Bone Health in Cancer Patients

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Contents

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Learning Objectives

By the end of chapter, the reader will

- Have learned the basic concept of bone metastasis physiopathology;
- Have reached in-depth knowledge of bone-targeted agents;
- Be able to put acquired knowledge into clinical practice in the management of bone metastatic patients.

24.1 Bone Metastases

Bone metastases are a common complication of several types of cancers, including breast, prostate, and lung cancer. The occurrence of bone metastases led to so-called skeletal-related events (SREs), which include pathological fractures, spinal cord compression, and severe bone pain that require palliative radiotherapy and/or orthopedic surgery [1]. These complications influence patients' quality of life, reducing mobility, social functioning, and overall survival (OS). The risk of bone fractures increases in patients of both sexes above the age of 70 years, even if postmenopausal women from age 50 years onward have a major risk to develop SREs compared to men [2, 3].

Bone metastases differ depending on their tumor origin and are divided in osteolytic (breast and lung cancers), sclerotic (prostate cancer), or mixed (gastrointestinal and squamous cancers) metastases. Tumor cells secrete factors that may disrupt physiological bone remodeling processes through the deregulation of the normal osteoclast and osteoblast functions. Indeed, osteolytic bone metastases are mediated by stimulation of osteoclast activity through tumor-derived cytokines, driving to bone matrix degradation [4]. Instead, sclerotic metastases are characterized by excessive abnormal bone formation mediated by activated osteoblasts, resulting in low bone strength. Mixed metastases present both sclerotic and osteoblast features.

The abnormal activity of osteoclasts and osteoblasts, responsible for bone metastasis development, lead to the release of mitogenic factors influencing tumor growth and establishing the so-called vicious cycle of cancer. The vicious cycle, described for the first time in 1997 by Mundy [5], is a complex process based on the interaction between tumor and bone cells, where the resorption/bone formation and tumor proliferation feed off each other.

24.2 Bone Metastasis Physiopathology

Bone is a dynamic tissue that undergoes a continuous vital process of remodeling made by bone cells: osteoblasts, osteoclasts, and osteocytes [6, 7]. These cells regulate the mineralization in a coordinating network responding to different stimuli such as mechanical load, cytokines, and hormonal signals. However, bone diseases, including tumors, alter the physiological balance between bone deposition and desorption, leading to the loss of the skeleton integrity.

Bone metastases development is a consequence of several complex mechanisms that include tumor cell seeding, tumor dormancy, and the subsequent metastatic growth.

In particular, some of cells released by primary tumor reach distant organs through the circulatory system, while the majority dies. Primary tumor itself can influence and alter the environment of secondary organs promoting the formation of supportive metastatic niche [8]. Bone metastatic niche represents the ideal site for dormant tumor cells (DTCs) stabilization, where they can survive in a dormant state stopping to proliferate or proliferating at a reduced rate. DTCs are resistant to cancer therapies and can remain in quiescence for long time, even beyond 10 years and then spread and colonize other organs [9]. The switch from dormant state to proliferative one is regulated by bone metastatic niche [10]. In particular, it was known that factors including vascular endothelial growth factor (VEGF), fibronectin, and matrix metalloproteinases (MMPs) secreted from myeloid cells in the niche promote the angiogenic switch necessary to tumor cell escape from dormancy [11]. Thus, the reactivated tumor cells establish a complex interplay with bone cells leading to the *vicious cycle* of cancer that support the subsequent metastatic growth (◘ Fig. 24.1, ◘ Table 24.1). In particular, tumor cells release several soluble factors such as parathyroid hormone-related protein (PTHrP9) and interleukine-6 (IL-6) that determine a switch in receptor activator of nuclear factor kappa-B ligand/osteoprotegerin (RANKL/OPG) balance in favor of RANKL [12]. RANKL overexpression stimulates osteoclastic bone resorption and then the release of growth factors including bone morphogenetic proteins (BMPs), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), tumor necrosis factor β (TGF-β) that, in turn, promote cancer cell survival and proliferation. Recent evidences have shown that tumor cells release other factors like endothelin-1 (ET-1) and activate Wnt pathway, resulting in OPG secretion [13, 14]. OPG stimulates osteoblast differentiation and activity promoting the formation of new, but unstructured bone, prone to fracture [15]. RANKL production by activated osteoblast promotes osteoclastic activity and thus the release of bone matrix-derived factors that, in turn, stimulate cancer cells closing the cycle [12].

Several agents targeting these molecular pathways have been investigated in preclinical and clinical trials (◘ Table 24.2).

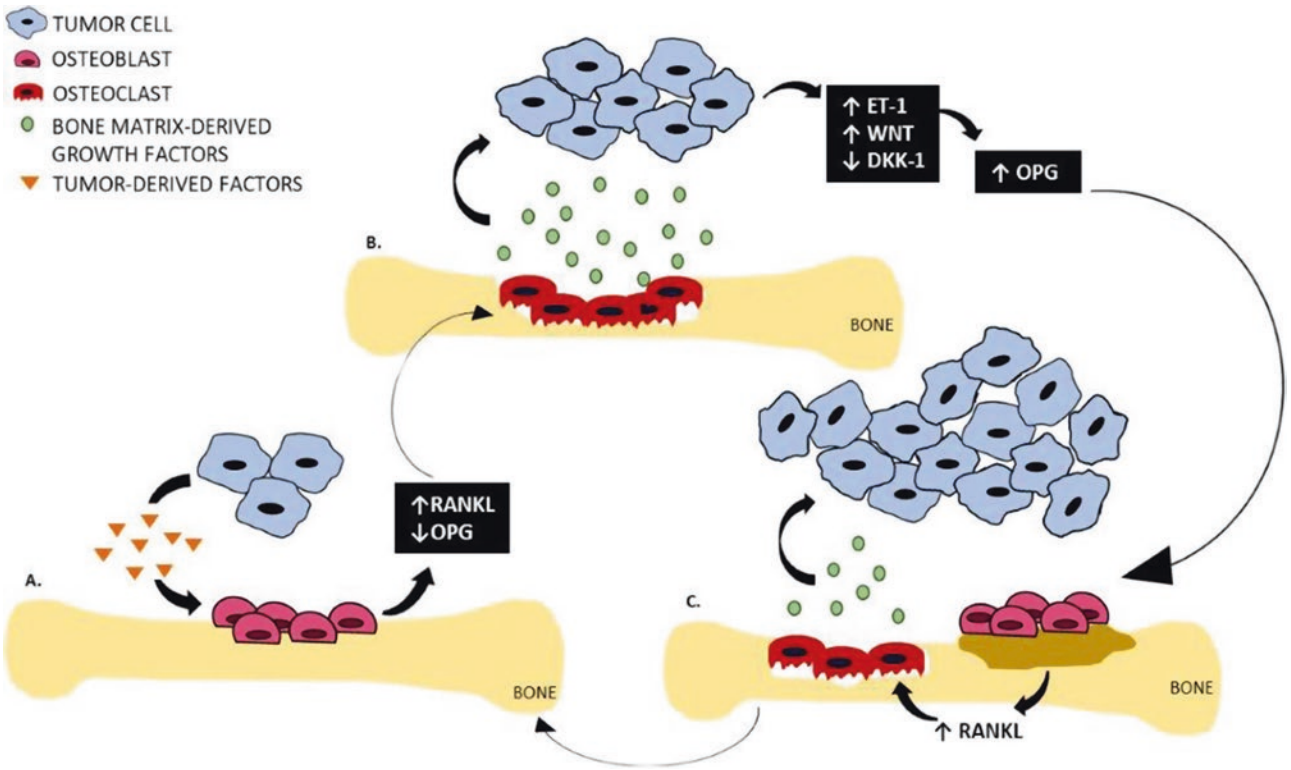

Fig. 24.1 The modern tumor vicious cycle: **a** Tumor-derived growth factors stimulate osteoblast activity inducing an increasing of RANKL that activates osteoclast bone resorption. **b** Growth factors released from bone matrix degradation promote the proliferation of tumor cells leading to OPG production through WNT pathway activation. **c** OPG stimulates osteoblast mineralization promoting RANKL secretion and thus, osteoclast activity. Osteoclastic bone resorption produces soluble factor that, in turn, stimulate cancer cells closing the cycle

Table 24.1 Principal activated pathways in the vicious cycle

Pathway	Function	References
RANK/ RANKL/ OPG axis	RANK expression on tumor cells facilities their migration into the bone Tumor cells induce a shift in RANKL/OPG balance in favor of RANKL RANKL up-regulation increases bone resorption and the release of pro-tumoral growth factors from bone matrix	[12, 15, 18–20]
Endothelin axis	ET-1 released by tumor cells stimulates osteoblast proliferation and activity	[13]
Wnt/DKK-1 axis	Canonical Wnt pathway induces OPG expression in osteoblasts promoting new bone apposition	[14]

RANK nuclear factor kappeB, *RANKL* nuclear factor kappeB ligand, *OPG* Osteoprotegerin, *ET-1* Endothelin1, *DKK-1* Dickkopf-related protein 1

24.3 Bone Metastasis Regulator Pathways

24.3.1 RANK–RANKL–OPG Axis

RANK–RANKL–OPG axis plays a crucial role in bone metastasis development. RANK expression has been founded in several tumor cell lines, including osteosarcomas and breast and prostate cancers [16, 17]. Moreover, RANK/RANKL expression has been reported in human tumor biopsies as well as breast and prostate cancers and hepatocellular carcinoma. Preclinical studies suggest that RANK expression in tumor cells facilities their migration to the bone, where RANKL is abundantly expressed. In particular, murine in vivo models showed RANKL as a potent chemoattractant in tumors and supported the pro-migratory activity of RANK-expressing breast and prostate cancer cell lines; moreover, in an in vivo melanoma model of bone metastases the inhibition of RANKL resulted in a reduction of bone lesions and tumor burden [18]. Finally, it has been demonstrated that RANK expression level in the primary tumor correlated with the occurrence of bone metastases, and RANK-expressing cancer could be found in up to 80% of bone metastases originated from solid tumor [19, 20]. Recently, evidences

