Effects of Denosumab versus Zoledronic Acid in Patients with Castration-Resistant Prostate Cancer and Bone Metastases

Neal Shore, MD, FACS[1] and Carsten Goessl, MD[2]

1. Director and Certified Physician Investigator, Carolina Urologic Research Center, South Carolina, US;
2. Clinical Research Medical Director, Amgen Inc, California, US

Abstract

Progression of castration-resistant prostate cancer often leads to bone metastases, increasing the risk of skeletal-related events (SREs). The use of antiresorptive therapies such as denosumab, a human monoclonal antibody and zoledronic acid (ZA), a bisphosphonate, reduces bone destruction by inhibiting osteoclast function and survival. In 2002, ZA was approved for the prevention of skeletal complications in patients with bone disease from myeloma or bone metastases from solid tumors including prostate cancer. Recently, efficacy analysis demonstrated superiority of denosumab to ZA for the prevention or delay of SREs in 1,901 patients with prostate cancer and bone metastases, significantly delaying the time to first SRE and time to first and subsequent SRE compared to ZA. Decreases in bone turnover markers were greater with denosumab, mirroring the reduction in SREs. The reported incidence of adverse events were similar between denosumab and ZA. Advanced prostate cancer patients require long-term disease management where maintenance of overall bone health is an essential component of a comprehensive treatment program.

Keywords

Denosumab; zoledronic acid, prostate cancer; bone metastases; skeletal related events

Disclosure: Neal Shore, MD, FACS, is an employee of Atlantic Urology Clinics and has been a consultant for Amgen Inc, Astellas, Bayer, Dendreon, Janssen, Medivation, and Sanofi. Dr Shore has also been an Investigator for Biotech, BMS, Millenium, Oncogenix, Progenics, BN Immunotherapeutics. Carsten Goessl, MD, is an employee of Amgen Inc and currently owns Amgen Inc stock and stock options.
Acknowledgment: Medical writing support was provided by Albert Y Rhee, PhD, Amgen Inc.
Received: August 6, 2012 **Accepted:** September 12, 2012 **Citation:** *Oncology & Hematology Review*, 2012;8(2):94–9 *DOI: 10.17925/OHR.2012.08.2.94*
Correspondence: Neal Shore, MD, FACS, Medical Director, Carolina Urologic Research Center, 823 82nd Parkway, Myrtle Beach, SC 29572, US. E: nshore@grandstrandurology.com

Worldwide, prostate cancer is one of the most commonly diagnosed cancers in men. Approximately 900,000 new cases are reported each year with an estimated 242,000 cases in the US alone.[1] Raised awareness leading to earlier detection and improved therapies have significantly extended life expectancy, as demonstrated by a decrease in US age-adjusted mortality of 3.7 % from 2004 to 2008.[1] However, cause-specific mortality rates are still at approximately 32,000 patients per year. First-line treatments for advanced prostate cancer often include androgen deprivation therapy (ADT) which decrease serum testosterone levels, thus inhibiting prostate cancer cell growth and delaying disease progression.[2] Initially, almost all advanced prostate cancer patients will respond to ADT with a reduction in prostate-specific antigen (PSA) in addition to radiographic regression. Nonetheless, biochemical and clinical responses to androgen deprivation are usually of limited duration. The castration-resistant cancer cells will proliferate and ultimately result in clinical progression. Castration-resistant prostate cancer (CRPC) can be broadly characterized as a progression of disease with an increase in PSA levels despite levels of testosterone less than 50 ng/dl.[3,4] In comparison with castration-sensitive prostate cancer, the prognosis for CRPC patients is poor and survival is markedly reduced.[5] Progression of CRPC often leads to bone metastases and skeletal-related events (SREs), leading to co-morbidities which may further reduce survival rates. Reported five-year survival rates for CRPC patients is 56 % without bone metastases, 3 % with bone metastases, and less than 1 % with bone metastases and SREs.[6]

