity is organized. The structural, myeloid, efferocytic, EV-related, metabolic and pulmonary modules of this context are therefore considered in the following sections (Fig. 1).

Structural basis of immune failure in the bone niche. The bone niche not only provides the anatomical setting for OS growth and dissemination but also actively shapes the tumor microenvironment (TME), which may progressively acquire an immune-restricted and tumor-permissive state (4,24). Mineralized matrix and osteoid-rich architecture may restrict the spatial access of immune cells and affect drug distribution in certain contexts, whereas osteolytic remodeling may release matrix-bound growth factors that support malignant adaptation (4,24,25). Abnormal vasculature and mechanical stress may further promote invasion, repair-associated remodeling and immune tolerance (14,25). Thus, normal skeletal architecture may be converted into a structural barrier that limits early therapeutic efficacy.

Beyond these structural constraints, the bone marrow compartment adds an additional regulatory layer (26). Myeloid progenitors, macrophages, osteoclast precursors

Table I. Mechanistic evidence grading matrix of the bone niche-driven framework.

Module	Mechanistic evidence tier	Evidence source	Main limitation	Validation priority	(Refs.)
Bone niche remodeling	Tier 1: Relatively better-supported OS-specific mechanism	Bone TME, osteoimmune remodeling, bone-mimetic models and single-cell/spatial studies	Limited longitudinal causality across treatment stages	Paired pre-/post-treatment sampling and spatial functional validation	(11-14,17,24-27)
Myeloid cell enrichment/TAM remodeling	Tier 1: Relatively better-supported OS-specific mechanism	Macrophage-enriched OS lesions, TAM-related risk models and spatial immune-exclusion studies	State, compartment and patient-context dependence	Lineage-resolved perturbation and macrophage-state functional assays	(8,11,13,27-31)
Pulmonary niche conditioning	Tier 2: OS-supported but longitudinally uneven	Metastatic lung microenvironment studies and OS-derived EV/chemokine findings	Few longitudinal datasets pairing primary tumors with lung specimens	Paired primary tumor-lung cohorts, EV/chemokine monitoring and recurrence endpoints	(15,19,20,32-34)
Efferocytosis	Tier 2: Emerging and incompletely validated	MerTK/efferocytosis-associated OS studies and transcriptomic/spatial inference	Limited direct blockade and causality testing in OS	MERTK/AXL perturbation, dying-cell-state mapping and immune readouts	(18,35-37)
EV-mediated bone-lung communication	Tier 2: Emerging and incompletely validated	OS-derived small EVs, EV-packaged S100A11 and lung niche-related EV studies	Cargo enrichment or recipient-cell inference does not prove causality	Functional EV cargo experiments and recipient cell validation in OS models	(19,32,33,41-43)
Physical/metabolic immune adaptation	Tier 3: Hypothesis-generating or contextual evidence	Multi-omics, mitophagy, UPR, pyruvate metabolism, hypoxia and immune-signature studies	Mostly prognostic modeling or computational inference	Metabolic perturbation with antigen-presentation, T-cell, NK-cell and ICI-sensitivity readouts	(21,34,44-47)

OS, osteosarcoma; TME, tumor microenvironment; UPR, unfolded protein response; TAM, tumor-associated macrophage; EV, extracellular vesicle; MERTK, MER proto-oncogene tyrosine kinase; AXL, AXL receptor tyrosine kinase; ICI, immune checkpoint inhibitor; NK, natural killer.

Table II. Candidate niche-reprogramming strategies, translational maturity, safety considerations and trial windows.

Therapeutic step	Candidate intervention	Evidence stage[a]	Preferred trial window	Major feasibility/safety concern	Key readout or candidate context	(Refs.)
Niche reprogramming	TAM blockade/ repolarization or TAM recruitment inhibition	Preclinical to early translational	Neoadjuvant or perioperative window	Myelosuppression, infection risk, impaired tissue repair, macrophage-state plasticity	Macrophage-state shift, T-cell infiltration, cytokine profile; myeloid-enriched or immune-excluded tumors	(28,31,49,50)
Niche reprogramming	Gas6-MERTK/AXL or efferocytosis-related blockade	Preclinical/ conceptual in OS	Post-therapy cell death window or perioperative window	Interference with physiological clearance, inflammation control and wound healing	Antigen presentation, PD-L1 change, T-cell activation after therapy; tumors with tolerogenic processing of therapy-induced cell death	(18,35-37,58)
Niche reprogramming	TGF-β mitigation, ECM modulation or vascular normalization	Conceptual to preclinical	Neoadjuvant or pre-cell therapy window	Stromal toxicity, impaired bone or wound repair, uncertain dosing window	Cell trafficking, persistence, exhaustion, stromal barrier reduction; stromal-rich lesions with poor homing	(14,21,53,65)
Immune activation	B7-H3-directed therapy, CAR-T/CAR-NK or checkpoint-based combinations	Early translational; variable by modality	After partial niche relief or in biomarker-selected disease	Antigen heterogeneity, on-target/off-tumor toxicity, poor homing and limited persistence	Response durability, cytotoxic function and antigen-positive tumors after partial niche relief	(3,64,67)
Pulmonary niche maintenance	EV/chemokine monitoring, lung-directed NK cell-supportive approaches or postoperative immuno-modulation	Preclinical/ conceptual	Postoperative surveillance or high-risk maintenance	Pulmonary delivery toxicity, immune overactivation and biomarker instability	Pulmonary recurrence-free survival, circulating EV/ chemokine biomarkers, lung niche activity	(19,33,63, 68,69)
Implementation framework	Biomarker-guided perioperative or window-of-opportunity testing	Conceptual trial-design framework	Neoadjuvant, perioperative or early postoperative window	Causality, safety, timing and validation of predictive biomarkers	Patients selected by myeloid, EV/chemokine, spatial or metabolic profiles	(8,11,19,33, 44-47,61,62)

[a]Evidence stage was defined as follows: Clinical, as supported by OS clinical studies or trials; early translational, as supported by clinically oriented platforms or limited human-context evidence; preclinical, as supported primarily by cell, organoid, animal or delivery-model studies; and conceptual, proposed as a trial-design or biomarker-stratification strategy requiring prospective validation. OS, osteosarcoma; TAM, tumor-associated macrophage; EV, extracellular vesicle; MERTK, MER proto-oncogene tyrosine kinase; AXL, AXL receptor tyrosine kinase; NK, natural killer; TGF-β, transforming growth factor-β; CAR, chimeric antigen receptor; PD-L1, programmed death-ligand 1; B7-H3, B7 homolog 3; ECM, extracellular matrix; Gas6, growth arrest-specific 6.