Table 24.2 Principal drugs targeting molecules involved in the vicious cycle

Drug	Target	Phase study	Evidences	References
Denosumab	RANKL	Phase III randomised study Phase III randomised study Phase III randomised study Post hoc analysis of the 3 previous phase III trials	Superior to ZA in delaying or preventing SREs in bone metastatic breast cancer patients Superior to ZA in preventing SREs in mCRPC patients Not inferior to ZA in preventing or delaying first on-study SRE in patients with advanced bone metastatic cancer (excluding breast and prostate cancers) or myeloma Superior to ZA in in preventing SREs in patients with bone metastases from advanced cancer	[23, 113–115]
Zibotentan Atrasentan	ETAR	Phase III randomised study Phase III randomised trail Phase III randomised trail Phase III randomised trail	Absence of survival benefits in non-mCRPC patients Not significant improvements in OS in mCRPC patients Not improvement in OS in mCRPC patients in combination with docetaxel Not delay disease progression in men with mCRPC patients	[147–150]
BHQ880	DKK-1	Phase lb trial	Potential clinical activity in patients with relapsed MM in combination with ZA and anti-myeloma therapy	[152]

ZA Zoledronic Acid, *SREs* Skeletal-related events, *mCRPC* metastatic castration resistant prostate cancer, *ETAR* Endothelin type A receptor, *OS* Overall survival, *MM* Multiple myeloma

suggest an important role for RANKL/RANK in the immune system including in lymph node development, lymphocyte differentiation, dendritic cell survival, T-cell activation, and tolerance induction. Detailed studies in mouse models have clearly demonstrated the involvement of RANKL signaling in the functions of immune regulatory cells, such as dendritic cells, M-cells (specialized epithelial cells in mucosal tissues), and mTECs (epithelial cells localized in the thymic medulla) [21]. Notably, the functions of dendritic cells and the maintenance of M-cell numbers were impaired by the inhibition of RANKL signaling in adult mice leading to T-regs lymphocytes expansion and subsequent local and systemic immunosuppression [22]. The result of these alterations was an increase in bone resorption, tumor invasiveness, and cancer cells immune system evasion. The development and approval of denosumab, a fully monoclonal antibody against RANKL, has heralded a new era in the treatment of bone diseases by providing a potent, targeted, and reversible inhibitor of bone resorption [24].

24.3.2 Endothelin-1 (ET-1)

Endothelin-1 (ET-1) is an important factor released by tumor cells with physiological and pathological functions that promotes bone metastasis development. ET-1 is responsible to induce the release of several pro-inflammatory molecules, such as IL-6, chemokine (C–C motif) ligand 2 (CCL2), monocyte chemoattractant protein 1 (MCP-1), cyclooxygenase (COX2), and MMPs that mediated tumor invasiveness and metastasis [25–27].

ET-1 promotes osteoblast proliferation and decreases osteoclast activity, leading to the formation of typical sclerotic lesions of metastatic prostate cancer [13]. Indeed, elevated ET-1 plasma concentrations were observed in hormone refractory prostate cancer patients compared to healthy control. Moreover, immunohistochemistry of prostate cancer biopsies showed ET-1 positivity [28, 29]. In addition, ET receptor expression is associated with reduced disease-free survival time and with the major clinicopathological markers of aggressiveness and poor prognosis in breast cancer patients [30].

Atrasentan is an inhibitor of the ETA receptor that has been showed to block formation of osteoblastic metastases in mice. Nevertheless, in a placebo-controlled phase III trial in men with metastatic prostate cancer, atrasentan failed to demonstrate a reduction of overall survival, risk of disease progression, and cancer-induced bone pain [31].

Zibotentan (ZD4054) is an oral, specific ETA receptor antagonist extensively investigated in the ENTHUSE clinical development program. ENTHUSE M1 trial showed no significant improvement in OS with zibotentan monotherapy versus placebo in men with mildly symptomatic CRPC (24.5 versus 22.5 months, respectively) [32]. Moreover, the ENTHUSE M0 trial of zibotentan monotherapy in patients with non-metastatic CRPC has not demonstrated survival benefits [33]. Finally, in the ENTHUSE M1C randomized phase III trial zibotentan in combination with docetaxel has not showed improvement in OS compared to docetaxel alone in mCRPC patients [34].

24.3.3 Integrin and Cadherin

Tumor metastases require the activity of several adhesion molecules including the superfamily of integrins and cadherins.

The heterodimeric (α and β monomers) transmembrane glycoproteins *integrins* have a cell-type specificity and anchor cells to the extracellular matrix (ECM) binding their ligands. Stable adhesion to the ECM is fundamental to cell survival, indeed detached cells undergo an apoptotic process, known as anoikis [35]. Metastatic cells elude this mechanism expressing aberrant integrins [36], activating different pathways like focal adhesion kinase (FAK) [37], epidermal growth factor receptor (EGFR) [38], and Src [40] and inhibiting apoptosis [39].

Several studies correlated integrin expression (αvβ3, αvβ5, α5β1, α6β4, α4β1, and αvβ6) with the progression of breast carcinoma, prostate, pancreatic and lung cancers, and melanoma [41]. In addition, a correlation between integrins α2 e α6 – and also c-MET- expression and bone metastases development was found [42]. Integrin β1 is another fundamental integrin in prostate cancer progression that promotes bone and node metastasis formation through the activation of Akt pathway [43].

Cadherins, calcium-dependent transmembrane proteins, regulate the formation of adherence junctions to bind cells with each other. Loss of function of cadherins has linked to bone metastasis development [44]. Depending on their form (E-cadherin or N-cadherin), these proteins can act as a suppressor or promotor of cancer invasion and metastases. Indeed, the switch from E-cadherin to N-cadherin is critical for epithelial to mesenchymal transition (EMT) and thus, for metastases onset [48]. In particular, Gravdal and colleagues demonstrated that this switch is associated with decreased OS and higher skeletal recurrence in patients with prostate cancer undergone radical prostatectomy [45]. Another group showed that in human samples E-cadherin is higher express in bone metastasis compared to primary tumor [46]. The overexpression of N-cadherin in prostate cancer cells [45] probably is due to a higher aggressiveness of the tumor and not by a bone tropic behavior of the cells, but nonetheless N-cadherin expression is a good marker of further skeletal recurrence.

Among all, cadherin 11 has demonstrated to promote bone metastases. In particular, it has observed that marrow stromal cells express cadherin-11 (OB-cadherin) that facilitates the homing of breast cancer cells to the bone as well as stimulates osteoclastogenesis [47].

Similarly, in preclinical models of prostate cancer, cadherin-11 enhances migration and invasiveness of tumor regulating also the expression of pro-invasive genes [49].

24.3.4 Wnt and Dkk-1

Wnt proteins represent a secreted group of glycoproteins that bind the 7-transmembrane domain receptors regulating several cellular functions (growth, differentiation, and death). Wnt activity is also important for osteoblasts formation from their precursors, inhibiting in the same time osteoclastogenesis [50]. The activity of Wnt pathway is negatively regulated by the Dickkopf-related protein 1 (Dkk-1) that binds its receptor blocking the downstream signaling.

The role of canonical Wnt signaling has been widely demonstrated in several tumor types [54].

Wnt pathway could be also activated by fibroblast-secreted exosomes that contain active Wnt ligands or β-catenin-promoting motility and invasiveness of breast cancer cells [55].

The balance between Wnt and Dkk-1 activity determines the nature of bone metastasis in prostate cancer: Several studies have showed in preclinical settings that Wnt activation or inhibition are, respectively, linked to sclerotic and lytic bone lesions [56–58]. Indeed, prostate cancers usually express lower levels of Dkk-1 compared to normal prostate tissues, presenting mostly sclerotic metastases [53].

Higher Dkk-1 serum levels are associated with poorer OS, as demonstrated by Rachner et al. [59]. Prognostic value of Wnt–DKK1 axis was further investigated by Chen et al. who showed that high expression of miR34a in primary tumor, a negative regulator of the

Wnt downstream effector TCF7, was found to be correlated to an improved OS in a retrospective analysis of 24 patients with metastatic prostate cancer [60].

BHQ88O is a fully human anti-DKK1 neutralizing immunoglobulin G1 (IgG1) with high affinity for his target. The phase Ib trial showed that BHQ880 in combination with zoledronic acid and anti-myeloma therapy was well tolerated and demonstrated potential clinical activity in patients with relapsed/refractory multiple myeloma [61].

24.3.5 CXCR4/CXCL12

The chemokine CXCL12, called also SDF-1, is a chemoattracted cytokines that binding its receptors (CXCR4 and CXCR7) regulates cellular migration. Several studies have demonstrated the involvement of CXCL12–CXCR4–CXCR7 axis in the establishment of metastases from different tumors [62]. Indeed, in prostate, cancer high levels of CXCL12 regulates the metastatic spread in the bone marrow and the binding with its receptors activates divergent cellular responses such as cell survival, proliferation, and angiogenesis. Moreover, high levels of CXCR7 protein are associated to most aggressive tumors and promotes the release of proangiopoietic factors such as IL-8 and VEGF [63].

In breast cancer, CXCR4 and CXCL12 have a key role in the metastatic process as showed by Muller and colleagues who observed a higher expression of CXCR4 in breast tumor samples compared to normal breast tissues. Moreover, CXCR4 expression in primary tumor could predict bone metastasis occurrence over visceral metastasis onset in a case series of 40 patients with breast cancer [64]. CXCR4 down-streamed signal activated by CXCL12 causes actin polymerization and pseudopodia formation, promoting migration [65]. CXCR4–CXCL12 axis is also activated by mesenchymal stem cells and is crucial for melanoma tumor cells extravasation to the bone marrow [66].