Bone Metastases

For patients with advanced prostate cancer, the axial skeleton represents the most common site for metastases and approximately 90 % of all patients have evidence of bone metastases upon autopsy.[7] In adults, the major sites for bone metastases are the vertebral column, pelvis, ribs, long bones, and skull,[8] which also represent areas of active hematopoiesis.[9] It has been postulated that these areas provide the primary tumor cells with a favorable environment for expansion and proliferation due to a high blood flow, nutrient-rich microenvironment with access to a large repository of growth factors often referred to as the 'seed-and-soil' hypothesis.[10] By the end of life, the tumor load for the majority of patients will have shifted from the primary tumor to the bone. Batson demonstrated that venous blood from pelvic organs, like the prostate, directly flowed into the vertebral-venous (Batson's) plexus.[11] The anatomic location of these hematogenous routes may explain the propensity of these cancers to predominantly metastasize to the axial

skeleton, as also suggested by the anatomical-mechanical theory.[12] Upon invading and transversing the bone marrow cavity, the primary tumor cells can alter the bone remodeling process by increasing the rates of osteoblast and osteoclast activity.[13] The severity of the pathologically increased bone remodeling initiated by metastatic CRPC is evident from the high serum levels of both bone-forming and -degrading biochemical markers when compared to patients with bone metastases from other solid tumors.[14,15] The increased activity of the osteoblasts and osteoclasts leads to a degradation of the quality of bone as weaker, sclerotic bone replaces normal trabecular bone. In addition, the homeostasis mechanism of remodeling uncouples as bone breakdown outpaces bone formation, resulting in a net loss of bone. Collectively, the formation of weaker bone architecture and localized loss of bone mass leads to a net loss of skeletal strength (compressive and bending forces), which may lead to an increase in SRE rates.[16]

Bone Turnover Markers

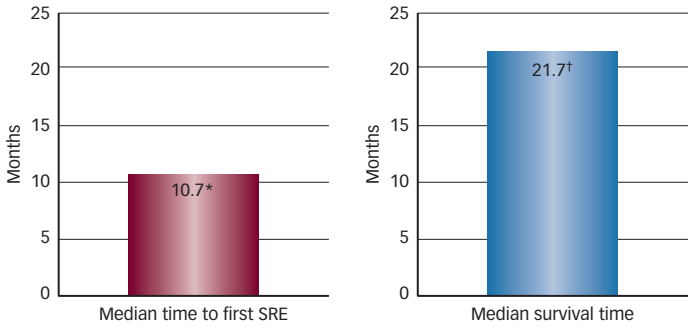
Biochemical markers of bone metabolism, both formation and resorption, can provide valuable insight into the impact of therapies and tumor and bone interactions.[17] Although there is still debate on their prognostic and predictive value in diagnosing bone metastases, bone turnover markers have been shown to indirectly measure the treatment effects for bone metastases in prostate cancer patients.[15] Urinary NTx (uNTx), a breakdown product of N-telopeptide (bone, type-1 collagen), and serum tartrate-resistant acid phosphatase 5b (TRAP 5b) are the primary biomarkers associated with bone resorption and disease progression. Bone-specific alkaline phosphatase (BAP), a measure of osteoblastic activity, is also considered a prognostic indicator in patients with CRPC.[15,18,19] Studies have demonstrated that elevated levels of uNTx indicate excessive bone resorption and can be predictive of SREs and progression of bone lesions across a wide range of tumor types.[20,21] Cancer patients receiving bisphosphonate therapy while continuing to have elevated uNTx levels ([moderate = 50–99 nmol/mmol creatinine] or [high = >100 nmol/mmol creatinine]), had a significantly increased risk for adverse outcomes such as SREs and death compared to patients with low values (<50 nmol/mmol creatinine) uNTx.[15]

Clinical Manifestation

The median overall survival for men with advanced prostate cancer and bone metastases has been reported to be up to two years.[22] Without bone-specific therapeutic intervention, progression of CRPC with bone metastases can lead to SREs such as pathologic fractures, spinal cord compression, and surgery or radiation to the bone.[23] More than half of all men with prostate cancer and bone metastases will experience an SRE in their lifetime and the median time to first SRE has been reported as short as 10.7 months (see *Figure 1*).[24] The mean incidence rate of SREs has been reported as 1.47 events per year in cancer patients with bone metastasis.[25]