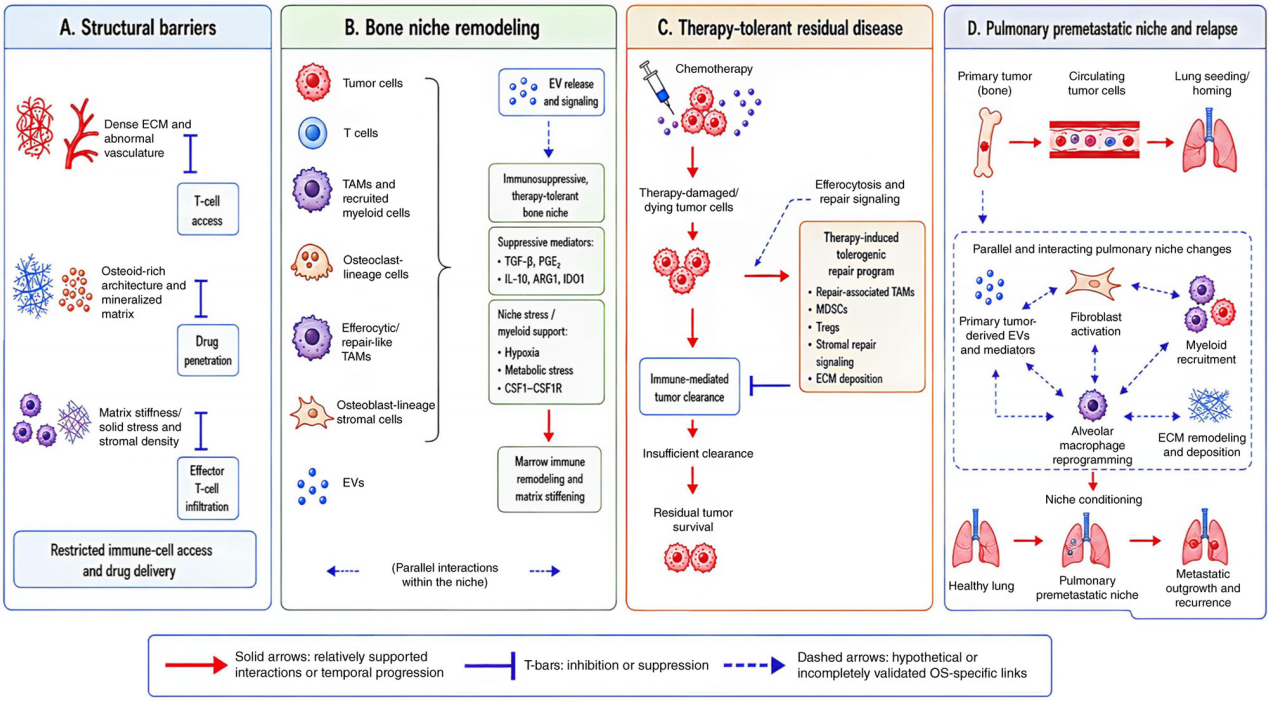

Figure 1. Bone niche-driven layered antitumor immune failure in OS. The schematic summarizes four partially overlapping layers: Structural restriction within mineralized or osteoid-rich bone; myeloid cell-predominant remodeling; tolerogenic processing of therapy-stressed or dying tumor cells; and systemic communication that may support pulmonary niche conditioning. Solid arrows indicate relatively better-supported OS-specific links, dashed arrows indicate candidate or hypothesis-generating links and the T-bar indicates inhibition or suppression. Figure created using BioRender. EV, extracellular vesicle; TAM, tumor-associated macrophage; IDO1, indoleamine 2,3-dioxygenase 1; ARG1, arginase 1; CSF1R, colony-stimulating factor 1 receptor; TGF-β, transforming growth factor-β; PGE_2, prostaglandin E2; LOX-1, lectin-like oxidised low-density lipoprotein receptor-1; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell; ECM, extracellular matrix; T cell, T lymphocyte; OS, osteosarcoma.

and immunomodulatory MSCs normally maintain skeletal homeostasis, tissue repair and regenerative remodeling (24). However, within the microenvironment of OS, these homeostatic programs may be co-opted to promote tumor persistence, immune evasion and stromal maintenance. Therefore, OS might exploit the intrinsic bone remodeling capacity rather than simply appear in defective tissue.

Such an interpretation is consistent with bone-mimetic experimental models (17). In co-culture systems comprising osteoid-like scaffolds and MSCs, the bone-like environment can promote OS cell proliferation, activate stemness-associated programs, stimulate matrix production and remodel the extracellular matrix (ECM) (17). These results suggest that the niche is not biologically passive. Instead, osteoid-like structures and stromal interactions may exert selective microenvironmental pressures that reinforce malignant adaptation and promote an invasive, immune-evasive tissue state (17).

Osteogenic and osteoclast-lineage cells coordinate bone modeling and remodeling via the receptor activator of nuclear factor κB ligand (RANKL)/RANK/osteoprotegerin system (48) under physiological conditions. This homeostatic program may be reprogrammed to support tumor signaling, immune regulation and metastatic progression in OS (24,25). This implies that biological processes that, under normal conditions, preserve skeletal integrity may, under malignant stress, contribute to tumor maintenance.

Bone niche remodeling is one of the more mechanistically well-supported anchors of the model (4,11-14,17,24,25) among the modules considered within the present review. It proposes a plausible link among structural constraints, myeloid accumulation, altered immunological handling of dying tumor cells, EV release, metabolic stress and conditioning of the pulmonary niche.

This integrative sequence is a synthesis of evidence across distinct modules rather than a single experimentally established cascade (17-19,21,33). Beyond a local anatomical context, the remodeled bone niche may connect tissue architecture to systemic relapse mechanisms, thereby linking skeletal turnover, immunosuppressive remodeling and metastatic preparation within a sustained pattern of treatment failure.

Myeloid cell-predominant local immune remodeling. OS does not arise within an immunologically inert tissue bed (49). Compared with several soft-tissue malignancies, it develops in an actively remodeling bone marrow compartment enriched in myeloid progenitors, bone marrow macrophages, osteoclast precursors and immunomodulatory MSCs (28). Myeloid cell enrichment may therefore be embedded within the baseline cellular architecture of the OS niche rather than merely representing a late consequence of tumor progression (49).

Within this bone marrow niche, tumor-associated macrophages (TAMs) occupy a potentially consequential regulatory position (29). OS lesions are frequently macrophage-enriched, and TAMs participate in antigen processing, inflammatory regulation, matrix remodeling, angiogenic remodeling and adaptive immune regulation (30). The function of TAMs cannot, therefore, be reduced to the conventional label of 'immunosuppressive cells'. More precisely, TAMs constitute

a multifunctional regulatory population through which skeletal remodeling, impaired antitumor immunity, stromal adaptation and therapeutic failure may become biologically interconnected (29).