24.3.6 TGF-β

TGF-β belongs to the TGF superfamily and has a central role in regulating cellular homeostasis. Indeed, TGF-β blocks cell cycle–inducing differentiation and apoptosis-preventing aberrant cellular proliferation [67]. Unfortunately, several tumors develop the resistance against this growth inhibition because of genetic loss of TGF-β signaling elements or downstream signaling perturbation. Moreover, TGF-β pathway is linked to bone metastasis onset in several tumor types. In particular, it has demonstrated that two TGF-β secreted proteins, bone sialoprotein and osteopontin highly expressed in prostate and breast cancer tissues, are associated with tumor grade and represent prognostic indicators for bone lesions [68, 69, 70, 71]. Although in a mouse melanoma model, TGF-β receptor 1 inhibition prevent bone metastasis development, it does not affect visceral metastases onset [73].

TGF-β exerts its protumor action, affecting directly bone microenvironment. Indeed, TGF-β secreted and activated from osteoclast bone resorption promotes the release of PTHrP from tumor cells. PTHrP promotes osteoclastogenesis, inhibiting at the same time osteoblastogenesis modulating RANKL OPG ratio [74].

24.3.7 mTOR

The mammalian target of rapamycin (mTOR) pathway is involved in cell growth and survival, thus mTOR signaling alterations are associated to several diseases such as bone metastatic cancers. Indeed, cancer cells exhibit a dysregulated growth due to genetic alterations that determine loss of function or persistent activation of common oncogenes leading to abnormal activation of mTOR. Based on these evidences, mTOR inhibitors could represent a promising treatment for bone metastases. Preclinical data demonstrated that mTOR pathway is involved in bone remodeling, decreasing osteoclast apoptosis, and promoting osteoclast survival and growth through the activation of RANK–OPG pathway. mTOR pathway influence also cathepsin K expression, in fact treatment with mTOR inhibitor (everolimus) induces a decrease of its mRNA and protein levels [72, 75–80]. Moreover, in vivo studies have showed that mTOR inhibition can also influence osteoblast differentiation [60].

24.4 Markers of Bone Metastases

Bone metastatic cancers determine changes in bone metabolism and then in bone remodeling proteins whose serum levels could predict metastasis onset [51]. These proteins represent the bone turnover markers and include markers of bone formation and markers of bone resorption [52]. Specifically, the bone formation markers include bone specific alkaline phosphatase (bALP), bone matrix proteins such as osteocalcin (OCN), and the procollagen extension peptides (P1NP and P1CP). bALP is an enzyme produced by osteoblasts that is released into circulation during the mineralization process [81].

OCN is a non-collagenous protein synthetized by osteoblasts that binds to hydroxyapatite and is involved in calcium binding [82].

P1NP and P1CP are derived from the extracellular processing of the procollagen type I molecule, which contains amino-terminal and carboxy-terminal extensions that are enzymatically cleaved upon procollagen secretion [83].

In different stages of disease of prostate cancer, several bone turnover markers could predict the presence of bone metastasis on further radiologic imaging.

Jung et al. [81] found a correlation between the levels of several cone turnover markers and the disease state (bone metastatic vs. nonmetastatic) and they found that bALP, P1NP, and CTX predict OS. Moreover, de la Piedra et al. found that high levels of these proteins can predict SREs occurrence [84].

Bone turnover markers might be a specific predictor of bone metastasis occurrence in a clinical setting since they could identify patients that are prone to bone metastasis formation due to comorbidities (i.e., osteoporosis), concomitant therapies (i.e., androgen deprivation therapy) or due to any metabolic condition that enhance bone remodeling [85].

Others bone metastasis markers are the amino-terminal-crosslinked telopeptide of type I collagen (NTX-I) and carboxy-terminal-crosslinked telopeptides of collagen type I (CTX-I and ICTP) [86]. These telopeptides are released from type I collagen degradation by proteases during bone resorption. Since serum CTX-I are influenced by food intake, urine NTX-I has been the preferred marker in the clinical setting [88].

The inhibitor of Wnt signaling Dkk-1 also represents a marker of bone metastases. With sclerostin, Dkk-1 is released into the blood and serum levels reflect inhibition of bone formation [89, 90].

Unfortunately, bone markers do not provide information about the specific lesion site and changes in serum levels are associated with only bone homeostasis alteration without identifying the specific cause [82]. Nevertheless, bone markers might be helpful in better defining the prognosis and the risk for bone complications in patients with bone metastatic disease [87, 91].

24.5 Treatment of Bone Metastases

Bone metastasis treatments depend on the features of disease and include bone-targeted agents and radiopharmaceuticals. Besides these, several molecules that are already approved, as anticancer agents (such as antiandrogens and mTOR inhibitors) are now in clinical evaluation for their potential beneficial effects on bone metabolism (Table 24.3). Bone metastatic patients commonly develop resistance to systemic treatments, thus periodic changes of therapy are required.

In order to manage patients with bone metastases a multidisciplinary team of oncologists, radiotherapists, orthopedic surgeons, and nuclear medicine physicians is necessary.

24.6 Bone-Targeted Agents

In the last two decades, the bisphosphonates and denosumab, a monoclonal antibody of receptor activator of nuclear factor kappa-B ligand (RANKL), have become established as promising therapies for bone metastasis treatment.

Bisphosphonates are analogues of pyrophosphate with a strong affinity for divalent metal ions, such as calcium ions, and thus for the skeleton. Bisphosphonates are the standard of care for the treatment of osteoporosis as well as bone metastases, thanks to their action against osteoclast bone resorption [92]. Indeed, binding hydroxyapatite crystals of bone matrix bisphosphonates form a barrier that prevents osteoclast activity and the subsequent osteoblast bone deposition. There are two classes of bisphosphonates, non-nitrogen-containing (alendronate, ibandronate, pamidronate, risedronate, and zoledronic acid) and nitrogen-containing (e.g., clodronate, etidronate, and tiludronate), that inhibit differently osteoclasts. Particularly, nitrogen-containing bisphosphonates are more active than other in blocking osteoclasts [93]. Indeed, they inhibit farnesyl pyrophosphatase, the fundamental enzyme for osteoclast function, survival, and morphology causing the accumulation of the cytotoxic nucleotide metabolite Appp1 [93–95]. Moreover, several data have demonstrated that bisphosphonates also affect immune cells (mainly macrophages and gamma delta T-cells) and tumor cells through antitumor and/or antiangiogenic effects [96].

The strong effect of bisphosphonates in bone metastatic breast cancer treatment was widely investigated. In particular, a meta-analysis which included 2806 patients showed a reduction of SREs rate after bisphosphonates treatment compared to the placebo group [97]. Although all bisphosphonates reduced SREs, the efficacy (by 20–40%) changed based on the agent [98–104]. Recently, a meta-analysis demonstrated that adjuvant bisphosphonates reduced breast cancer recurrence in bone and improved breast cancer survival in women who were postmenopausal when treatment began [105]. Starting from these evidences, the use of bisphosphonates is recommended as part of the adjuvant breast treatment in this group of women [106].

Zoledronic acid demonstrated beneficial effects also in bone metastatic prostate cancer patients. Indeed,

Table 24.3 Anticancer agents with bone effect

Drug	Subject/cells type	Bone effect	References
Everolimus	Ovariectomiced rat model metastatic ER+ breast cancer patients	Decrease of bone loss associated with estrogen deprivation Reduction of bone tumover markers and bone disease progression (BOLERO study)	[76, 127]
Abiraterone	Human primary bone cells mCRPC patients	Increase of osteoblast differentiation and activity and reduction of osteociastogenesis and bone resorption Delay of SREs development and radiologival skeletal progression (COU-AA-301 study)	[133, 128]
Enzalutamide	mCRPC patients mCRPC	Improvement of survival and skeletal responses (AFFIRM study) Reduction of radiographic progression and risk of first SRE (PREVAIL study)	[135, 161]
Cabozantinib	Human primary bone cells mCRPC patients metastatic clear-cell renal cell carcinoma	Inhibition of ostaoclast differentiation and activity Improvement of bone scan responses and reduction of SRE rates (COMET-1) Delay of SRE onset (METEOR study)	[147, 150, 151]

ER Estrogen Receptor, *SREs* Skeletal Related Events, *mCRPC* metastatic castration resistant prostate cancer

Zoledronic acid treatment increased bone density and significantly reduced bone fractures at 6, 12, 24 months in patients with nonmetastatic prostate cancer after Androgen Deprivation Therapy [107]. Zoledronic acid reduced SREs onset and pain also patients that developed hormone-therapy resistance [108, 109].

In a phase III clinical study (STAMPEDE), the addition of zoledronic acid to docetaxel showed no evidence of survival improvement or delay of SREs incidence [110]. Similar results were obtained from the CALGB/ALLIANCE 90202 study comparing early treated hormone-sensitive prostate cancer versus delayed treatment in Castration Resistant Prostate Cancer (CRPC) [111, 149].

Denosumab is a monoclonal antibody against RANKL, developed for the treatment of osteoporosis, skeletal pathologies, and bone metastasis thanks to its inhibiting activity on osteoclasts [24]. The superiority of denosumab compared to zoledronic acid in reducing SREs onset was demonstrated in a large randomized controlled trial [23]. Nevertheless, no differences in OS disease progression and rate of adverse events were observed [112]. In a castration-resistant prostate cancer patient population presenting bone metastases, the median time-to-first on-study SRE for the denosumab arm was significantly prolonged (21 months) compared to the zoledronic acid ones (17 months), with no improvements in OS or progression of disease [113]. Another trial enrolled 1776 patients with myeloma-induced osteolysis and solid tumors other than breast and prostate cancers [114]. The results showed a median time-to-first on-study SRE of 21 months in the denosumab group and 16 months in the arm receiving zoledronic acid demonstrating a non-inferiority for denosumab versus zoledronic acid, but neither a superiority after adjustment for multiple comparison nor an advantage in OS of denosumab over zoledronic acid. Nevertheless, a post hoc analysis of these three phase III trials in patients with breast cancer [23], prostate cancer [113], or other solid tumors [114] (excluding of multiple myeloma patients), showed that denosumab was superior to zoledronic acid in preventing SREs in patients with bone metastases, regardless of ECOG PS, bone metastasis number, baseline visceral metastasis presence/absence, and uNTx level [115].

