Table S1. Therapeutic Modalities to Treat Metastatic Bone Disease

Conventional Therapies

Modality	Examples	Effect on Bone	Possible Off-Target Effects
Surgical Interventions	Tumor Debulking Arthroplasty Limb Amputation Spinal Decompression	Bone Malformations Limb Removal Infection/Osteomyelitis Prosthesis Complications	Impaired Mobility Thrombosis Dermal Infection Nerve Damage Bleeding
Analgesic	Paracetamol (Acetaminophen)	Palliative Care for Bone Pain	Nausea Liver Damage Fatigue Paleness Diaphoresis
NSAIDs	Ibuoprofen Naproxin Celecoxib	Palliative Care for Bone Pain	Nausea Liver Damage Fatigue Hemorrhage Anemia Hypertension/Stroke
Corticosteroids	Dexamethasone Prednisolone Hydrocortisone	Palliative Care for Bone Pain Increase Bone Resorption Reduced Osteoblast and Osteocyte Function and Number Osteonecrosis Growth Deceleration (in Children)	Weight Gain/Cushingoid Features Irritability Suppression of Hormone Production via Hypothalamic-Pituitary Axis (Adrenal Atrophy) Neuropsychiatric/Depression Gastrointestinal Complications Liver Damage Cardiovascular Effects Skin Alterations Cataracts
Opiates	Tramadol Codeine Buprenorphine	Palliative Care for Bone Pain Increase Fall-Risk Induce Bone Loss	Addiction Nausea Constipation Vomiting Drowsiness
Chemotherapeutic Agents	Anti-Metabolites Taxanes Topoisomerases Proteasome Inhibitors	Impairment of Kidney Function Block Osteoblast Maturation Increase Bone Resorption	Anemia Fatigue Impaired Cognition Muscle Weakness
Hormone Deprivation	SERMs Aromatase Inhibitors Luteinizing Hormone Enzalutamide	Increase Osteoclast Activity Increase Bone Resorption Inhibit Androgen and Estrogen Synthesis Osteoporosis	Premature Menopause Muscle Weakness Fatigue
Anti-Resorptive Agents	Bisphosphonates Denosumab (α-RANKL)	Reduce Bone Turnover Block Osteoclast Activity Induce Osteoclast Apoptosis Reduce Bone Resorption	Prolonged Use Can lead to Osteonecrosis Prohibited Use in Adolescents Mild Anti-Tumor Effect in Bone Rebound Bone Resorption and Tumor Progression (following Denosumab holiday)

Anabolic Agents	*Parathyroid Hormone (PTH) Romosozumab (α-Sclerostin)	Induce Osteogenic Bone Growth Decrease Bone Resorption	Reduce Tumor Growth Stiffness Joint Pain Shortness of Breath Muscle Spasm ***Previous Black Box Warning Removed (PTH)**
Hyperthermia	n / a	Palliative Care for Bone Pain Inhibit Bone Destruction Induce Bone Formation	Thermal Damage, Blisters Discomfort Blood Clot Bleeding Bone Marrow Ablation Temporary Jaundice

Innovative Therapeutic Strategies

Modality	Examples	Effect on Bone	Possible Off-Target Effects
Small Molecule Inhibitors	TGF-β Inhibitors	Reduce Bone Resorption	Increase Cardiovascular Toxicity
Immunotherapeutic Agents	PD-1 / PD-L1 CTLA-4	Unknown	Secondary Inflammatory Response
Senescence	Senolytic Compounds	Reduce Bone Loss	Gastrointestinal Discomfort Shortness of Breath
Cryoablation	n/a	Palliative Care for Bone Pain Secondary Fracture Focal Loss of Bone	Thermal Damage to Adjacent Tissue Bone Marrow Damage
Radionuclide	$Radium^{223}$ $Samarium^{153}$ $Strontium^{89}$	Palliative Care for Bone Pain Destroy Progenitor Cells in Marrow	Anemia Risk of Infection Bruising
Radiofrequency Ablation	n / a	Palliative Care for Bone Pain	Thermal Damage to Adjacent Tissue from Probe
Palliative Pharmacologics	Corticosteroids Cannabinoids Tricyclic Anti-Depressants	Palliative Care for Bone Pain Increase Bone Resorption (Corticosteroids and Tricyclic Anti-Depressants)	Unknown

Table S2. Highly Specific Therapies to Target Metastatic Bone Disease (Not Discussed in the Main Text)

Therapeutic Target	Examples	References
Wingless Integrated (Wnt)	Wnt3a Wnt5a	• [247-250]
Dickkopf-1 (DKK-1)	BHQ880	• [251]
NOTCH	γ-Secretase Inhibitor	• [252-253]
Mammalian Target of Rapamycin (mTOR)	Everolimus	• [254-255]
Tyrosine Kinase Inhibitors (TKI) of:		• [256-262]
	<u>Kinase Inhibitor Target</u>	
Epidermal Growth Factor Receptor (EGFR)	Gefitinib - (EGFR)	
Human Epidermal Growth Factor Receptor Type 1,2 (HER1,2)	Lapatinib - (HER2/ERBB2) & (HER1)	
Rearranged During Transfection (RET)	Cabozantinib - (RET) (cMET) (VEGFR2)	
Mesenchymal Epithelial Transition (MET)	Bevacizumab - (VEGF-A)	
Vascular Endothelial Growth Factor-A (VEGF-A)	Imatinib - (BCR-ABL)	
Breakpoint Cluster Region (BCR)		
Ableson Murine Leukemia Virus (ABL)		
CD20 (B Cell)	Rituximab	• [263]

Epidermal Growth Factor Receptor (EGFR)	Trastuzumab Pertuzumab	• [264-266]
Nanomedicine	Caelyx (Doxorubicin in Liposome-Carrier) DepoVax SGT53 NK-105	• [267-268]

Additional References for Treatment of Metastatic Bone Disease

• [269-277]

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