The binary M1/M2 dichotomy is also likely to be overly restrictive in this setting (50). Macrophages occupy a functional continuum, an observation that is particularly relevant in OS, where macrophage-rich and immune-excluded niches have been identified (8,11,13,27,31). TAM-fibroblast crosstalk, antigen-presenting macrophage states, and perivascular macrophage or endothelial-associated niches may alter T-cell localization, activation thresholds and exhaustion-like phenotypes (11,13,28,51,52). Macrophages may therefore reshape the spatial and functional organization of antitumor immunity rather than uniformly suppress it.

This interpretation has therapeutic implications (53). In OS, T-cell dysfunction may arise less from an autonomous defect in T cells than from a surrounding microenvironment dominated by suppressive myeloid, stromal, vascular and metabolic constraints (8). Even when effector T cells are present, their spatial access to tumor cells and their capacity to form productive cytotoxic contacts may remain limited (8). Impaired antigen presentation, myeloid-derived inhibitory signals, stromal immune exclusion, aberrant vasculature and metabolic deprivation may collectively reduce cytotoxic efficacy. Failure of T-cell-directed therapy may therefore reflect persistent myeloid-dominated tissue regulation and insufficient downstream immune activation (50).

TAMs may consequently represent a rational therapeutic entry point, particularly in myeloid-rich tumors (28,29,31,49). This rationale is supported by OS-specific datasets and by broader immuno-oncology evidence linking macrophage states to immune exclusion, treatment resistance and metastatic progression (50,51). The importance of the TAM axis lies in its ability to integrate local immunosuppression, dying cell clearance, extracellular communication, matrix remodeling and mechanisms of systemic recurrence (18,28,54). Targeting TAM recruitment or state may therefore provide a mechanistically coherent strategy when downstream T-cell activation remains constrained by a myeloid-dominated suppressive environment (49,50).

One candidate process through which myeloid remodeling may convert therapy-induced tumor cell death into immune tolerance is efferocytosis. Efferocytosis is the phagocytic clearance of apoptotic cells by macrophages and other phagocytes (55). Given that direct causal evidence in OS remains limited, this process is treated here as an emerging extension of the myeloid-remodeling framework rather than as an established mechanism.

4. Efferocytosis as a potential mediator of therapy-induced immune tolerance

In OS, efferocytosis may be particularly relevant since treatment-induced tumor cell death occurs within a bone tissue environment already characterized by repair, remodeling and resolution of inflammation (18). Physiologically, efferocytosis limits excessive inflammation and restores tissue integrity (55). Within the OS niche, however, this program may have different consequences. Clearance of dying tumor cells may trigger repair-associated signaling, reprogram macrophage activity, attenuate pro-inflammatory activation and weaken effective antitumor immune responses in selected contexts (18).

The central issue is not just whether M2-like polarization occurs after therapy, but why tumor cell death from chemotherapy, radiotherapy or thermal damage does not consistently result in long-lasting immune-mediated tumor clearance (18,56). In healthy tissues, efferocytosis terminates inflammation and maintains tissue architecture (55). In OS, such a clearance program could also promote immune tolerance at a time when an immunogenic activation would be therapeutically desirable. Thus, therapy-induced cell death may provide a substrate for repair-associated immunosuppression in specific conditions of the bone niche (18).

Direct OS data link MER proto-oncogene tyrosine kinase (MerTK)-mediated efferocytosis with M2-like macrophage polarization, programmed death-ligand 1 (PD-L1) induction and immune-tolerant progression (18), and an MAGEA11-growth arrest-specific 6 (Gas6)-MERTK/AXL receptor tyrosine kinase (AXL) transcriptomic signature has been associated with prognostic and immune landscape features (35). The broader efferocytosis and TAM-receptor literature supports biological plausibility, but it remains contextual (36,37,57,58). The priority is therefore not further correlation, but treatment stage-specific perturbation that tests whether this pathway affects antigen presentation and effector activation.

At present, efferocytosis is well positioned as a testable link between therapy-induced tumor cell death and myeloid tolerance. Enhanced framework integration will require paired pre- and post-treatment specimens, dying cell state mapping, and direct evaluation of whether Gas6-MERTK/AXL modulations improve T-cell infiltration, cytotoxic contact or antigen presentation beyond tumor burden reduction.

5. Extracellular vesicles as a candidate bone-lung communication axis

EVs are increasingly recognized as active mediators rather than inert tumor-derived secretions (38); they may transmit signals originating from the primary bone TME beyond the local lesion (39). Experimental observations suggest that EV cargo can influence skeletal remodeling, stromal activation, myeloid suppression, vascular remodeling and metabolic reprogramming (40). Through this vesicle-mediated exchange, primary OS may communicate with circulating and pulmonary cell populations (32).

Across sarcoma and broader tumor literature, EVs may modulate macrophage polarization, alter dendritic cell maturation, affect the cytotoxic function of natural killer (NK) cells and $CD8^+$ T cells, activate cancer-associated fibroblasts, remodel vasculature and reorganize the ECM (38-40). These effects likely reflect population-level vesicle signaling rather than the action of individual vesicles. Collectively, EV-mediated communication may contribute to a matrix-rich, immunosuppressive and invasion-permissive microenvironment; however, not all these effects have been functionally validated in OS.

A particularly important but incompletely validated question concerns the pulmonary activity of OS-derived

EVs (19,32,33,41). These vesicles may target pulmonary fibroblasts, alveolar macrophages, endothelial cells and bone marrow-derived myeloid populations, thus favoring stromal activation, ECM remodeling and the recruitment or reprogramming of immunosuppressive myeloid cells. EV-packaged S100A11 provides direct, OS-specific evidence of pulmonary granulocytic myeloid-derived suppressor cell (gMDSC) recruitment and premetastatic niche formation (33). In some settings, EV-mediated conditioning may precede, rather than simply accompany, radiologically detectable metastatic colonization (19,32,33).

Current OS data support the role of EVs in pulmonary niche remodeling, gMDSC recruitment and inflammatory stromal conditioning (19,32,33,41). The stronger assertion that EVs mediate a lasting bone-lung program driving relapse still requires paired primary blood-lung sampling and perturbation of defined cargo, as cargo enrichment and inferred recipient cell interactions alone do not establish causality (33,34).

Key validation studies should include EV depletion or cargo perturbation, pulmonary recipient cell mapping, alveolar macrophage and fibroblast functional endpoints, and pulmonary recurrence endpoints. Until then, EVs provide a feasible bone-lung communication module, but not a stand-alone explanation for pulmonary metastasis.