On the basis of these evidences the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the European Society of Medical Oncology (ESMO) recommend zoledronic acid or denosumab as the standard of care in bone metastatic patients [116–118].

24.7 Radiopharmaceutical

Radiopharmaceuticals are a group of radioactive drugs that recognize reactive metastatic bone sites and emit radiations according to their nature (commonly beta emission). In patients who present metastases in different bone sites, the radiopharmaceuticals are more effec-

tive than external local beam radiation, even if the combination of both is recommended for the most painful bone lesions [119–121].

Different types of radiopharmaceuticals are currently used for bone metastasis treatment such as 131-iodine that is the approved treatment for bone metastases of follicular thyroid carcinoma. In bone metastatic breast and prostate cancers, stronzium-89 and samarium-153 represent useful palliation of bone pain. Therefore, in a randomized control trial, stronzium-89 improved progression free survival in mCRPC patients after six cycle of docetaxel [122, 123].

Most recently, FDA approved the α-particle-emitting radiopharmaceutical, radium-223 as treatment for bone metastatic prostate cancer patients. As α-emitter, radium-223 delivers a highly localized radiation to bone surface than beta-emitters, causing DNA damages and the subsequent cell death giving less irradiation to healthy bone marrow [124]. Radium-223 improved OS of bone metastatic CRPC patients previously treated with docetaxel or unfit to receive docetaxel [125]; moreover, it showed efficacy in all secondary end-points including time to the first symptomatic skeletal events (median, 15.6 months vs. 9.8 months respectively). Ongoing phase III trial are designed to evaluate the effect of a combined treatment of radium-223 and other new target therapies as abiraterone acetate in this group of patients (NCT01106352 and NCT02097303).

24.8 Anticancer Agents with Bone Effect

24.8.1 mTOR Inhibitor

The mammalian target of rapamycin (mTOR) inhibitor, everolimus, had a positive effect on bone in preclinical and clinical studies. Indeed, in vivo study in ovariectomized rat model showed that everolimus directly blocks osteoclastic bone resorption [76].

In addition, in BOLERO-2 study, the combination of the mTOR inhibitor everolimus with aromatase inhibitor showed a significant benefit in progression free survival (PFS) in postmenopausal women with estrogen receptor–positive breast cancer [126]. In particular, it has also demonstrated that this combination reduced bone disease progression, decreasing bone markers levels at 6 months and 12 months from baseline [127].

The benefit of long-term treatment with everolimus in bone metastatic breast patients who do not progress within 8 weeks of treatment has demonstrated in RADAR study showing an improvement of time to progression (37 weeks vs 12.6 weeks of placebo group).

These evidences from phase III clinical trials suggest that mTOR inhibition in combination with exemestane may have both a beneficial effect on bone health in patients with bone metastases, reducing the incidence of bone metastases morbidity and mortality.

Currently, a phase II study is ongoing in order to evaluate whether the addition to radium-223 dichloride to aromatase inhibitor and everolimus could improve skeletal response in metastatic HER2 negative hormone receptor positive breast cancer patients (NCT02258451).

24.8.2 Antiandrogen Agents

Abiraterone acetate is an androgen biosynthesis inhibitor that blocks both the hydroxylase and lyase activity of CYP17. In particular, abiraterone inhibition of CYP17A blocks glucocorticoid and adrenal androgen synthesis, leading to a virtually undetectable serum and intratumoral androgen production in the adrenals, testes, and prostate cancer cells [130, 131]. Abiraterone is co-administered with prednisone to ameliorate the secondary rise in adrenocorticotropic hormone (ACTH) that can lead to excess mineralocorticoid synthesis [132]. This agent showed not only a significant survival advantage in metastatic prostate cancer patients [128, 129], but also a strong skeletal response. Indeed chemotherapy-treated patients treated with abiraterone showed better pain relief from skeletal metastases, a delay in time to development SREs (25 months vs 20.3 of placebo group), and in radiological skeletal progression [128]. Abiraterone effects on metastatic bone disease may be not only secondary to a systemic control of the disease due to a direct antitumor effect but also due to a specific effect on bone microenvironment. Recently the effect of abiraterone both in vitro and in mCRPC patients as bone anti-resorption agents was demonstrated [133]. Our research team demonstrated that abiraterone was able to specifically modulate bone cells leading to direct anabolic and anti-reabsorptive effects, suggesting a non-canonical mechanism of action [133].

Enzalutamide is an oral AR inhibitor that targets multiple steps in the AR signaling pathway. Two large phase III trials have demonstrated the efficacy of enzalutamide in the treatment of patients with mCRPC [134, 135]. In particular, the AFFIRM study showed that mCRPC patients treated with docetaxel and then with enzalutamide had improvements in survival and skeletal responses compared to placebo group [135]. In addition, the PREVAIL study demonstrated similar results in mCRPC patients treated with enzalutamide, who had not received docetaxel compared to placebo. Indeed, it has observed improvements in primary endpoints (OS and radiographic progression) and also in the secondary endpoints, including delayed initiation of chemotherapy and reduction in risk of first SRE [134].

24.8.3 Cabozantinib

Cabozantinib is a multiple receptor tyrosine kinase inhibitor with a strong activity against c-MET and vascular endothelial growth factor receptor 2 (VEGFR2). The hepatocyte growth factor (HGF), the only known ligand for c-MET, and c-MET signaling axis, is important in the regulation of bone remodeling [136–139]. Indeed, both osteoclasts and osteoblasts express c-MET and VEGFR2, and secrete HGF [140–143]. Several preclinical studies demonstrated the involvement of cabozantinib in bone remodeling; in particular, cabozantinib inhibited tumor proliferation and bone resorption in metastatic prostate cancer animal models [144–146]. Moreover, our group showed that cabozantinib inhibited osteoclast differentiation and bone resorption activity, both directly and indirectly reducing the RANKL/OPG ratio in osteoblasts [147]. In phase II studies of CRPC patients, cabozantinib was associated with an increased resolution in bone scans, a pain relief in more than 60% of patients and a marked improvement in progression free survival (PFS) compared with placebo [111, 148, 149].

In the subsequently COMET-1 study, although cabozantinib did not increase the OS of mCRPC patients, it improved bone scan responses, progression-free survival, and reduced SRE rates, compared to prednisone [150]. In metastatic renal cell carcinoma, METEOR study demonstrated that cabozantinib reduced the risk of tumor progression and death compared to everolimus, and improved the progression-free survival and the delay of SRE onset [151–153].

24.9 Osteoimmunology in Bone Metastases

The immune system has long been known to have a central role in preventing tumor growth, but more recent evidence suggest the importance of the immune cell response in the tumor bone microenvironment as main regulator of cancer progression and metastases.

Once in the bone marrow, tumor cells can, directly or not, interact with different resident immune cells and modify the balance of immune effector and suppressor cells creating a microenvironment suitable for their growth [154, 155].

In advanced bone metastatic cancers there is a prevalence of immunosuppressive cells, mainly myeloid-derived suppressors cells (MDSCs) and regulatory T-cells. Indeed, tumor cells secrete soluble factors such as IL-4, IL-13 VEGF, granulocyte–macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), and TGF-β that recruit and activate MDSCs. MDSCs stimulates osteoclast differentiation and activity and also support the polarization of macrophages into a tumor-promoting phenotype [156–158]. Recent evidences support a role of osteoblasts in osteoimmunology mediated by the release of cytokines and growth factors in the microenvironment [159]. In particular, PTHrP, produced by tumor cells, stimulates osteoblasts to produce CCL2, IL-6, and VEGF (A) that recruit and stimulate MDSCs.

Tumor-associated inflammation is not always a signal of immune system response to tumor cell growth, but sometimes creates a microenvironment that facilities neoplastic development.

Indeed, CD68+ osteal macrophages, that have a pro-tumor phenotype, establish a complex crosstalk with cancer and bone cells, leading to tumor progression in the skeleton, especially in breast and prostate cancers [160].

Finally, different immune cell types are involved in the establishment of tumor cells in the metastatic niche, mainly in bone. Indeed, some inflammatory cells express RANKL that mediates RANK+ tumor cells migration into the bone [18–20].

24.10 Conclusion

Recent advances supported the important role of bone microenvironment for metastasis adaptation and the subsequent crosstalk between tumor and bone cells that lead to cancer progression. Despite different approaches have been investigated to target this crosstalk, up to now only denosumab and bisphosphonates demonstrated to be a changing practice agent in delaying SRE. Besides these agents, others are anticancer drugs, but at the same time, have effects on bone microenvironment altering bone turnover. Anyway, currently, we are still far from fully understanding what really happens when disrupting the RANK–RANKL axis in the "real world" and we do not know which patients could benefit from these approaches. For these reasons, the goal of ongoing clinical trials is to evaluate whether combinations of different treatments could improve patient bone health.