With the recent discovery of effective systemic therapies, the progression of prostate cancer can be slowed allowing for improved survival rates. However, the probability of a potentially debilitating SRE also increases with the prolongation of survival. Prior studies in men with prostate cancer suggest that pathologic fractures can occur at any skeletal site and are associated with significant decreases in functional and psychological well being.[27] Bone pain, a common consequence of bone metastases,

Figure 1: The Median Time to First Skeletal-related Event is Shorter than the Median Survival Time in Patients with Metastatic Prostate Cancer



**Data are from the placebo arm (n=208) of a randomized, controlled multicenter study (versus zoledronic acid) of 643 men with metastatic castration-resistance prostate cancer (CRPC).[25] †Data are from the placebo arm (n=171) of a randomized, controlled multicenter study (versus sipuleucel-T) of 512 men with metastatic CRPC.[26] SRE = skeletal-related event.*

is the most common source of severe pain in patients with advanced cancer[23,28] and the exact pathophysiology has not been elucidated. It has been reported that approximately 90 % of patients with metastatic or advanced stage cancer will experience significant cancer related bone pain[29] which has been associated with a reduction in the quality of life (QOL). In a recent Phase 3 study to assess the differences in patient-reported pain severity in CRPC patients with bone metastases, patients receiving denosumab reported an 18 % risk reduction in time to first on-study SRE ($p<0.008$), lower 'pain-worsening', and a lower rate shift to stronger opioid use compared to patients receiving zoledronic acid.[30] In addition, in an analysis of several studies of men with CRPC with bone metastases, patients with high pain scores had a 43 % increased risk of death versus patients with low pain scores.[31] Hip fractures are a particularly severe skeletal complication and are associated with high morbidity rates and mortality rates. A retrospective analysis found that shortly after a hip fracture (<30 days), 16 % of men died and approximately 60 % of the men who survived had seriously compromised functionality requiring physical assistance. Assisted living arrangements were required for 79 % of the men with hip fractures due to non-malignant causes, thus contributing substantially to the estimated $13.8 billion (1995) cost of treating osteoporotic fractures.[32] A more recent study estimated the cumulative costs at $12,469 per patient in the first year after identification of an SRE. In an analysis of the same time period, the cumulative cost per patient more than doubled to $26,384 when the patient experienced more than one SRE.[33]

Prevention of Skeletal-related Events

A key goal of therapy is to preserve the patients' functional independence and maintain their QOL by preventing or delaying SREs. Bisphosphonates have been part of the standard of care for CRPC patients with bone metastases; however, improved understanding of bone physiology has led to the development of more efficacious therapeutic agents for preventing SREs.

Bisphosphonates

Bisphosphonates are a class of pharmacologic agents used for the treatment of bone diseases associated with excessive bone resorption. Structurally, they are analogs of inorganic pyrophosphate and interfere

with osteoclast metabolism and survival.[34] The first generation of bisphosphonates (non-nitrogen) included etidronate, clodronate, and tiludronate are able to induce osteoclast apoptosis by metabolism into cytotoxic analogs of adenosine 5'-triphosphates.[35] The primary mechanism of action of the newer nitrogen-containing compounds; alendronate, ibandronate, pamidronate, risedronate, and zoledronic acid, is through the inhibition of farnesyl diphosphate synthase which in turn suppresses osteoclast mediated bone resorption.[34]

In 1995, pamidronate gained US Food and Drug Administration (FDA) approval for the prevention of SREs in patients with bone metastases due to breast cancer or bone disease from advanced multiple myeloma.[36,37] However, in randomized, controlled trials of men with prostate cancer and bone metastases, both pamidronate and clodronate failed to demonstrate long-term risk reductions for SREs versus placebo.[38–40] In a later study, a more efficacious bisphosphonate, zoledronic acid (Zometa® 704 trial) was also compared with placebo for the time to development of first bone metastases.[41] Although terminated, analysis of the partial cohorts revealed no significant difference in time to first bone metastasis. In 2002, after completion of three large, Phase 3 trials, intravenous (IV) zoledronic acid was approved for the prevention of disease-related skeletal complications in patients with bone disease from myeloma or bone metastases from prostate, breast, or lung cancer.[42–44] In these trials, IV zoledronic acid reduced the number of SREs compared with placebo in CRPC patients with bone metastases.