6. Physical and metabolic stress adaptation in the osteosarcoma niche

Metabolic reprogramming should not be interpreted solely as an autonomous consequence of accelerated tumor proliferation (21). Instead, it should be considered within the physical, vascular and metabolic constraints imposed by the OS bone niche. Mineralized matrix, aberrant ECM deposition, increased tissue stiffness, hypoxia, heterogeneous perfusion, nutrient competition and acidic metabolic waste may jointly impose selective pressures on both malignant and immune cells. These constraints can limit oxygen and substrate availability, impair perfusion, and reshape tumor cell adaptation and immune cell function (21).

OS studies have associated GABA type A receptor-associated protein-mediated mitophagy and pyruvate-metabolism programs with disease progression (44), endoplasmic reticulum (ER) stress and unfolded protein response-related signatures with prognosis and therapy resistance (45,47), BCL2 interacting protein 3 (BNIP3)-related hypoxic and mitophagy programs with immune features (46), and tumor-microenvironmental cell communication with metastatic behavior (34). These studies provide useful stratification signals but do not by themselves establish direct metabolic suppression of antitumor immunity; they may instead reflect proliferation, regional hypoxia, necrotic burden, therapy-induced clonal selection or general aggressiveness rather than immune escape itself (21,34,44-47,59).

Causal testing should ask whether metabolic perturbation restores major histocompatibility complex (MHC) expression, antigen presentation, T-cell infiltration, NK cell activity, immune checkpoint sensitivity or control of pulmonary recurrence, independently of tumor burden reduction (21,47).

Physical and metabolic stress adaptation is therefore retained as a lower-tier extension of the framework; it should be upgraded only when perturbation studies link metabolic or mechanical constraints to immune recognition, effector function and recurrence-related endpoints (21,34).

7. Pulmonary premetastatic niche formation and recurrence

The pulmonary premetastatic niche should not be seen as merely a result of metastatic disease; it might also be a distant indication of systemic conditioning from the initial bone lesion (60). Myeloid-mediated immunosuppression, EV-mediated communication, chemokine network remodeling, ECM reorganization, mechanical cues and hypoxia-associated stress may converge prior to radiographically visible metastatic expansion. Such activities may therefore generate a permissive pulmonary milieu that enables survival, lodging and subsequent proliferation of disseminated OS cells (15,60).

Pulmonary metastasis is the most common cause of death due to OS (1,2), although the processes dictating whether disseminated cells survive and proliferate are still not well understood. The lung can serve as the physical site of tumor cell spread, but also as a conditioned milieu comprising inflammatory, stromal, vascular and myeloid changes preceding detectable metastatic development (15,60). Therefore, biological relapses may precede clinical or radiographic recurrence.

Potential mediators include chemokines, EV cargo, macrophage-derived signals and other soluble components. C-C motif chemokine ligand 5 (CCL5) has been associated with OS development and immune-stromal interactions, suggesting a potential, rather than established, role in promoting a metastasis-permissive milieu (61). C-X-C motif chemokine ligand 10 (CXCL10)/C-X-C chemokine receptor type 3 signaling has been identified as a potential axis for regulating immune cell trafficking and metastatic behavior; however, its precise role in pulmonary niche conditioning remains unclear (62). Another way tumor-lung communication occurs is via OS-derived EVs, with direct data implicating EV cargo, pulmonary macrophages and gMDSC recruitment in stromal and immunological remodeling (19,32,33).

The core of this approach is temporal dynamics. Pulmonary niche conditioning may begin before radiographic metastases become detectable, and recurrence may reflect not only tumor-cell dissemination but also systemic conditioning of the lung by signals released from the primary tumor (60). Monitoring circulating biomarkers of pulmonary niche activity may therefore complement conventional assessment of the primary lesion, particularly during the perioperative period and post-chemotherapy surveillance. Treatment-induced inflammatory and stromal responses during these intervals may further modify metastatic permissiveness (60,63).

Pulmonary recurrence should nevertheless not be attributed exclusively to ongoing bone-lung communication. Occult micrometastatic dissemination, tumor cell dormancy and reactivation, therapy-driven clonal selection and tumor cell-intrinsic pulmonary tropism are alternative or complementary explanations. Studies of metastasis-initiating OS subpopulations and organotropic EV biology are conceptually consistent with some of these processes (20,43), but they do not establish the relative contribution of each mechanism. The proposed framework, therefore, distinguishes pulmonary