Expert Opinion

Antonio Russo

Key points

- Bone metastases led to so-called "skeletal-related events" (SREs) that negatively affect patients' quality of life.
- Tumors alter the physiological balance between bone deposition and resorption, leading to the loss of the skeleton integrity.
- Bone metastatic niche is the ideal site for dormant tumor cells (DTCs) colonization.
- Bone metastasis onset is regulated by several pathways, including RANK–RANKL–OPG, ET-1, integrins and cadherins, WNT–DKK1, CXCR4–CXCL12, TGF-β and mTOR.
- bALP, OCN P1NP, P1CP, NTX-I, CTX-I, and ICTP are the principal markers of bone metastases.
- Bone metastasis treatments include bone-targeted agents (bisphosphonates and denosumab) and radiopharmaceuticals.
- mTOR inhibitors, antiandrogen drugs, and cabozantinib are anticancer agents with bone effects.
- In advanced bone metastatic cancers there is a prevalence of immunosuppressive cells, mainly myeloid-derived suppressors cells (MDSCs) and regulatory T-cells.
- Different immune cell types are involved in the establishment of tumor cells in the bone metastatic niche.

Hints for Deeper Insight

- Besides bone target agents, others new anticancer drugs have effects on bone microenvironment altering bone turnover. It would be interesting to deepen the direct effects of these new agents on bone cells.
- The bone marrow is a fertile soil containing a complex composition of immune cells that may actually provide an immune-privileged niche for disseminated tumor cells to colonize and proliferate. It would be interesting to investigate deeply the role of immune cells in promoting tumor cells seeding in bone niche.

Suggested Reading

- Croucher PI, McDonald MM, Martin TJ. Bone metastasis: the importance of the neighbourhood. Nat Rev Cancer. 2016 May 25;16(6):373–86.
- Xiang L, Gilkes DM. The Contribution of the Immune System in Bone Metastasis Pathogenesis. Int J Mol Sci. 2019 Feb 25;20(4).
- Coleman R, Body JJ, Aapro M, et al. Bone health in cancer patients: ESMO Clinical Practice Guidelines, Annals of Oncology, Volume 25, Issue suppl_3, September 2014, Pages iii124–iii137
- Gdowski AS, Ranjan A, Vishwanatha JK. Current concepts in bone metastasis, contemporary therapeutic strategies and ongoing clinical trials. J Exp Clin Cancer Res. 2017;36(1):108.

References

1. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12:6243s–9s. https://doi.org/10.1158/1078-0432.CCR-06-0931.
2. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19:385–97.
3. Melton LJ 3rd, Chrischilles EA, Cooper C, Lane AW, Riggs BL. Perspective: how many women have osteoporosis? J Bone Miner Res. 1992;7:1005–10.
4. Vessella RL, Corey E. Targeting factors involved in bone remodeling as treatment strategies in prostate Cancer bone metastasis. Clin Cancer Res. 2006;12:6285–91. https://doi.org/10.1158/1078-0432.CCR-06-0813.
5. Mundy GR. Malignancy and the skeleton. Horm Metab Res. 1997;29:120–7.
6. Raisz LG. Physiology and pathophysiology of bone remodeling. Clin Chem. 1999;8:1353–8.
7. Dallas SL, Prideaux M, Bonewald LF. The osteocyte: an endocrine cell and more. Endocr Rev. 2013;34:658–90. https://doi.org/10.1210/er.2012-1026.
8. Weilbaecher KN, Guise TA, McCauley LK. Cancer to bone: a fatal attraction. Nat Rev Cancer. 2011;11:411–25. https://doi.org/10.1038/nrc3055.
9. Mohme M, Riethdorf S, Pantel K. Circulating and disseminated tumour cells - mechanisms of immune surveillance and escape. Nat Rev Clin Oncol. 2017;14:155–67. https://doi.org/10.1038/nrclinonc.2016.144.
10. Croucher PI, McdDonald MM, Martin TJ. Bone metastasis: the importance of the neighbourhood. Nat Rev Cancer. 2016;16:373–86. https://doi.org/10.1038/nrc.2016.44.
11. Sceneay J, Smyth MJ, Möller A. The pre-metastatic niche: finding common ground. Cancer Metastasis Rev. 2013;32:449–64. https://doi.org/10.1007/s10555-013-9420-1.

12. Roodman GD. Mechanisms of bone metastasis. N Engl J Med. 2004;350:1655–64.
13. Nelson J, Bagnato A, Battistini B, Nisen P. The endothelin axis: emerging role in cancer. Nat Rev Cancer. 2003;3:110–6. PubMed PMID: 12563310.
14. Takahashi N, Maeda K, Ishihara A, Uehara S, Kobayashi Y. Regulatory mechanism of osteoclastogenesis by RANKL and Wnt signals. Front Biosci (Landmark Ed). 2011;16:21–30. PubMed PMID: 21196156.
15. Dougall WC, Holen I, González Suárez E. Targeting RANKL in metastasis. Bonekey Rep. 2014;3:519. https://doi.org/10.1038/bonekey.2014.14.
16. Van Poznak C, Cross SS, Saggese M, Hudis C, Panageas KS, Norton L, et al. Expression of osteoprotegerin (OPG), TNF related apoptosis inducing ligand (TRAIL), and receptor activator of nuclear factor k B ligand (RANKL) in human breast tumours. J Clin Pathol. 2006;59:56–64. https://doi.org/10.1136/jcp.2005.026534.
17. Danovi SA. Tumorigenesis: hormonally driven. Nat Rev Cancer. 2010;10:45. https://doi.org/10.1038/nrc2880.
18. Gonzalez-Suarez E, Jacob AP, Jones J, Miller R, Roudier-Meyer MP, Erwert R, et al. RANK ligand mediates progestin-induced mammary epithelial proliferation and carcinogenesis. Nature. 2010;468:103–7. https://doi.org/10.1038/nature09495.
19. Santini D, Schiavon G, Vincenzi B, Gaeta L, Pantano F, Russo A, et al. Receptor Activator of NF-kB (RANK) expression in primary tumors associates with bone metastasis occurrence in breast cancer patients. PLoS One. 2011a;6:e19234. https://doi.org/10.1371/journal.pone.0019234.
20. Santini D, Perrone G, Roato I, Godio L, Pantano F, Grasso D, et al. Expression pattern of receptor activator of NFκB (RANK) in a series of primary solid tumors and related bone metastases. J Cell Physiol. 2011b;226:780–4. https://doi.org/10.1002/jcp.22402.
21. Loser K, Mehling A, Loeser S, Apelt J, Kuhn A, Grabbe S, et al. Epidermal RANKL controls regulatory T-cell numbers via activation of dendritic cells. Nat Med. 2006;12:1372–9.
22. Tan W, Zhang W, Strasner A, Grivennikov S, Cheng JQ, Hoffman RM, et al. Tumour-infiltrating regulatory T cells stimulate mammary cancer metastasis through RANKL-RANK signalling. Nature. 2011;470:548–53. https://doi.org/10.1038/nature09707.
23. Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol. 2010;28:5132–9.
24. Lacey DL, Boyle WJ, Simonet WS, Kostenuik PJ, Dougall WC, Sullivan JK, et al. Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the development of denosumab. Nat Rev Drug Discov. 2012;11:401–19. https://doi.org/10.1038/nrd3705.
25. Kandalaft LE, Facciabene A, Buckanovich RJ, Coukos G. Endothelin B receptor, a new target in cancer immune therapy. Clin Cancer Res. 2009;15:4521–8. https://doi.org/10.1158/1078-0432.CCR-08-0543.
26. Spinella F, Rosanò L, Di Castro V, Nicotra MR, Natali PG, Bagnato A. Inhibition of cyclooxygenase-1 and -2 expression by targeting the endothelin a receptor in human ovarian carcinoma cells. Clin Cancer Res. 2004;10:4670–9.
27. Sutcliffe AM, Clarke DL, Bradbury DA, Corbett LM, Patel JA, Knox AJ. Transcriptional regulation of monocyte chemotactic protein-1 release by endothelin-1 in human airway smooth muscle cells involves NF-kappaB and AP-1. Br J Pharmacol. 2009;157:436–50. https://doi.org/10.1111/j.1476-5381.2009.00143.x.
28. Nelson JB, Hedican SP, George DJ, Reddi AH, Piantadosi S, Eisenberger MA, et al. Identification of endothelin-1 in the pathophysiology of metastatic adenocarcinoma of the prostate. Nat Med. 1995;1:944–9.
29. Nelson JB, Chan-Tack K, Hedican SP, Magnuson SR, Opgenorth TJ, Bova GS, et al. Endothelin-1 production and decreased endothelin B receptor expression in advanced prostate cancer. Cancer Res. 1996;56:663–8.
30. Wülfing P, Diallo R, Kersting C, Wülfing C, Poremba C, Rody A, et al. Expression of endothelin-1, endothelin-A, and endothelin-B receptor in human breast cancer and correlation with long-term follow-up. Clin Cancer Res. 2003;9:4125–31.
31. Carducci MA, Saad F, Abrahamsson PA, Dearnaley DP, Schulman CC, North SA, et al. Atrasentan Phase III Study Group Institutions. A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer. Cancer. 2007;110:1959–66.
32. Nelson JB, Fizazi K, Miller K, Higano C, Moul JW, Akaza H, et al. Phase 3, randomized, placebo-controlled study of zibotentan (ZD4054) in patients with castration-resistant prostate cancer metastatic to bone. Cancer. 2012;118:5709–18.
33. Miller K, Moul JW, Gleave M, Fizazi K, Nelson JB, Morris T, et al. Phase III, randomized, placebo-controlled study of once-daily oral zibotentan (ZD4054) in patients with non-metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis. 2013;16:187–92.
34. Fizazi K, Higano CS, Nelson JB, Gleave M, Miller K, Morris T, et al. Phase III, randomized, placebo-controlled study of docetaxel in combination with zibotentan in patients with metastatic castration-resistant prostate cancer. J Clin Oncol. 2013;31:1740–7. Erratum in: J Clin Oncol. 2014;32:3461. Fizazi, Karim S [Corrected to Fizazi, Karim].
35. Frisch SM, Screaton RA. Anoikis mechanisms. Curr Opin Cell Biol. 2001;13:555–62. PubMed PMID: 11544023.
36. Bissell MJ, LaBarge MA. Context, tissue plasticity, and cancer: are tumor stem cells also regulated by the microenvironment? Cancer Cell. 2005;7:17–23. https://doi.org/10.1016/j.ccr.2004.12.013.
37. Frisch SM, Vuori K, Ruoslahti E, Chan-Hui PY. Control of adhesion-dependent cell survival by focal adhesion kinase. J Cell Biol. 1996;134:793–9. PubMed PMID: 8707856.
38. Demers MJ, Thibodeau S, Noël D, Fujita N, Tsuruo T, Gauthier R, et al. Intestinal epithelial cancer cell anoikis resistance: EGFR-mediated sustained activation of Src overrides Fak-dependent signaling to MEK/Erk and/or PI3-K/Akt-1. J Cell Biochem. 2009;107:639–54. https://doi.org/10.1002/jcb.22131.
39. Simpson CD, Anyiwe K, Schimmer AD. Anoikis resistance and tumor metastasis. Cancer Lett. 2008;272:177–85. https://doi.org/10.1016/j.canlet.2008.05.029.
40. Windham TC, Parikh NU, Siwak DR, Summy JM, McConkey DJ, Kraker AJ, et al. Src activation regulates anoikis in human colon tumor cell lines. Oncogene. 2002;21:7797. https://doi.org/10.1038/sj.onc.1205989.
41. Desgrosellier JS, Cheresh DA. Integrins in cancer: biological implications and therapeutic opportunities. Nat Rev Cancer. 2010;10:9–22.
42. Ricci E, Mattei E, Dumontet C, Eaton CL, Hamdy F, van der Pluije G, et al. Increased expression of putative cancer stem cell markers in the bone marrow of prostate cancer patients is associated with bone metastasis progression. Prostate. 2017;73:1738–46. https://doi.org/10.1002/pros.22689.
43. Lee YC, Jin JK, Cheng CJ, Huang CF, Song JH, Huang M, et al. Targeting constitutively activated β1 integrins inhibits prostate cancer metastasis. Mol Cancer Res. 2013;11:405–17. https://doi.org/10.1158/1541-7786.mcr-12-0551.

