Novel Bone Targeted Strategies in Oncology

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Running head: Management of Bone Disease

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TRANSLATIONAL RELEVANCE

Advances in understanding the pathogenesis of bone disease in solid and hematological cancers have led to the identification of novel targets. Critical to the development of osteolytic or osteoblastic bone metastasis are the deregulated activities of osteoblasts and osteoclasts leading to altered bone remodeling. Additionally, preclinical and clinical studies suggest that the altered bone microenvironment may facilitate tumor growth. Therefore, restoring bone homeostasis is a strategy for novel bone-directed therapies. This review highlights the challenges in the treatment of bone metastasis and discusses current clinical trials for the treatment of bone metastasis with a specific focus on novel targets.
ABSTRACT

Most patients with bone metastases experience skeletal complications resulting in significant morbidity and increased risk of death. Although bisphosphonates are well-established supportive care treatment for bone metastasis, complications arising from long-term use require schedule optimization and search for alternate strategies. Moreover, the scope of use of bone-targeted agents in oncology has widened to include therapy-induced bone loss and anti-tumor effects. Indeed, bone provides a permissive niche to tumor growth and targeting the interactions within the bone microenvironment is a promising anti-tumor strategy. In addition, the pathogenesis of cancer-related bone disease has been partially unraveled with a focus on the anabolic bone compartment and the rapid bench to bedside translation has resulted in the identification of novel therapeutically amenable targets.

This review focuses on studies optimizing bisphosphonate use and recent clinical data on denosumab in the treatment of bone disease. We also provide data on trials evaluating their anti-tumor effects and summarize the most recent discoveries on the role of the bone niche in cancer development, with insights into the preclinical rationale and clinical assessment of novel antiresorptive and anabolic bone-targeted agents.
SCOPE OF THE PROBLEM

Bone involvement is a common feature in solid and hematological cancers. Multiple myeloma localizes to the bone in nearly all patients, and the incidence of bone metastasis in solid cancers ranges between 20 and 75% (1, 2). Disease-related skeletal complications result in significant morbidity due to pain, pathological fractures and spinal cord compression (3). In addition, the occurrence of pathologic fractures increases the risk of death by 20-40% (4). Not only is bone involvement due to metastatic disease of significance, but the increasing incidence of therapy-related bone loss has widened the scope of use of bone targeted agents in oncology (5). In addition, recent preclinical and clinical studies suggest that bone provides a permissive niche to tumor cell growth and targeting the interactions within the bone milieu may represent an important strategy to suppress tumor development (6, 7). Therefore, restoring a balanced bone environment may not only positively impact bone disease but also be of benefit to reduce tumor burden.

Here, we provide an overview of novel biologically based therapeutic strategies aiming at preventing and/or decreasing disease-related skeletal complications and discuss the evidence for anti-tumor effects from restored bone homeostasis.
BIOLOGY OF BONE DISEASE AND METASTASIS

The skeleton is a dynamic organ that undergoes extensive remodeling throughout life. Modest changes in the kinetics of bone resorption and formation result in dramatic net effects on bone architecture (8). In the cancer setting, the cross-talk between tumor and bone cells disrupts normal bone homeostasis, leading to development of skeletal lesions (Figure 1). Although activation of osteoclasts (OC), the bone-resorbing cells, is a common feature in both osteolytic and osteoblastic bone metastasis; the development of either type of lesions depends on the effects on osteoblasts (OB), the bone-forming cells. Inhibition of OB results in osteolysis, typical of myeloma and breast cancer metastasis, while OB hyperactivity results in osteoblastic lesions seen in prostate and sometimes breast cancer metastasis (3, 9).

Several cytokines are upregulated in the tumoral-bone milieu promoting OC activity. Receptor activator of NF-kappa β-ligand (RANKL) together with its antagonist osteoprotegerin (OPG) regulate osteoclastogenesis, and disruption of this balance is demonstrated in many cancers (10, 11). OC differentiation and activity are also promoted by several tumor-cell derived OC activating factors (OAF), such as parathyroid hormone-related protein (PTHrp), interleukins, and chemokines (12-16).