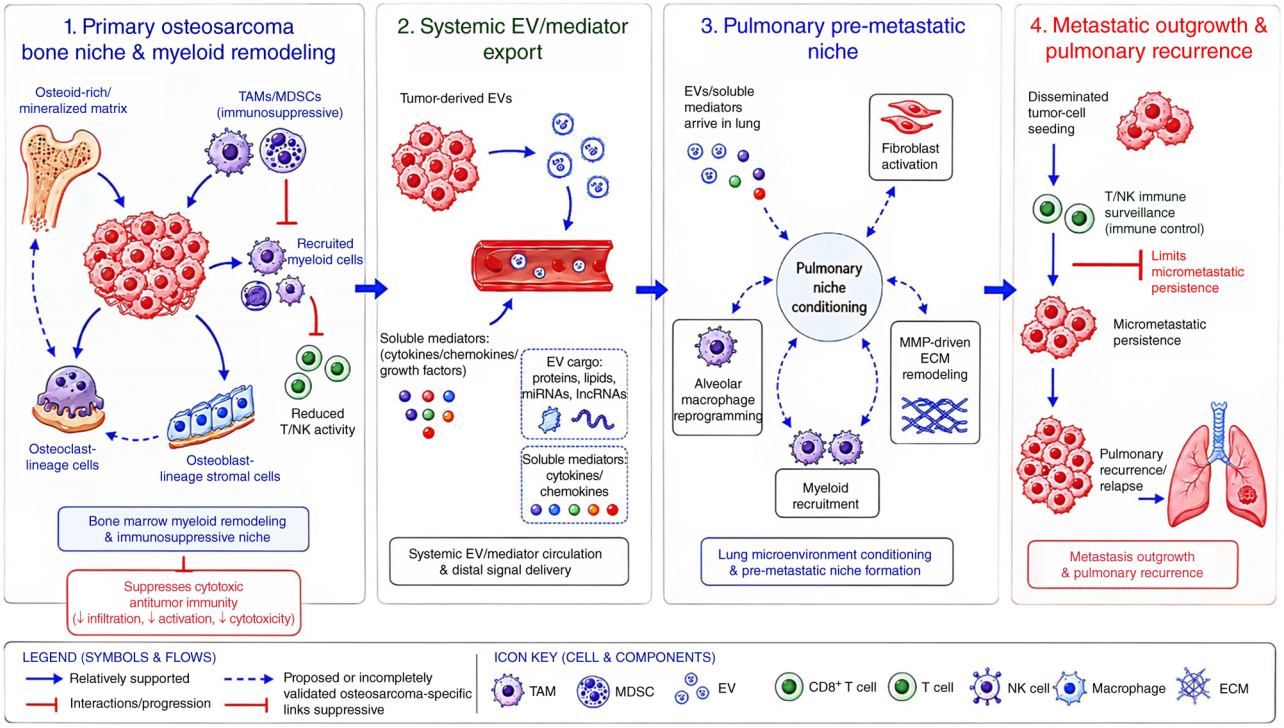

Figure 2. Proposed bone-circulation-lung axis linking primary OS niche remodeling to pulmonary premetastatic conditioning and recurrence progression. The schematic depicts primary bone niche remodeling, export of circulating EVs/chemokines, lung-niche conditioning, micrometastatic maintenance and metastatic outgrowth. Solid links indicate relatively better-supported OS evidence, dashed links indicate OS-supported candidate mechanisms, and dotted links indicate contextual extrapolation requiring functional validation. Figure created using BioRender. MDSC, myeloid-derived suppressor cell; EV, extracellular vesicle; CCL5, C-C motif chemokine ligand 5; CXCL10, C-X-C motif chemokine ligand 10; lncRNAs, long non-coding RNAs; ECM, extracellular matrix; Mϕ, macrophage; MMP, matrix metalloproteinase; DTC, disseminated tumor cell; MDSC, myeloid-derived suppressor cell; OS, osteosarcoma; TAM, tumor-associated macrophage; NK, natural killer; miRNA, microRNA.

premetastatic conditioning from micrometastatic maintenance and metastatic outgrowth. Longitudinal cohorts with paired primary tumors and lung specimens will be required to resolve these stages (Fig. 2).

8. Therapeutic implications, validation strategies and future perspectives

Therapeutic bottlenecks and sequential treatment logic. Chemotherapy, checkpoint blockade and engineered cellular therapies encounter distinct but partly convergent microenvironmental limitations (3). Chemotherapy can reduce tumor burden while leaving regenerative and immunosuppressive networks intact. Checkpoint blockade can attenuate inhibitory signaling but may act too late in immune-excluded or myeloid cell-predominant lesions (8). Chimeric antigen receptor (CAR)-T and CAR-NK cells provide antigen-specific cytotoxicity, yet their homing, persistence and effector function remain constrained by transforming growth factor-β (TGF-β) signaling, suppressive myeloid circuits, structural barriers, and physical or metabolic stress within the TME (64). These shared barriers suggest that therapeutic failure may occur upstream of final cytotoxic engagement.

These observations can be organized into a staged translational logic rather than a catalogue of experimental strategies. The first stage, niche reprogramming, aims to relieve dominant myeloid, stromal, EV-related or metabolic constraints before or alongside immune activation. Representative approaches include TAM recruitment blockade or state reprogramming, Gas6-MerTK/AXL-axis inhibition, TGF-β or stromal modulation, metabolic immunomodulation, and exploratory EV-directed strategies (18,19,21,28,31,35-37,49,58,65). These interventions should be interpreted as candidate approaches for testing whether niche-directed modulation can improve immune trafficking, antigen presentation and effector-cell function, rather than as established therapeutic requirements.

The second stage, immune activation, would deploy checkpoint blockade, B7 homolog 3 (B7-H3)-directed therapy, CAR-T/CAR-NK platforms, organoid-guided T-cell reconstruction or other engineered cellular approaches after at least partial relief of upstream constraints (3,64,66,67). This timing is intended to reduce the mismatch between downstream cytotoxic activation and an upstream immune-restrictive niche, although antigen heterogeneity, inefficient homing, limited persistence, stromal exclusion, metabolic stress and suppressive myeloid populations remain major barriers (64,67,68).

The third stage, pulmonary niche maintenance, focuses on high-risk relapse settings after local treatment or during minimal residual disease surveillance. EV/chemokine monitoring, lung-directed immune support, CAR macrophages generated *in situ* using EV-delivered mRNA, inhaled NK cell-supportive platforms and postoperative immunomodulatory strategies may be considered as investigational approaches, but this stage remains predominantly preclinical or conceptual (19,33,63,68,69). The preferred endpoint should