44. Beavon IR. The E-cadherin-catenin complex in tumour metastasis: structure, function and regulation. Eur J Cancer. 2000;36:1607–20. PubMed PMID: 10959047.
45. Gravdal K, Halvorsen OJ, Haukaas SA, Akslen LA. A switch from E-cadherin to N-cadherin expression indicates epithelial to mesenchymal transition and is of strong and independent importance for the progress of prostate cancer. Clin Cancer Res. 2007;13:7003–11. PubMed PMID: 18056176.
46. Saha B, Arase A, Imam SS, Tsao-Wei D, Naritoku WY, Groshen S, et al. Overexpression of E-cadherin and beta-catenin proteins in metastatic prostate cancer cells in bone. Prostate. 2008;68:78–84. PubMed PMID: 18008331.
47. Tamura D, Hiraga T, Myoui A, Yoshikawa H, Yoneda T. Cadherin-11-mediated interactions with bone marrow stromal/osteoblastic cells support selective colonization of breast cancer cells in bone. Int J Oncol. 2008;33:17–24. PubMed PMID: 18575746.
48. Jin JK, Dayyani F, Gallick GE. Steps in prostate cancer progression that lead to bone metastasis. Int J Cancer. 2011;128:2545–61. https://doi.org/10.1002/ijc.26024.
49. Huang CF, Lira C, Chu K, Bilen MA, Lee YC, Ye X, et al. Cadherin-11 increases migration and invasion of prostate cancer cells and enhances their interaction with osteoblasts. Cancer Res. 2010;70:4580–9. https://doi.org/10.1158/0008-5472.can-09-3016.
50. Wang Y, Li YP, Paulson C, Shao JZ, Zhang X, Wu M, et al. Wnt and the Wnt signaling pathway in bone development and disease. Front Biosci. 2014;19:379–407.
51. Manca P, Pantano F, Iuliani M, Ribelli G, De Lisi D, Danesi R, et al. Determinants of bone specific metastasis in prostate cancer. Crit Rev Oncol Hematol. 2017;112:59–66. https://doi.org/10.1016/j.critrevonc.
52. Ferreira A, Alho I, Casimiro S. Bone remodeling markers and bone metastases: from cancer research to clinical implications. BoneKEy Rep. 2015;668:1–9. https://doi.org/10.1038/bonekey.2015.35.
53. Hall CL, Bafico A, Dai J, Aaronson SA, Keller ET. Prostate cancer cells promote osteoblastic bone metastases through Wnts. Cancer Res. 2005;65:7554–61. https://doi.org/10.1158/0008-5472.CAN-05-1317.
54. Duchartre Y, Kim YM, Kahn M. The Wnt signaling pathway in cancer. Crit Rev Oncol Hematol. 2016;99:141–9. https://doi.org/10.1016/j.critrevonc.2015.12.005.
55. Luga V, Zhang L, Viloria-Petit AM, Ogunjimi AA, Inanlou MR, Chiu E, et al. Exosomes mediate stromal mobilization of autocrine Wnt-PCP signaling in breast cancer cell migration. Cell. 2012;151:1542–56. https://doi.org/10.1016/j.cell.2012.11.024.
56. Hall CL, Daignault SD, Shah RB, Pienta KJ, Keller ET. Dickkopf-1 expression increases early in prostate cancer development and decreases during progression from primary tumor to metastasis. Prostate. 2008;68:1396–404. https://doi.org/10.1002/pros.20805.
57. Thudi NK, Martin CK, Murahari S, Shu ST, Lanigan LG, Werbeck JL, et al. Dickkopf-1 (DKK-1) stimulated prostate cancer growth and metastasis and inhibited bone formation in osteoblastic bone metastases. Prostate. 2011;71:615–25. https://doi.org/10.1002/pros.21277.
58. Dai J, Hall CL, Escara-Wilke J, Mizokami A, Keller JM, Keller ET. Prostate cancer induces bone metastasis through Wnt-induced bone morphogenetic protein-dependent and independent mechanisms. Cancer Res. 2008;68:5785–94. https://doi.org/10.1158/0008-5472.CAN-07-6541.
59. Rachner TD, Thiele S, Göbel A, Browne A, Fuessel S, Erdmann K, et al. High serum levels of Dickkopf-1 are associated with a poor prognosis in prostate cancer patients. BMC Cancer. 2014;14:649. https://doi.org/10.1186/1471-2407-14-649.
60. Chen WY, Liu SY, Chang YS, Yin JJ, Yeh HL, Mouhieddine TH, et al. MicroRNA-34a regulates WNT/TCF7 signaling and inhibits bone metastasis in Ras-activated prostate cancer. Oncotarget. 2015;6:441–57. PubMed PMID: 25436980; PubMed Central PMCID: PMC4381606.
61. Iyer SP, Beck JT, Stewart AK, Shah J, Kelly KR, Isaacs R, et al. A Phase IB multicentre dose-determination study of BHQ880 in combination with anti-myeloma therapy and zoledronic acid in patients with relapsed or refractory multiple myeloma and prior skeletal-related events. Br J Haematol. 2014;167:366–75.
62. Zlotnik A, Burkhardt AM, Homey B. Homeostatic chemokine receptors and organ-specific metastasis. Nat Rev Immunol. 2011;11:597–606. https://doi.org/10.1038/nri3049.
63. Wang J, Shiozawa Y, Wang J, Wang Y, Jung Y, Pienta KJ, et al. The role of CXCR7/RDC1 as a chemokine receptor for CXCL12/SDF-1 in prostate cancer. J Biol Chem. 2008;283:4283–94. PubMed PMID: 18057003.
64. Ibrahim T, Sacanna E, Gaudio M, Mercatali L, Scarpi E, Zoli W, et al. Role of RANK, RANKL, OPG, and CXCR4 tissue markers in predicting bone metastases in breast cancer patients. Clin Breast Cancer. 2011;11:369–75. https://doi.org/10.1016/j.clbc.2011.05.001.
65. Müller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME, et al. Involvement of chemokine receptors in breast cancer metastasis. Nature. 2001;410:50–6. PubMed PMID: 11242036.
66. Correa D, Somoza RA, Lin P, Schiemann WP, Caplan AI. Mesenchymal stem cells regulate melanoma cancer cells extravasation to bone and liver at their perivascular niche. Int J Cancer. 2016;138:417–27. https://doi.org/10.1002/ijc.29709.
67. Derynck R, Akhurst RJ. Differentiation plasticity regulated by TGF-beta family proteins in development and disease. Nat Cell Biol. 2007;9:1000–4. PubMed PMID: 17762890.
68. Bellahcène A, Kroll M, Liebens F, Castronovo V. Bone sialoprotein expression in primary human breast cancer is associated with bone metastases development. J Bone Miner Res. 1996;11:665–70. https://doi.org/10.1002/jbmr.5650110514.
69. Coppola D, Szabo M, Boulware D, Muraca P, Alsarraj M, Chambers AF, et al. Correlation of osteopontin protein expression and pathological stage across a wide variety of tumor histologies. Clin Cancer Res. 2004;10:184–90. PubMed PMID: 14734468.
70. Zhang L, Hou X, Lu S, Rao H, Hou J, Luo R, Huang H, Zhao H, Jian H, Chen Z, Liao M, Wang X. Predictive significance of bone sialoprotein and osteopontin for bone metastases in resected Chinese non-small-cell lung cancer patients: a large cohort retrospective study. Lung Cancer. 2010;67:114–9.
71. Waltregny D, Bellahcène A, de Leval X, Florkin B, Weidle U, Castronovo V. Increased expression of bone sialoprotein in bone metastases compared with visceral metastases in human breast and prostate cancers. J Bone Miner Res. 2000;15:834–43. PubMed PMID: 10804012.
72. Bertoldo F, Silvestris F, Ibrahim T, Cognetti F, Generali D, Ripamonti CI, et al. Targeting bone metastatic cancer: role of the mTOR pathway. Biochim Biophys Acta. 2014;1845:248–54. https://doi.org/10.1016/j.bbcan.2014.01.009.
73. Mohammad KS, Javelaud D, Fournier PG, Niewolna M, McKenna CR, Peng XH, et al. TGF-beta-RI kinase inhibitor SD-208 reduces the development and progression of melanoma bone metastases. Cancer Res. 2011;71:175–84. https://doi.org/10.1158/0008-5472.CAN-10-2651. Erratum in: Cancer Res. 2011;71(5):2023. PubMed PMID: 21084275; PubMed Central PMCID: PMC3225124.
74. Yin JJ, Selander K, Chirgwin JM, Dallas M, Grubbs BG, Wieser R, et al. TGF-beta signaling blockade inhibits PTHrP secretion by breast cancer cells and bone metastases development. J Clin Invest. 1999;103:197–206. PubMed PMID: 9916131; PubMed Central PMCID: PMC407876.