OB inhibition induced by breast cancer and myeloma cells depends on contact-mediated RUNX2 downregulation (17) and secretion of inhibitory cytokines, such as activin A and DKK1 (Figure 1A) (18-20). In contrast,
downregulation of DKK1 by prostate cancer-derived endothelin 1 induces OB hyperactivity (21). Here the uncoupled osteoblastic response to increased OC resorption leads to disorganized new bone formation and osteosclerotic lesions (Figure 1B).

The bone microenvironment creates a supportive niche for tumor growth. OCs and BMSCs, along with extracellular matrix and cytokines stimulate tumor cell proliferation and confer chemoresistance (22, 23). Therefore, the reciprocal interactions between tumor cells, OC, OB and BMSC represent an important but underexploited clinical target to restore physiologic bone remodeling and suppress tumor growth.

**BISPHOSPHONATES: ALTERNATE DOSING SCHEDULES AND NOVEL INDICATIONS**

Bisphosphonates (BPs) are the only FDA-approved agents for the treatment of bone metastases from solid tumors and multiple myeloma, in conjunction with standard antineoplastic therapy (24). The inhibitory effects of BPs on bone resorption are long-lasting and persist after therapy discontinuation. Interestingly, a parallel decrease in bone formation has been observed with BP treatment, probably related to high doses rather than cumulative doses, since this trend reverses with therapy discontinuation (25, 26). A recent in vivo study showed that high-cumulative doses of zoledronic acid (ZA), in contrast to low-cumulative doses, interferes with bone remodeling by inhibiting both OC and OB
function and may influence the mechanical properties of bone (27). These profound effects on bone turnover may in part contribute to complications such as osteonecrosis of the jaw (ONJ). In the oncologic setting BPs have often been used on a monthly-schedule for long periods of time, leading to high cumulative exposures. Myeloma patients with ONJ have a gene and protein profiling consistent with suppression of both bone resorption and formation (28). Moreover, a recent retrospective analysis of 4000 BP-treated patients identified median dose and duration of treatment as significant risk factors for ONJ development (29). The ASCO guidelines for the use of BPs in myeloma-related bone disease have been recently updated to address concerns about ONJ (30) and new clinical trials are underway to optimize BP administration schedule.

As shown in table 1, BPs are currently being evaluated with alternate dosing and scheduling and with the use of bone biomarker directed schedules. Monthly vs every 3-month based ZA schedules in breast cancer patients are evaluated in the OPTIMIZE trial (NCT00424983). Alternate dosing schedules of BPs based on markers of bone resorption are also under assessment. N-telopeptide of type 1 collagen (NTX) is a product of bone catabolism. Elevated NTX levels are highly predictive of skeletal complications (pain, fractures and need for intervention) (31), and therefore useful to monitor response to antiresorptive agents. The BISMARK (NCT00458796) and Z-MARK (NCT00622505) trials aim at tailoring ZA treatment according to NTX levels in breast and myeloma patients. These are important studies and their results will
validate the usefulness of NTX as a surrogate marker of bone resorption to predict SREs and tailor BP therapy.