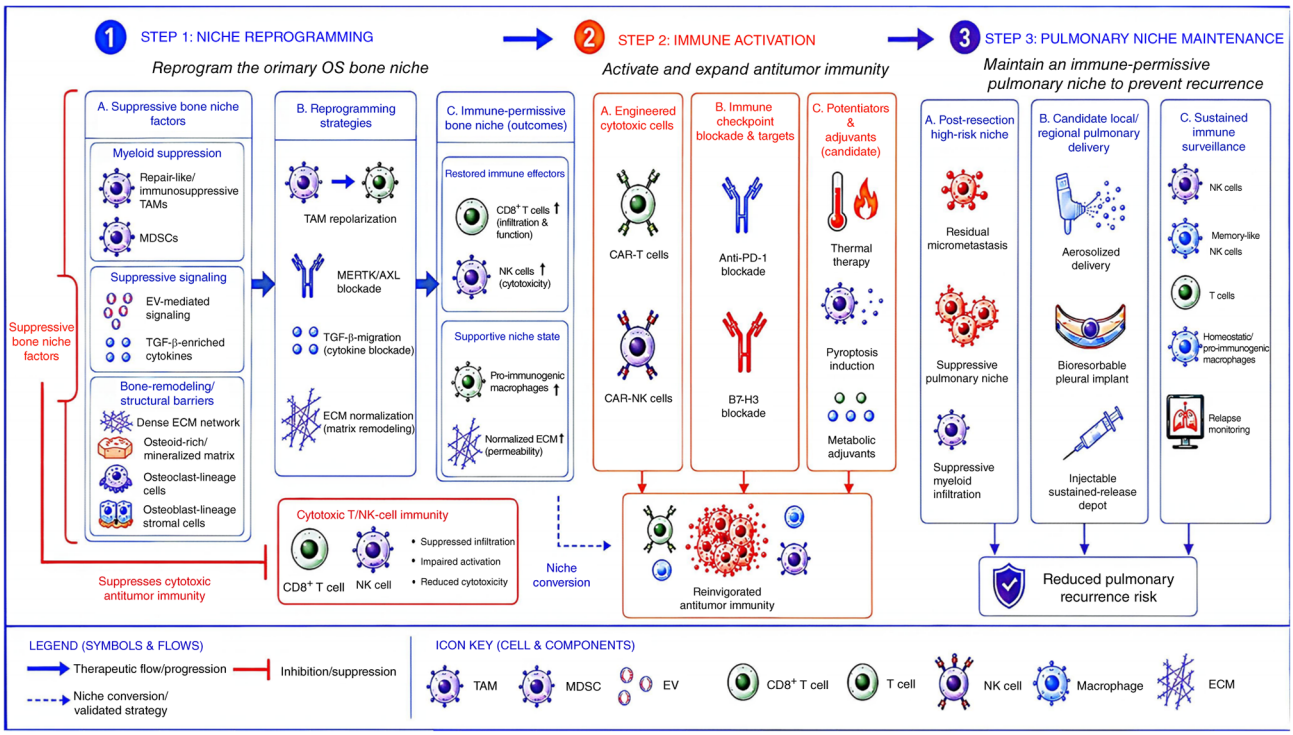

Figure 3. Conceptual three-step therapeutic sequence aligned with the proposed bone-lung immune axis in OS. Niche reprogramming during the neoadjuvant/perioperative window aims to relieve structural, myeloid, stromal, EV-related, or metabolic constraints; immune activation follows partial niche relief through checkpoint, B7-H3, CAR-T/CAR-NK or other engineered approaches; and pulmonary niche maintenance during postoperative minimal-residual-disease surveillance focuses on lung-directed immune support, EV/chemokine monitoring, NK cell-supportive platforms and relapse monitoring. The sequence is evidence-staged and should not be interpreted as an established clinical algorithm. Figure created using BioRender. TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cell; EV, extracellular vesicle; ECM, extracellular matrix; TME, tumor microenvironment; Gas6, growth arrest-specific 6; MERTK, MER proto-oncogene tyrosine kinase; AXL, AXL receptor tyrosine kinase; TGF-β, transforming growth factor-β; CAR, chimeric antigen receptor; ICB, immune checkpoint blockade; PD-1, programmed cell death protein 1; B7-H3, B7 homolog 3; NK, natural killer; OS, osteosarcoma.

shift from short-term tumor shrinkage alone to suppression of micrometastatic persistence and improvement in pulmonary recurrence-free survival.

Clinical implementation would require careful patient selection, explicit timing and predefined biological readouts. Candidate populations may include patients at high risk of perioperative pulmonary recurrence, patients with primary resistance to T-cell-directed immunotherapy, and patients whose tumors show myeloid enrichment, abnormal EV or chemokine profiles, or spatially organized suppressive niches (8,11,19,33,61,62,70). EV cargo, CCL5/CXCL10 profiles, macrophage-distribution patterns and spatial immune features may help identify candidates for niche reprogramming or pulmonary niche maintenance, but these biomarkers require prospective validation.

Accordingly, the proposed sequence should be regarded as a trial-design framework rather than a clinically established algorithm. Future studies should map candidate interventions to the phase in which they are most biologically plausible: Niche reprogramming before or during cytotoxic injury; immune activation after partial relief of upstream constraints; and pulmonary niche maintenance during postoperative surveillance or in high-risk minimal residual disease. Myeloid-enrichment biomarkers, spatial immune profiling, EV/chemokine monitoring, pulmonary recurrence endpoints and safety outcomes should be incorporated rather than relying solely on tumor-size response (Fig. 3; Table II).

Future directions and testable hypotheses. Efferocytosis should be explored as a potential proximal cause of immune suppression in specific OS cases (18,35). The impact of blocking Gas6-MERTK/AXL or related pathways on macrophage status, antigen presentation, PD-L1 expression and T-cell activation should be studied. Additionally, metabolism-associated decreases in immune recognition may exist in certain types of tumors; however, this is one of the least established sections of the model. Studies investigating mitophagy, BNIP3-mediated adaptability, ER stress or metabolic buffering should directly assess immune recognition, rather than merely tumor proliferation (44-47).

Third, the risk of pulmonary recurrence may potentially be classified prior to radiographic development. EV cargo, CCL5, CXCL10, spatial macrophage patterns and other niche-related traits are possible biomarkers. Prospective validation in cohorts with specific pulmonary outcomes is needed to evaluate their predictive value (19,33,61,62).

Fourth, spatial organization may be more informative than mean expression levels. 3D spatial transcriptomics and multimodal imaging can uncover compact suppressive niches of macrophages, fibroblasts, endothelial cells and defective lymphocytes (11,52,71). Such microenvironments may be better predictors of the response to therapy than bulk transcriptome averages; however, prospective predictive validation is yet to be shown. This approach can be operationalized using a claim evidence gap validation matrix (Table III) (72-77). A minimal validation strategy for a bone

Table III. Claim evidence gap validation matrix for the bone niche-driven framework.

Claim	Direct OS evidence	Contextual evidence	Current gap	Falsifiable validation test	(Refs.)
Bone niche remodeling restricts effective antitumor immunity	Single-cell/spatial atlases, bone TME studies and bone-mimetic models	Osteoimmunology and bone malignancy literature	Limited longitudinal evidence across neoadjuvant therapy, surgery and recurrence	Paired pre-/post-treatment spatial mapping showing that niche remodeling changes immune trafficking, tumor-cell contact, antigen presentation and recurrence risk	(11-14,17, 24-27)
Myeloid-rich niches impair downstream cytotoxic function	Macrophage-enriched lesions, immune-exclusion studies and TAM-related OS models	Pan-cancer TAM and macrophage-ecosystem literature	Unclear state-specific causality and patient-context dependence	Lineage-resolved TAM perturbation showing restored $CD8^+$ T-cell or NK cell function without merely reducing tumor burden	(8,11,13,27-31, 50,51,53)
Efferocytosis converts therapy-induced cell death into tolerance	MerTK/efferocytosis studies and OS transcriptomic patterns	TAM receptor and cancer efferocytosis literature	Few OS-specific blockade studies and little longitudinal dying cell state mapping	Gas6-MERTK/AXL perturbation after chemotherapy-induced cell death with antigen-presentation, PD-L1, TAM-state and T-cell-activation readouts	(18,35-37, 57,58)
EV-mediated bone-lung communication conditions pulmonary relapse	OS-derived EV studies, EV-packaged S100A11 and lung premetastatic-niche findings	Organotropic EV and premetastatic-niche literature	Cargo enrichment and recipient-cell inference do not prove causality; paired primary-lung data are scarce	EV depletion or cargo perturbation with recipient-cell validation in lung models and pulmonary recurrence-free survival endpoints	(19,32,33, 41-43,63)
Physical/metabolic stress suppresses immune recognition	OS multi-omics, mitophagy, UPR, pyruvate, BNIP3, hypoxia and immune-signature studies	Tumor ecology, hypoxia and metabolic immune-suppression literature	Mostly prognostic modeling or computational inference rather than direct immune causality	Metabolic perturbation coupled to MHC expression, antigen presentation, $CD8^+$ T-cell and NK cell assays, ICI sensitivity and lung recurrence endpoints	(21,34, 44-47,59)
Timed niche reprogramming improves immunotherapy efficacy	Macrophage-directed, B7-H3, organoid, biomaterial, hyperthermia, NK and engineered cell OS studies	Microenvironment-modulation and immunotherapy-combination literature	Optimal timing, safety and biomarker selection remain undefined	Biomarker-guided window or perioperative trials testing niche reprogramming before immune activation with safety and pulmonary recurrence endpoints	(49,53,56, 64-69,72-77)