75. Glantschnig H, Fisher JE, Wesolowski G, Rodan GA, Reszka AA. M-CSF, TNFalpha and RANK ligand promote osteoclast survival by signaling through mTOR/S6 kinase. Cell Death Differ. 2003;10:1165–77. PubMed PMID: 14502240.
76. Kneissel M, Luong-Nguyen NH, Baptist M, Cortesi R, Zumstein-Mecker S, Kossida S, et al. Everolimus suppresses cancellous bone loss, bone resorption, and cathepsin K expression by osteoclasts. Bone. 2004;35:1144–56. PubMed PMID: 15542040.
77. Mogi M, Kondo A. Down-regulation of mTOR leads to up-regulation of osteoprotegerin in bone marrow cells. Biochem Biophys Res Commun. 2009;384:82–6. https://doi.org/10.1016/j.bbrc.2009.04.084.
78. Moriceau G, Ory B, Mitrofan L, Riganti C, Blanchard F, Brion R, et al. Zoledronic acid potentiates mTOR inhibition and abolishes the resistance of osteosarcoma cells to RAD001 (Everolimus): pivotal role of the prenylation process. Cancer Res. 2010;70:10329–39. https://doi.org/10.1158/0008-5472.CAN-10-0578.
79. Chen J, Long F. mTORC1 signaling promotes osteoblast differentiation from preosteoblasts. PLoS One. 2015;10(6):e0130627. https://doi.org/10.1371/journal.pone.0130627.eCollection.
80. Ory B, Moriceau G, Redini F, Heymann D. mTOR inhibitors (rapamycin and its derivatives) and nitrogen containing bisphosphonates: bi-functional compounds for the treatment of bone tumours. Curr Med Chem. 2007;14:1381–7. PubMed PMID: 17584050.
81. Jung K, Lein M. Bone turnover markers in serum and urine as diagnostic, prognostic and monitoring biomarkers of bone metastasis. BBA. 2014;1846:425–38. https://doi.org/10.1016/j.bbcan.2014.09.001.
82. Seibel MJ. Biochemical markers of bone turnover: part I: biochemistry and variability. Clin Biochem Rev. 2005;26:97–122. PubMed PMID: 16648882; PubMed Central PMCID: PMC1320175.
83. Hlaing TT, Compston JE. Biochemical markers of bone turnover - uses and limitations. Ann Clin Biochem. 2014;51:189–202. https://doi.org/10.1177/0004563213515190.
84. de la Piedra C, Castro-Errecaborde NA, Traba ML, Méndez-Dávila C, García-Moreno C, Rodriguez de Acuña L, et al. Bone remodeling markers in the detection of bone metastases in prostate cancer. Clin Chim Acta. 2003;331:45–53. PubMed PMID: 12691863.
85. Galvano A, Scaturro D, Badalamenti G, et al. Denosumab for bone health in prostate and breast cancer patients receiving endocrine therapy? A systematic review and a meta-analysis of randomized trials. J Bone Oncol. 2019;18:100252. Published 2019 Jul 16. https://doi.org/10.1016/j.jbo.2019.100252.
86. Garnero P, Vassy V, Bertholin A, Riou JP, Delmas PD. Markers of bone turnover in hyperthyroidism and the effects of treatment. J Clin Endocrinol Metab. 1994;78:955–9. PubMed PMID: 8157727.
87. Coleman R, Costa L, Saad F, Cook R, Hadji P, Terpos E, et al. Consensus on the utility of bone markers in the malignant bone disease settin. Crit Rev Oncol Hematol. 2011;80:411–32. https://doi.org/10.1016/j.critrevonc.2011.02.005.
88. Wheater G, Elshahaly M, Tuck SP, Datta HK, van Laar JM. The clinical utility of bone marker measurements in osteoporosis. J Transl Med. 2013;11:201. https://doi.org/10.1186/1479-5876-11-201.
89. Kyvernitakis I, Rachner TD, Urbschat A, Hars O, Hofbauer LC, Hadji P. Effect of aromatase inhibition on serum levels of sclerostin and dickkopf-1, bone turnover markers and bone mineral density in women with breast cancer. J Cancer Res Clin Oncol. 2014;140:1671–80. https://doi.org/10.1007/s00432-014-1726-z.
90. Anastasilakis AD, Polyzos SA, Gkiomisi A, Bisbinas I, Gerou S, Makras P. Comparative effect of zoledronic acid versus denosumab on serum sclerostin and dickkopf-1 levels of naive postmenopausal women with low bone mass: a randomized, head-to-head clinical trial. J Clin Endocrinol Metab. 2013;98:3206–12. https://doi.org/10.1210/jc.2013-1402.
91. Leto G, Incorvaia L, Flandina C, et al. Clinical impact of cystatin C/Cathepsin L and Follistatin/Activin a systems in breast cancer progression: a preliminary report. Cancer Invest. 2016;34(9):415–23. https://doi.org/10.1080/07357907.2016.1222416.
92. Roelofs AJ, Thompson K, Gordon S, Rogers MJ. Molecular mechanisms of action of bisphosphonates: current status. Clin Cancer Res. 2006;12:6222s–30s.
93. Luckman SP, Hughes DE, Coxon FP, Graham R, Russell G, Rogers MJ. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTPbinding proteins, including Ras. J Bone Miner Res. 1998;13:581–9.
94. van Beek E, Pieterman E, Cohen L, Löwik C, Papapoulos S. Nitrogen-containing bisphosphonates inhibit isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase activity with relative potencies corresponding to their antiresorptive potencies in vitro and in vivo. Biochem Biophys Res Commun. 1999;255:491–4. PubMed PMID: 10049736.
95. Mönkkönen H, Auriola S, Lehenkari P, Kellinsalmi M, Hassinen IE, Vepsäläinen J, et al. A new endogenous ATP analog (ApppI) inhibits the mitochondrial adenine nucleotide translocase (ANT) and is responsible for the apoptosis induced by nitrogencontaining bisphosphonates. Br J Pharmacol. 2006;147:437–45.
96. Coleman R, Gnant M, Morgan G, Clezardin P. Effects of bone-targeted agents on cancer progression and mortality. J Natl Cancer Inst. 2012;104:1059–67. https://doi.org/10.1093/jnci/djs263.
97. Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2012;2:CD003474.
98. Body JJ. Rationale for the use of bisphosphonates in osteoblastic and osteolytic bone lesions. Breast. 2003;12:S37–44. PubMed PMID:14659142.
99. Heras P, Kritikos K, Hatzopoulos A, Georgopoulou AP. Efficacy of ibandronate for the treatment of skeletal events in patients with metastatic breast cancer. Eur J Cancer Care (Engl). 2009;18:653–6. https://doi.org/10.1111/j.1365-2354.2008.00980.x.
100. Kohno N, Aogi K, Minami H, Nakamura S, Asaga T, Iino Y, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. J Clin Oncol. 2005;23(15):3314–21. PubMed PMID: 15738536.
101. Kristensen B, Ejlertsen B, Groenvold M, Hein S, Loft H, Mouridsen HT. Oral clodronate in breast cancer patients with bone metastases: a randomized study. J Intern Med. 1999;246:67–74. PubMed PMID: 10447227.
102. Lipton A. Bisphosphonates and breast carcinoma: present and future. Cancer. 2000;88:3033–7. PubMed PMID: 10898348.
103. Paterson AH, Powles TJ, Kanis JA, McCloskey E, Hanson J, Ashley S. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. J Clin Oncol. 1993;11:59–65. PubMed PMID: 8418243.
104. Tubiana-Hulin M, Beuzeboc P, Mauriac L, Barbet N, Frenay M, Monnier A, et al. Double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases. Bull Cancer. 2001;88:701–7. PubMed PMID: 11495824.
105. Coleman R, Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised

trials. Lancet. 2015;386:1353–61. https://doi.org/10.1016/S0140-6736(15)60908-4.
106. Hadji P, Coleman RE, Wilson C, Powles TJ, Clézardin P, Aapro M, et al. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. Ann Oncol. 2016;27:379–90. https://doi.org/10.1093/annonc/mdv617.
107. Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol. 2003;169:2008–12. PubMed PMID: 12771706.
108. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94:1458–68.
109. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastic hormone refractory prostate carcinoma. J Natl Cancer. Inst. 2004;96:879–82.
110. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP. Spears MR, et al; STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387:1163–77. https://doi.org/10.1016/S0140-6736(15)01037-5.
111. Smith MR, Halabi S, Ryan CJ, Hussain A, Vogelzang N, Stadler W, et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). J Clin Oncol. 2014a;32:1143–50. https://doi.org/10.1200/JCO.2013.51.6500.
112. Martin M, Bell R, Bourgeois H, Brufsky A, Diel I, Eniu A, et al. Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. Clin Cancer Res. 2012;18:4841–9. PubMed PMID: 22893628.
113. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377:813–22.
114. Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol. 2011;29:1125–32. https://doi.org/10.1200/JCO.2010.31.3304.
115. Lipton A, Fizazi K, Stopeck AT, Henry DH, Smith MR, Shore N, et al. Effect of denosumab versus zoledronic acid in preventing skeletal-related events in patients with bone metastases by baseline characteristics. Eur J Cancer. 2016;53:75–83. https://doi.org/10.1016/j.ejca.2015.09.011.
116. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J, ESMO Guidelines Working Group. Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2014;25(Suppl 3):iii124–37. https://doi.org/10.1093/annonc/mdu103.
117. Gralow JR, Biermann JS, Farooki A, Fornier MN, Gagel RF, Kumar R, et al. NCCN task force report: bone health in cancer care. J Natl Compr Cancer Netw. 2013;11(Suppl 3):S1–50. PubMed PMID: 23997241.
118. Van Poznak CH, Temin S, Yee GC, Janjan NA, Barlow WE, Biermann JS, et al. American Society of Clinical Oncology. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. J Clin Oncol. 2011;29(9):1221–7. https://doi.org/10.1200/JCO.2010.32.5209. Erratum in: J Clin Oncol. 2011 Jun 1;29(16):2293. PubMed PMID: 21343561.
119. Agarawal JP, Swangsilpa T, van der Linden Y, Rades D, Jeremic B, Hoskin PJ. The role of external beam radiotherapy in the management of bone metastases. Clin Oncol (R Coll Radiol). 2006;18:747–60.
120. Lutz S, Chow E. A review of recently published radiotherapy treatment guidelines for bone metastases: contrasts or convergence? J Bone Oncol. 2012;1:18–23.
121. Roqué I, Figuls M, Martinez-Zapata MJ, Scott-Brown M, Alonso-Coello P. Radioisotopes for metastatic bone pain. Cochrane Database Syst Rev. 2011;(7):CD003347.
122. Sartor O, Reid RH, Bushnell DL, Quick DP, Ell PJ. Safety and efficacy of repeat administration of samarium Sm-153 lexidronam to patients with metastatic bone pain. Cancer. 2007;109:637–43.
123. Silberstein EB. Dosage and response in radiopharmaceutical therapy of painful osseous metastases. J Nucl Med. 1996;37:249–52.
124. Allen BJ. Clinical trials of targeted alpha therapy for cancer. Rev Recent Clin Trials. 2008;3:185–91.
125. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213–23.
126. Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012;366:520–9.
127. Gnant M, Baselga J, Rugo HS, Noguchi S, Burris HA, Piccart M, et al. Effect of everolimus on bone marker levels and progressive disease in bone in BOLERO-2. J Natl Cancer Inst. 2013;105:654–63.
128. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13:983–92.
129. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368:138–48.
130. O'Donnell A, Judson I, Dowsett M, Raynaud F, Dearnaley D, Mason M, Harland S, et al. Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. Br J Cancer. 2004;90:2317–25.
131. Barrie SE, Potter GA, Goddard PM, Haynes BP, Dowsett M, Jarman M. Pharmacology of novel steroidal inhibitors of cytochrome P450(17) alpha (17 alpha-hydroxylase/C17-20 lyase). J Steroid Biochem Mol Biol. 1994;50:267–73.
132. Attard G, Reid AH, Auchus RJ, Hughes BA, Cassidy AM, Thompson E, et al. Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. J Clin Endocrinol Metab. 2012;97:507–16.
133. Iuliani M, Pantano F, Buttigliero C, Fioramonti M, Bertaglia V, Vincenzi B, et al. Biological and clinical effects of abiraterone on anti-resorptive and anabolic activity in bone microenvironment. Oncotarget. 2015;6(14):12520–8.
134. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, PREVAIL Investigators, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371:424–33. https://doi.org/10.1056/NEJMoa1405095.
135. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, AFFIRM Investigators, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367:1187–97. PubMed PMID: 22894553.
136. Tsai SY, Huang YL, Yang WH, Tang CH. Hepatocyte growth factor-induced BMP-2 expression is mediated by c-Met receptor,

FAK, JNK, Runx2, and p300 pathways in human osteoblasts. Int Immunopharmacol. 2012;13:156–62. https://doi.org/10.1016/j.intimp.2012.03.026.
137. Taichman R, Reilly M, Verma R, Ehrenman K, Emerson S. Hepatocyte growth factor is secreted by osteoblasts and cooperatively permits the survival of haematopoietic progenitors. Br J Haematol. 2001;112:438–48.
138. Sonnenberg E, Meyer D, Weidner KM, Birchmeier C. Scatter factor/hepatocyte growth factor and its receptor, the c-met tyrosine kinase, can mediate a signal exchange between mesenchyme and epithelia during mouse development. J Cell Biol. 1993;123:223–35.
139. Takai K, Hara J, Matsumoto K, Hosoi G, Osugi Y, Tawa A, et al. Hepatocyte growth factor is constitutively produced by human bone marrow stromal cells and indirectly promotes hematopoiesis. Blood. 1997;89:1560–5.
140. Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther. 2011;10:2298–308. https://doi.org/10.1158/1535-7163.mct-11-0264.
141. Grano M, Galimi F, Zambonin G, Colucci S, Cottone E, Zallone AZ, et al. Hepatocyte growth factor is a coupling factor for osteoclasts and osteoblasts in vitro. Proc Natl Acad Sci U S A. 1996;93:7644–8.
142. Deckers MM, Karperien M, van der Bent C, Yamashita T, Papapoulos SE, Lowik CW. Expression of vascular endothelial growth factors and their receptors during osteoblast differentiation. Endocrinology. 2000;141:1667–74. https://doi.org/10.1210/endo.141.5.7458.
143. Gerber HP, Vu TH, Ryan AM, Kowalski J, Werb Z, Ferrara N. VEGF couples hypertrophic cartilage remodeling, ossification and angiogenesis during endochondral bone formation. Nat Med. 1999;5:623–8. https://doi.org/10.1038/9467.
144. Graham TJ, Box G, Tunariu N, Crespo M, Spinks TJ, Miranda S, et al. Preclinical evaluation of imaging biomarkers for prostate cancer bone metastasis and response to cabozantinib. J Natl Cancer Inst. 2014;106:dju033. https://doi.org/10.1093/jnci/dju033.
145. Nguyen HM, Ruppender N, Zhang X, Brown LG, Gross TS, Morrissey C, et al. Cabozantinib inhibits growth of androgen-sensitive and castration-resistant prostate cancer and affects bone remodeling. PLoS One. 2013;8:e78881. https://doi.org/10.1371/journal.pone.0078881.
146. Dai J, Zhang H, Karatsinides A, Keller JM, Kozloff KM, Aftab DT, et al. Cabozantinib inhibits prostate cancer growth and prevents tumor-induced bone lesions. Clin Cancer Res. 2014;20:617–30. https://doi.org/10.1158/1078-0432.ccr-13-0839.
147. Fioramonti M, Santini D, Iuliani M, Ribelli G, Manca P, Papapietro N, et al. Cabozantinib targets bone microenvironment modulating human osteoclast and osteoblast functions. Oncotarget. 2017;8(12):20113–21. https://doi.org/10.18632/oncotarget.15390.
148. Smith DC, Smith MR, Sweeney C, Elfiky AA, Logothetis C, Corn PG, et al. Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial. J Clin Oncol. 2013;31:412–9. https://doi.org/10.1200/jco.2012.45.0494.
149. Smith MR, Sweeney CJ, Corn PG, Rathkopf DE, Smith DC, Hussain M, et al. Cabozantinib in chemotherapy-pretreated metastatic castration-resistant prostate cancer: results of a phase II nonrandomized expansion study. J Clin Oncol. 2014b;32:3391–9. https://doi.org/10.1200/jco.2013.54.5954.
150. Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III study of cabozantinib in previously treated metastatic castration-resistant prostate cancer: COMET-1. J Clin Oncol. 2016;34:3005–13. https://doi.org/10.1200/jco.2015.65.5597.
151. Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1814–23. https://doi.org/10.1056/NEJMoa1510016.
152. Santini D, Tonini G. Treatment of advanced renal-cell carcinoma. N Engl J Med. 2016;374:888–9. https://doi.org/10.1056/NEJMc1515613#SA2.
153. Motzer RJ, Escudier B, Choueiri TK. Treatment of advanced renal-cell carcinoma. N Engl J Med. 2016;374:889–90. https://doi.org/10.1056/NEJMc1515613.
154. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3:991–8.
155. Swann JB, Smyth MJ. Immune surveillance of tumors. J Clin Invest. 2007;117:1137–46.
156. Danilin S, Merkel AR, Johnson JR, Johnson RW, Edwards JR, Sterling JA. Myeloid-derived suppressor cells expand during breast cancer progression and promote tumor-induced bone destruction. Oncoimmunology. 2012;1:1484–1494.
157. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol. 2012;12:253–68.
158. Sawant A, Ponnazhagan S. Myeloid-derived suppressor cells as osteoclast progenitors: a novel target for controlling osteolytic bone metastasis. Cancer Res. 2013;73:4606–10.
159. Buenrostro D, Park SI, Sterling JA. Dissecting the role of bone marrow stromal cells on bone metastases. Biomed Res Int. 2014;2014:875305.
160. Sinder BP, Pettit AR, McCauley LK. Macrophages: Their Emerging Roles in Bone. J Bone Miner Res. 2015;30:2140–9.
161. Loriot Y, Miller K, Sternberg CN, Fizazi K, De Bono JS, Chowdhury S, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. Lancet Oncol. 2015;16:509–21.