The most likely mechanism of action of nitrogen-containing BPs is inhibition of farnesyl pyrophosphate synthase in the mevalonate pathway (32). In addition to inhibition of signaling proteins, such as RAS-ERK (33), BP anti-tumor effects are mediated by downregulation of telomerase expression, induction of apoptosis and inhibition of cell proliferation (34, 35). BPs may play an anti-tumor role also by modifying the tumor microenvironment via anti-OC, anti-angiogenic and immunomodulatory effects (36). Interestingly, ZA in combination with IL-2 achieved a clinical response in prostate cancer patients (37, 38). Preclinical studies suggest that the anti-tumor effects of BPs may rely on the administration schedules. For example, metronomic ZA downregulates VEGF with stronger anti-angiogenic effects (36) and sequential chemotherapy-ZA treatment induces synergistic cytotoxicity on both breast and prostate cancer cell lines. (39) Clinical studies with pamidronate suggest a survival advantage to second-line treated myeloma patients (40). More recently, improved overall survival has been shown in metastatic prostate cancer patients treated with oral clodronate in combination with hormonal therapy (41). The ABCSG-12 trial (NCT00295646) in breast cancer patients demonstrates an advantage to disease-free survival in the subgroup receiving ZA and adjuvant endocrine therapy (94% vs 90.8% with a median follow-up of 47.8 months) (42) (Table 2). Similarly, the AZURE trial (NCT00072020) suggests that addition of ZA to neoadjuvant chemotherapy improves response by decreasing residual invasive tumor size (43) (Table 2).
These results although intriguing need further study and ongoing clinical trials are addressing potential anti-tumor effects of BPs in breast and prostate cancer.

DENOSUMAB: A NOVEL RANKL-TARGETED THERAPY.

The significant catabolic effects of RANKL on bone remodeling, and its key pathogenetic role played in many cancers provide the rationale for the development of RANKL inhibitors, such as denosumab (AMG 162, Amgen, Thousand Oaks, CA), a subcutaneously-injected neutralizing antibody against human RANKL (44). Denosumab induces a sustained inhibition of bone resorption markers (45). In oncologic patients with elevated NTX levels despite BP treatment, denosumab inhibited bone resorption and prevented SREs in a higher proportion of patients compared to BP continuation (46).

Not only is denosumab a promising alternative for patients refractory to BPs, but recent studies suggest that monthly denosumab (120 mg) is superior to ZA (4 mg monthly) in delaying time to first and subsequent SREs in breast cancer patients (47) (NCT00321464, table 1). A similar study in myeloma and solid cancers showed that the two agents were comparable (48) (NCT00330759, table 1). Notably, the incidence of adverse events, including infections and ONJ, did not differ between the two treatment groups. A large head-to-head study in castration-resistant prostate cancer showed the superiority of denosumab to ZA in the treatment of bone metastases (Amgen, data on file) (NCT00321620, table 1).
RANKL triggers bone metastasis by stimulating migration and homing of RANK-expressing epithelial and melanoma cancer cells (49). Increased RANKL expression is an independent predictor of recurrence and confers poor prognosis in renal and prostate cancer (50, 51). In preclinical models, inhibition of the RANKL pathway resulted not only in decreased bone metastasis and osteolytic lesions, but also decrease in tumor burden and improved survival (52-54). Single agent Denosumab induced an 86% response rate in patients with giant cell tumor of bone, characterized by OC proliferation among RANKL expressing stromal cells (55). Denosumab has also been assessed for its anti-tumor effects in relapsed or refractory myeloma patients (n=50) (NCT00259740, table 2) (56). Although monthly injections of denosumab 120 mg induced stable disease in a subset of patients, the small number of patients enrolled in the study did not allow any conclusions on the anti-tumor effect of denosumab in myeloma. In the setting of hormone refractory prostate cancer, an ongoing randomized trial is assessing denosumab (120 mg monthly) versus placebo on bone metastasis-free and overall survival (NCT00286091, table 1). Further studies in combination strategies or in a remission setting will be useful to clarify any anti-tumor effects.

OTHER BIOLOGICALLY-BASED NOVEL DRUGS

Novel targets to inhibit OC-mediated bone resorption

In addition to the RANKL/OPG ratio imbalance, cancer-induced OC activation is associated with secretion of several OAFs that represent important
therapeutic targets (Figure 2). MM-derived CCL3 stimulates OC precursor fusion into active resorptive cells by interacting with the receptor CCR1 (57). Preclinical studies on inhibition of the CCR1/CCL3 pathway by antisense strategies and small molecule CCR1 inhibitors showed restoration of normal bone architecture together with interruption of OC-MM cell interactions (57, 58). Since CCL3 has a stimulatory effect on MM cell growth, strategies to inhibit the CCL3/CCR1 pathway may also have an effect on tumor burden. Therefore, agents targeting the CCL3/CCR1 pathway may soon be assessed in the clinical setting.