This matrix separates claim strength from validation priority. A module should be upgraded only when perturbation changes immune trafficking, antigen presentation, effector-cell function or pulmonary recurrence risk beyond nonspecific tumor-burden reduction. OS, osteosarcoma; TAM, tumor-associated macrophage; EV, extracellular vesicle; MERTK, MER proto-oncogene tyrosine kinase; AXL, AXL receptor tyrosine kinase; NK, natural killer; PD-L1, programmed death-ligand 1; B7-H3, B7 homolog 3; Gas6, growth arrest-specific 6; TME, tumor microenvironment; UPR, unfolded protein response; MHC, major histocompatibility complex; BNIP3, BCL2 interacting protein 3; ICI, immune checkpoint inhibitor.

niche-driven framework should include paired pre- and post-treatment primary tumor specimens, circulating EV and chemokine profiling during neoadjuvant therapy and postoperative surveillance, matched pulmonary metastatic or recurrent specimens when available, and spatial mapping of myeloid, stromal, endothelial and T-cell compartments. In parallel, candidate pathways such as TAM recruitment, MerTK/AXL signaling, EV cargo transfer and metabolic stress adaptation should be tested through cell type-resolved perturbation models. The clinical relevance of this framework would be strengthened by predefined pulmonary recurrence endpoints and external validation in an independent cohort. Evidence would be particularly compelling if niche-directed disruption altered immune trafficking, antigen presentation, effector-cell function and pulmonary recurrence risk beyond changes in tumor burden alone.

Evidence hierarchy and model architecture. The present review argues that therapeutic resistance in OS and pulmonary relapse requires a tissue-specific explanation that extends beyond tumor cell intrinsic mechanisms. The bone niche provides a testable architecture in which structural barriers, marrow-derived myeloid enrichment, treatment-induced repair, extracellular communication, metabolic stress and pulmonary surveillance converge.

The evidence hierarchy is deliberately separated from therapeutic maturity. Bone niche remodeling and myeloid cell enrichment are the most mature OS-supported anchors; pulmonary niche conditioning, efferocytosis and EV-mediated bone-lung communication have growing but incomplete longitudinal or functional support, and physical/metabolic adaptation remains a lower-tier extension.

Accordingly, the framework should be read as a falsifiable model, not a fixed cascade; its modules may operate in parallel or only in selected molecular, immune, age-related or metastatic contexts, with Table III defining the claim evidence validation boundaries.

Heterogeneity, scope and patient context. OS is biologically and clinically heterogeneous; therefore, the proposed bone niche-driven framework should not be assumed to operate uniformly across all patients. Molecular subtypes, transcriptional states, immune infiltration patterns, age-related skeletal and immune contexts, chemotherapy response and metastatic trajectory may all influence the contribution of the bone niche to antitumor immune failure (11,13,27,70,78). Tumors with myeloid-enriched, immune-excluded or stromal-activated phenotypes may depend more on macrophage-centered regulation and niche-mediated immune restraint, whereas other tumors may be driven predominantly by tumor cell intrinsic genomic instability or therapy-resistant clonal evolution.

Pediatric, adolescent and adult patients may also differ in marrow composition, bone-remodeling activity, immune competence and treatment tolerance, which may modify the strength and timing of niche-mediated immune regulation. Similarly, chemotherapy-sensitive and -resistant tumors may differ in the immunological consequences of therapy-induced cell death, with dying tumor cells being processed through more immunogenic pathways in some contexts and through tolerogenic repair or efferocytosis-associated programs in others. Finally, localized disease, synchronous pulmonary metastasis and delayed pulmonary recurrence may reflect different degrees of primary bone lesion-lung communication. Therefore, the present framework should be viewed as a context-dependent and testable model that helps organize heterogeneous immune-failure patterns rather than as a universal mechanism shared by all patients with OS.

Bone niche reprogramming and integration with mainstream immunotherapy. Bone niche reprogramming can be viewed as a translational extension of the proposed framework. In the present review, bone niche reprogramming refers to the attempt to shift the OS microenvironment from a structurally constrained, myeloid-enriched, stromal-protective and metabolically suppressive state toward a more immune-permissive and therapeutically responsive state. This concept does not imply that niche-directed intervention should replace established or emerging immunotherapies. Rather, it suggests that the efficacy of immune activation strategies may depend, at least in part, on whether upstream bone niche constraints have been relieved.

This concept is particularly relevant to current immunotherapy approaches in OS. Immune checkpoint blockade may be insufficient when effector T cells remain spatially excluded, functionally exhausted or exposed to persistent myeloid and stromal inhibitory signals (3,6,8). B7-H3-targeted therapy and CAR-T or CAR-NK strategies may also be limited by poor homing, reduced persistence, antigen heterogeneity, TGF-β-rich stromal niches, metabolic stress and suppressive macrophage or MDSC populations (64,67). Bone niche reprogramming may therefore provide a rational preparatory step before immune activation. Candidate approaches include TAM repolarization or recruitment inhibition, Gas6-MERTK/AXL blockade, TGF-β mitigation, matrix or vascular normalization, EV-directed intervention and metabolic monosensitization (18,21,35-37,49,58,65). These strategies may help convert an immune-restricted bone lesion into a state in which immune-activating treatments can act more effectively, but most remain preclinical or early translational.

The same logic may apply in preventing pulmonary relapses. If the primary bone lesion releases EVs, chemokines and myeloid-recruiting signals that contribute to pulmonary niche conditioning, bone niche reprogramming may need to be considered together with pulmonary niche maintenance in selected high-risk patients (19,33). Local or regional lung-directed immune strategies, including CAR macrophages generated through EV-delivered mRNA and inhaled NK cell-supportive platforms, warrant investigation as relapse-prevention strategies (68,69). However, these approaches remain preclinical or early translational and should be evaluated in biomarker-guided perioperative studies, window-of-opportunity trials and longitudinal cohorts incorporating spatial immune readouts, EV/chemokine monitoring and pulmonary recurrence endpoints.

Testing and falsifying the bone niche-driven framework. Prespecified studies should test whether niche-directed perturbation improves immune trafficking, antigen presentation, effector-cell function or pulmonary niche quiescence beyond

tumor shrinkage alone. Failure to change these readouts after adequate pathway perturbation would restrict the model to specific phenotypes, windows or metastatic contexts.