Denosumab

Denosumab is a fully human, IgG2 monoclonal antibody designed to target the bone remodeling system and inhibit bone destruction by binding RANKL with high specificity and affinity (Kd = $3x10^{-12}$).[45] It binds to both soluble and membrane-bound RANKL and does not cross-react with other TNF ligand family members. Similar to osteoprotegerin (OPG), denosumab is a reversible antagonist of RANKL that interferes with RANKL and RANK interactions. In the late 1990s, elucidation of the RANKL, RANK, and osteoprotegerin (OPG) pathway revealed a central molecular paradigm in osteoclast functionality which provided key insights to the basic mechanism of bone remodeling.[46,47] The reciprocal interactions between RANKL and the RANK receptor are central for the regulation of bone osteoclast-mediated resorption, which in turn mediates bone remodeling under both normal and pathological conditions. OPG, a member of the TNFR family, was shown to bind RANKL and behave as a type of decoy receptor for RANKL.[48,49] The key role of OPG in bone remodeling was demonstrated in transgenic mice overexpressing OPG,[50] where the reduction in the number of osteoclasts led to osteopetrosis and conversely, osteopenia in OPG knockout mice.[51] These observations led to the hypothesis that the bone microenvironment and interplay of RANK, RANKL, and OPG are critical for osteoclastogenesis and homeostatic bone remodeling, thus providing the clinical rationale to pursue RANKL as a key pharmaceutical target to curb aberrant bone remodeling in human cancers and bone metastases.

To evaluate the pharmocodynamics of denosumab-induced RANKL inhibition in humans, a randomized, double-blind, double-dummy, active-controlled Phase 1 study was conducted in patients with metastatic breast cancer and multiple myeloma.[52] In this study, patients with bone lesions due to breast cancer or myeloma received either denosumab as a single, SC injection or IV pamidronate. Denosumab suppressed the bone turnover marker uNTx through 84 days and demonstrated a half-life of approximately one month. The magnitude of uNTx suppression was similar to IV pamidronate but was considerably more sustained.[52] In a Phase 2 study of women with breast cancer and bone metastases, treatment with either denosumab or IV bisphosphonates suppressed uNTx levels in the first week of treatment.[53] By the end of the 13-week study, decreases in the bone turnover markers were comparable between denosumab and bisphosphonate treated patients. Equally important, denosumab reported a reduced incidence of first on-study SREs compared to bisphosphonates; 9 % for denosumab versus 16 for IV bisphosphonate-patients.[53] A second Phase 2 study examined the effects of denosumab or bisphosphonate therapies in cancer patients with bone metastases and elevated uNTx levels despite prior bisphosphonate therapy. The primary endpoint of lower uNTx levels (<50) at week 13 was achieved by 71 % of patients receiving denosumab compared to 29 % of patients continuing bisphosphonates, $p<0.001$.[54] The lower uNTx levels were sustained at week 25, 64 % for the denosumab arm versus 37 % for the bisphosphonate arm, $p<0.01$. Similar to an earlier Phase 2 study, reported SRE rates were lower for denosumab- (8 %) versus bisphosphonate- (17 %) treated patients.