Novel agents with both anti-tumor and anti-OC activity are the B-cell activating factor (BAFF) neutralizing antibodies. BAFF is an OC-derived MM growth factor and its inhibition reduces tumor burden as well as lytic lesions in in-vivo models of bone disease (59). Since the neutralizing BAFF antibody impairs MM-BMSCs interactions, the anti-OC activity observed in vivo may be mediated by reduction in MM burden or decreased secretion of pro-OC cytokines. (60) Based on these promising data, clinical trials of BAFF neutralizing antibody (LY2127399) in combination with Velcade® (Millennium Takeda Oncology) are currently ongoing to confirm the effects on bone lesions and tumor burden (NCT00689507, table 3).

Bone resorption by mature OC relies on sequential steps that represent therapeutically amenable targets. OCs adhesion to the bone surface is mediated by integrins, the most important being αVβ3, and subsequent formation of the ruffled border depends on the tyrosine kinase Src. Two orally active c-Src inhibitors are currently being studied in Phase II/III clinical trials. AZD0530 is
evaluated in breast and prostate cancer patients in comparison to zoledronic acid (NCT00558272, table 3). Single-agent dasatinib normalizes NTX and ALP levels in more than 50% of patients with metastatic castration resistant prostate cancer. (61) The combination with docetaxel suggests an anti-tumor together with anti-OC activity (62) and a phase III randomized trial is ongoing to evaluate docetaxel with or without dasatinib (NCT00744497, table 3). Bone matrix degradation is achieved via secretion of acid, depending on chloride channels and protonic ATP-pumps, and release of collagenolytic enzymes, such as cathepsins (63). Cathepsin K is a lysosomal proteinase, whose knockdown induces an osteopetrotic phenotype (64). Inhibition of cathepsin K via the orally available Odanacatib reduced NTX levels similar to BPs in metastatic breast cancer patients (65). These studies will provide novel antiresorptive agents for use in the setting of bone metastasis.

**Targeting OB function.**

To date, attention has largely been focused on targeting the OC. However, osteolytic lesions in myeloma and breast cancer patients are associated with impaired OB function leading to an imbalanced OC/OB axis. Therefore, therapeutic strategies aiming at restoring OB differentiation are now being explored as well (Figure 2).

DKK1 is a WNT inhibitor that binds and sequesters the WNT receptor subunit LRP5, therefore inhibiting WNT/β-catenin signaling. We have studied the anabolic effects of two clinical-grade DKK1 neutralizing antibodies, BHQ880
(Novartis International, Basel, Switzerland) and Mab B3 (Ely Lilly, Indianapolis, Indiana) in our preclinical model of human MM-bone disease. DKK1 inhibition increased bone formation, decreased osteolytic lesions and provided an anti-tumor activity (66, 67). A clinical trial combining BHQ880 and BPs in relapsed/refractory myeloma patients is currently ongoing (NCT00741377, Table 3). Other WNT inhibitors may be involved in the pathogenesis of OB inhibition by myeloma cells, in particular sclerostin is an OB inhibitor released by osteocytes. The promising bone-anabolic effects of sclerostin antagonists in osteoporotic patients establish sclerostin as a novel appealing target also in cancer-induced bone disease (68). Of note, however the safety profile of these anabolic agents raises some concerns regarding potential tumorigenic effects. Indeed, tumor cells are characterized by active WNT signaling and inhibition of the β-catenin pathway reduces tumor burden (69, 70). Therefore, all anabolic agents acting on the WNT/β-catenin pathway require further studies to exclude any stimulatory effects on tumor growth (7).