A perioperative window study is the most direct first test: Paired pre- and post-neoadjuvant specimens should be profiled for TAM state, MerTK/AXL activity, PD-L1 induction, antigen-presentation markers, T cell-tumor spatial contact, stromal barriers and circulating EV/chemokine signals.

A primary-lung paired cohort should integrate primary tumor, serial blood EV/chemokine data, and pulmonary metastatic or recurrent tissue to determine whether primary bone niche states predict pulmonary myeloid recruitment, stromal activation, micrometastatic persistence and pulmonary recurrence-free survival.

Functional perturbation models should pair TAM modulation, Gas6-MERTK/AXL blockade, EV cargo perturbation, TGF-β or matrix modulation, and metabolic-stress intervention with antigen-presentation assays, $CD8^+$ T-cell and NK cell function, killing assays, and *in vivo* lung recurrence endpoints.

Potential trial-design scenarios. Table IV (72-77) translates the framework into three practical settings. In poor histological responders after neoadjuvant chemotherapy, perioperative profiling of TAM state, MerTK/AXL activation, PD-L1, tumor cell MHC and $CD8^+$ T-cell proximity could determine whether niche reprogramming should precede or accompany immune activation.

In high-risk localized disease after definitive surgery, serial EV cargo, CCL5/CXCL10, myeloid signatures and spatial features from the resected tumor could support pulmonary recurrence-prevention studies that use pulmonary recurrence-free survival rather than short-term shrinkage as the primary endpoint.

In pulmonary micrometastatic disease or early lung recurrence, the lung immune state, systemic EV/chemokine communication and cytotoxic cell function should be assessed alongside lung-directed immune support or engineered cell approaches, with predefined monitoring for pulmonary toxicity, immune overactivation, infection and impaired repair.

Limitations. The present review has limitations. As a mechanistic narrative review rather than a systematic review or meta-analysis, it was designed to construct and stress-test a conceptual framework, not to capture every eligible study, pool effects or formally grade risk of bias. Selection and evidence weighting, therefore, involve author judgment, and the proposed hierarchy should be viewed as a practical organizational tool rather than a validated grading system. The maturity of evidence is also uneven: Bone niche remodeling and myeloid cell enrichment have broader OS support, while efferocytosis, EV-mediated bone-lung communication and metabolic immune adaptation are more reliant on transcriptomic, computational, spatial-inference or limited functional data. Heterogeneity between patients, models, ages, treatment settings and illness stages further limits generalizability. Future validation will need a longitudinal sample, coupled with primary lung specimens, independent replication, lineage-resolved perturbation, clinically relevant immune readouts and predefined pulmonary recurrence endpoints.

Table IV. Practical trial-design scenarios for testing the bone niche-driven framework[a].

Scenario	Candidate population	Key biological assessment	Intervention window	Primary endpoint/readout
Poor histological response after neoadjuvant chemotherapy	Poor necrosis, residual viable or tumor persistent myeloid-enriched/immune-excluded spatial niche	TAM density and state; MerTK/AXL activity; PD-L1 induction; tumor-cell MHC expression; $CD8^+$ T-cell proximity to viable tumor cells	Perioperative or immediate post-chemotherapy window	Shift toward an immune-permissive niche, improved antigen presentation, effector-cell contact and recurrence-risk biomarkers
High-risk localized OS after definitive surgery	No visible lung disease but high-risk clinicopathological, spatial, EV or chemokine features	Serial circulating EV cargo; CCL5/CXCL10 profiles; myeloid signatures; spatial immune features in the resected tumor	Postoperative surveillance or minimal residual disease window	Pulmonary recurrence-free survival, biomarker stability and safety of maintenance immunomodulation
Pulmonary micrometastatic disease or early lung recurrence	Micrometastatic lung disease, early recurrence or high likelihood of pulmonary niche activation	Lung immune niche, alveolar-macrophage state, myeloid recruitment, systemic EV/chemokine communication and cytotoxic cell function	Lung-directed immune-support window or early recurrence treatment window	Pulmonary control, immune safety, pulmonary delivery toxicity, infection risk and micrometastatic persistence

[a]These scenarios are intended as trial-design templates rather than established treatment algorithms; they should be implemented only with prespecified biological readouts, pulmonary recurrence endpoints and safety monitoring. OS, osteosarcoma; TAM, tumor-associated macrophage; EV, extracellular vesicle; MERTK, MER proto-oncogene tyrosine kinase; AXL, AXL receptor tyrosine kinase; MHC, major histocompatibility complex; PD-L1, programmed death-ligand 1; CCL5, C-C motif chemokine ligand 5; CXCL10, C-X-C motif chemokine ligand 10.

9. Conclusion

The present review proposes an evidence-graded and testable bone niche-driven framework for understanding layered antitumor immune failure in OS. Within this framework, treatment resistance and pulmonary relapse may partly reflect the interaction of structural constraints within the bone niche, myeloid cell-predominant immune remodeling, tolerogenic processing of therapy-induced tumor cell death, systemic niche communication and impaired pulmonary immune surveillance. Bone niche remodeling and myeloid cell enrichment represent the relatively better-supported components of this model, whereas pulmonary niche conditioning is increasingly supported but remains uneven. Efferocytosis, EV-mediated bone-lung communication, and physical or metabolic immune adaptation remain emerging or hypothesis-generating modules that require OS-specific functional validation.

The principal translational implication is a shift from treatment intensification alone toward biologically timed intervention according to niche state. The proposed strategy follows a three-step sequence: Niche reprogramming to relieve upstream structural, stromal and myeloid immunosuppressive constraints; immune activation to restore effective antitumor responses; and pulmonary niche maintenance to limit disseminated-cell survival, micrometastatic persistence and pulmonary recurrence. This sequence should be regarded as a conceptual framework for biomarker-guided trial design rather than as an established clinical algorithm.

The model is unlikely to explain treatment failure uniformly across all patients. Its relevance may vary according to molecular subtype, age, immune and stromal phenotype, chemotherapy response and metastatic trajectory. Future studies should therefore combine longitudinal paired sampling of primary tumors and pulmonary metastases or recurrences, spatial and single-cell profiling, lineage-resolved functional perturbation, perioperative intervention studies and pulmonary recurrence endpoints. Such work will be required to distinguish causal mechanisms from associative signals and to define the patient and disease contexts in which bone niche-directed intervention may provide clinical value.

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Authors' contributions

BT and YW contributed to study conception, literature review, manuscript drafting and table organization. JL and RP supervised the study design, revised key academic content and approved the final manuscript. All authors contributed to writing and revising the manuscript. All authors read and approved the final version of the manuscript. JL is the primary corresponding author. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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