A novel mechanism of OB inhibition involving the activin/SMAD2/DLX5 pathway has been recently identified. High BM plasma activin A levels correlate with osteolysis and DLX5 downregulation in BM biopsies of myeloma patients (20). In vivo targeting of this pathway with an activin A inhibitor improves bone disease and reduces tumor burden in a humanized model of MM. The effects of the humanized activin A inhibitor, ACE-011 (Acceleron Pharma, Cambridge, MA) in restoring the bone balance are currently under study in a phase II clinical trial in MM patients with osteolytic lesions (NCT00747123, table 3).
A different pathogenic mechanism is involved in the development of osteosclerotic lesions in prostate and breast cancer patients. Cancer cell-derived endothelin-1 stimulates OB function via inhibition of DKK1 synthesis (21). Inhibition of endothelin-A receptor via atrasentan or ZD4054 impairs the tumor-induced OB response in preclinical model of prostate and breast cancer (71). However, in hormone-refractory prostate cancer the effects of atrasentan on disease progression are discordant (72-74). Also in combination strategies with conventional chemotherapy agents such as docetaxel in prostate cancer and carboplatin/paclitaxel in lung cancer, atrasentan did not add any benefits on overall or progression-free survival (75, 76). In the setting of bone metastasis of prostate cancer, atrasentan and ZA did not prove synergistic on markers of bone metabolism (77). More extensive studies are required to assess the efficacy of endothelin inhibition strategies (NCT005554229) (Table 3). Another option to achieve OB inhibition is provided by radiopharmaceuticals, strontium-89 and samarium-153, that localize preferentially to areas of active bone formation. (78) Not only do they provide pain relief in patients with bone metastasis, but may also improve survival in combination with chemotherapy. (79)

Although OC activation is a common pathogenic event in bone disease, OB activity determines the development of osteolytic or osteoblastic metastasis and, therefore, represents an important target. In order to treat bone disease and suppress tumor growth, future strategies will require a combination of antiresorptive and anabolic agents.
CONCLUSIONS

Bench to bedside translation in the field of bone-targeted agents will provide oncologists with several novel therapeutic options for the treatment of bone metastasis. The identification of optimal parameters to assess therapeutic efficacy is therefore critical. Bone surrogate markers like NTX levels have been used to evaluate the efficacy of novel bone-targeted agents. However, clinical endpoints such as number of bone metastasis and survival rates still remain important parameters to determine the therapeutic potential of novel agents in cancer-induced bone disease. Additionally, novel functional imaging modalities will become a part of assessing responses to these agents.

To understand the role of bone-targeted agents, it is also critical that we take into account the role of anti-tumor strategies with effects on bone remodeling. For example, immunomodulatory drugs like lenalidomide and pomalidomide exert anti-OC effects (80, 81). Bortezomib, a proteasome inhibitor, stimulates OB differentiation via upregulation of RUNX2 and inhibits OC development (82, 83). Therefore, the effects of bone-targeted drugs should be assessed in the context of bone effects of these novel anti-tumor agents.

The stage is set to study therapeutic strategies not only to inhibit cancer-related bone disease but also to target the dissemination of cancer cells to sanctuary sites in the bone. Greater understanding of bone biology will inform these strategies. Novel biomarkers and functional imaging modalities will facilitate future drug development.
REFERENCES


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FIGURE LEGENDS:

**Figure 1: Biology of bone metastasis.**

The crosstalk between tumor and bone cells disrupt normal bone homeostasis, leading to development of skeletal lesions. Increased osteoclast activity is a common event in bone metastasis, resulting from upregulation of growth factors like RANKL, interleukins (IL) and chemokines (CCL2 and CCL3). However, development of osteolytic or osteosclerotic lesions depends on osteoblast number and function. (A) Osteolytic lesions are characterized by inhibition of osteoblast differentiation and activity that is at least partially related to high levels of activin and dickkopf-1 (DKK1) that impairs the expression of osteogenic transcription factors. (B) In contrast, tumor cell derived endothelin-1 induces osteoblast hyperactivity that translates in disorganized new bone formation and development of osteoblastic lesions seen in prostate and sometimes breast cancer metastasis.

**Figure 2: Novel drug targets**

Recent understanding of the pathogenesis of bone disease has translated in the development of novel bone-targeted agents. Other than bisphosphonates, osteoclast activation can be targeted by RANKL neutralizing antibodies (denosumab) and CCR1 inhibitors (MLN3897) that impair osteoclastogenesis; as well as Src inhibitors (AZD0530) blocking mainly OC bone resorptive activity. Inhibition of tumor growth factors via BAFF neutralizing antibodies (LY2127355) proved indirect anti-osteoclast effects. To restore the bone remodeling balance,
patients with osteolytic lesions whose osteoblasts are inactive may benefit from anabolic agents, such as DKK1 neutralizing antibodies (BHQ880) and activin antagonists (ACE-011) (left side). In case of osteoblastic metastatic lesions, characterized by osteoblast hyperactivity and uncoupled bone formation, endothelin-1 inhibitors (ZD4054) are under study for their anti–osteoblastic effects (right side).
Table 1. Clinical trials on treatment of cancer-related skeletal complications with BP and denosumab.

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<th>PATIENTS</th>
<th>AGENT and SCHEDULE</th>
<th>ENDPOINTS</th>
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<tbody>
<tr>
<td>NCT00424983, phase I</td>
<td>Breast cancer patients</td>
<td>Zoledronic acid every 4 weeks versus every 12 weeks</td>
<td>• Sequential plasma and urine concentrations of zoledronic acid</td>
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<td>• Concentration of bone resorption markers</td>
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<td>• Time to first SRE and proportion of SRE</td>
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<tr>
<td>NCT00458796, phase III</td>
<td>Breast cancer with bone metastasis treated with bisphosphonate for ≥ 4 months</td>
<td>Zoledronic acid iv monthly vs every 3-4, or 8-9, or 15-16 weeks based on serum NTX:creatinine ratio for 24 months</td>
<td>• Time to first SRE and proportion of SRE</td>
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<td>• Quality of life</td>
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<td>• Incidence of new bone metastases</td>
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<td>• Overall survival</td>
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<tr>
<td>NCT00622505, phase IV</td>
<td>Multiple myeloma on iv bisphosphonate for one to two years</td>
<td>Zoledronic acid iv 4 mg either 4 or 12 weeks for 96 weeks according to NTX levels</td>
<td>• Time to first SRE and proportion of SRE</td>
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<td>• Changes in bone biomarkers</td>
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<td>• Overall survival</td>
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<tr>
<td>NCT00321464, phase III (47)</td>
<td>Breast cancer patients with bone metastasis</td>
<td>Zoledronic acid iv 4 mg vs denosumab sc 120 mg monthly</td>
<td>• Time to first and subsequent on-study SRE</td>
</tr>
<tr>
<td>NCT00330759, phase III (48)</td>
<td>Solid tumors excluding breast and prostate, multiple myeloma, and lymphoma patients</td>
<td>Zoledronic acid iv 4 mg vs denosumab sc 120 mg monthly</td>
<td>• Time to the first and subsequent on-study SRE</td>
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<td>• Incidence of anti-denosumab antibody</td>
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<tr>
<td>NCT00321620, phase III</td>
<td>Prostate cancer patients with bone metastasis</td>
<td>Zoledronic acid iv 4 mg vs denosumab sc 120 mg monthly</td>
<td>• Time to the first and subsequent on-study SRE</td>
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<td>• Adverse eventsIncidence of anti-denosumab antibody</td>
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Abbreviations: iv, intravenous; sc, subcutaneous; NTX, N-telopeptide of type 1 collagen; SRE, skeletal related events.
Table 2. Clinical trials evaluating anti-tumor effects of Bisphosphonates or Denosumab

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<th>AGENT and SCHEDULE</th>
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| NCT00295646, phase III (42).  | Premenopausal, hormone receptor-positive breast cancer patients (stage I, II) | Anastrozole 1mg/day or tamoxifen 20mg/day, each with or without zoledronate 8mg/month for 3 years               | • Disease-free survival in each group.  
• Recurrence free survival and overall survival in each group.  
• Assess whether zoledronate added to standard adjuvant therapy can decrease or even prevent bone loss.  
• Adverse events                                                                 |
| NCT00072020, phase III (43)   | Stage II or stage III breast cancer patients                             | Neoadjuvant or adjuvant chemotherapy and/or hormonal therapy with or without zoledronate iv monthly for 6 doses, every 3 months for 8 doses, and then every 6 months for 5 doses | • Disease-free survival as assessed annually for 10 years  
• Time to bone metastases and to distant metastases  
• Overall survival  
• SRE prior to development and following development of bone metastases  
• Safety and toxicity of zoledronic acid                                                                 |
| NCT00259740, phase II (56)    | Relapsed or plateau-phase multiple myeloma patients                      | Denosumab 120 mg sc days 1, 8, 15, and 29 and every 28 days thereafter                                       | • Proportion of subjects that have a complete response or partial response to treatment  
• Overall safety profile of denosumab                                                                                                                                                                |
| NCT00286091, phase III        | Hormone refractory prostate cancer without bone metastasis at baseline   | Denosumab 120 mg sc monthly                                                                              | • Time to first occurrence of bone metastasis or death from any cause  
• Overall survival                                                                                                                                                                                    |

Abbreviations: iv, intravenous; sc, subcutaneous; SRE, skeletal related events.
Table 3. Clinical trials validating novel bone-targeted agents

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| NCT00689507, phase I       | Relapsed or refractory multiple myeloma | Dose escalation LY2127399 iv on day 1 and 1.3 mg/m² bortezomib iv on days 1, 4, 8, and 11 of each 21 day cycle | • Pharmacokinetic/dynamic modeling of LY2127399  
• Safety and toxicity profile for LY2127399 in combination with bortezomib  
• Response rate, duration of response, and time to progression of LY2127399 as a single-agent and in combination with bortezomib |
| NCT00558272, phase II      | Prostate or breast cancer with metastatic bone disease | AZD0530 daily oral dose compared to zoledronic acid                                | • Bone resorption markers  
• Safety and tolerability of AZD0530                                          |
| NCT00744497, phase III     | Castration-resistant prostate cancer   | Docetaxel/prednisone ± placebo or dasatinib daily oral dose                          | • Overall survival  
• Rate of change in urinary N-telopeptide values  
• Time to first skeletal related event  
• Rate of change in pain intensity  
• Time to prostate specific antigen (PSA) progression  
• Safety and tolerability of combination                                                   |
| NCT00741377, phase I/II    | Relapse/refractory multiple myeloma    | Phase I: escalating doses of BHQ880 in combination with standard chemotherapy and zoledronic acid.  
Phase II: BHQ880 in combination with standard chemotherapy. Zoledronic acid will be added after the first 28 days of therapy. | Phase I:  
• Maximum-tolerated dose and dose limiting toxicity  
Phase II:  
• Time to first SRE and change in bone markers for bone resorption and formation  
• Safety profile of BHQ880  
• Immunogenicity of BHQ880                                                               |
| NCT00747123, phase II      | Multiple myeloma with osteolytic lesions | Escalating doses of ACE-011 sc monthly vs placebo                                  | • Safety and tolerability of ACE-011  
• Change in biochemical markers of bone formation and resorption  
• Incidence of SREs                                                                  |
| NCT00554229, Phase III     | Castration-resistant prostate cancer and bone metastasis | ZD4054 orally 10 mg vs placebo                                                      | • Overall survival, progression-free survival  
• Tolerability and safety profile of ZD4054  
• Incidence of SREs and bone metastases                                                 |

Abbreviations: sc, subcutaneous; iv, intravenous; SREs, skeletal related events.
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