Recently, the results of a large Phase 3 trial comparing denosumab with zoledronic acid in bisphosphonate-naive patients with advanced CRPC and bone metastases were reported.[55] The trial was a randomized, double-blind, double-dummy, active comparison of SC denosumab (120 mg) or IV zoledronic acid (4 mg, adjusted for creatinine clearance) every four weeks. A total of 1,904 patients were randomized, of whom 1,901 were eligible for the efficacy analysis: 950 were assigned to denosumab and 951 were assigned to zoledronic acid. The primary endpoint was time to first on-study SRE and was defined as a pathological fracture, radiation therapy, surgery to the bone, or spinal cord compression. In the efficacy analysis, denosumab demonstrated superiority to zoledronic acid for the delay or prevention of SREs in patients with advanced prostate cancer and significantly delayed time to first on-study SRE by 18 % ($p=0.008$ for superiority analysis) (see *Figure 2*). Time to first and subsequent SRE was also significantly delayed ($p=0.008$) compared to zoledronic acid (see *Figure 3*).

These results established that denosumab was more efficacious than the prior standard of care, zoledronic acid, for the delay or prevention of SREs in patients with advanced prostate cancer. Decreases in the bone turnover markers of uNTx and BSAP were significantly greater with denosumab versus zoledronic acid ($p<0.0001$) by week 13, mirroring the reduction in SREs. For both groups, the median overall survival of 20 months was expected for the study population and not different between the treatment groups. Reported disease progression was not comparably different between the treatment groups.

Safety

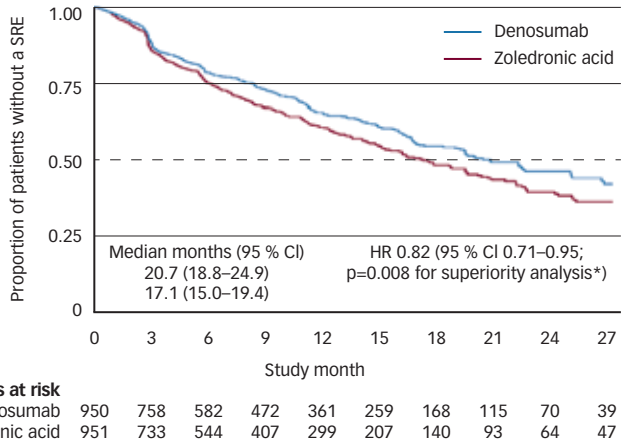
In the reported Phase 3 trial of denosumab versus zoledronic acid in men with advanced CRPC with bone metastases, the overall occurrences of adverse events (AEs) and serious adverse events (SAEs) were similar between the two arms, including the two-year cumulative incidence of ONJ (2 % denosumab, 1 % zoledronic acid) and renal impairment (15 % denosumab, 16 % zoledronic acid).[55] Unexpected changes in serum

creatinine levels, were not observed in the denosumab arm. A greater incidence of hypocalcemia was reported in the denosumab arm (13 % denosumab, 6 % zoledronic acid). Hypocalcemia is an expected risk with potent anti-resorptive therapies and forms the basis for the clinical recommendation that all patients receive supplemental calcium and vitamin D. Neutralizing antibodies to denosumab were not detected in any patients tested in the clinical studies.[56] Reported deaths were attributable to cancer or its complications and none were considered related to denosumab or zoledronic acid.[57] Unlike IV zoledronic acid, the AEs associated with acute phase reactions (APRs) (within three days after treatment) were significantly lower for denosumab arm (8 %) than for zoledronic acid arm (18 %). The increased incidence of reported APRs for patient receiving IV zoledronic acid is similar to other studies where flu-like symptoms has been reported in approximately one-third of patients receiving bisphosphonate treatment, primarily after the first infusion.[58] In addition, IV bisphosphonates are associated with dose- and infusion-rate dependent effects on renal function[46,59,60] and require systematic monitoring to ensure renal health. A spectrum of complications associated with renal toxicity has been associated with IV administration of bisphosphonates, ranging from elevated creatinine concentrations to dialysis dependence. In one series of cases, zoledronic acid was intravenously administered as a 4 mg dose over a 15-minute period and early signs of renal toxicity emerged in one-fourth of the patients that developed renal failure after a single dose.[61] Zoledronic acid or pamidronate are not recommended for patients with elevated baseline serum creatinine levels[62,63] or patients with significantly impaired renal function. Due to the potential for progressive decreases in renal functions with continued IV zoledronic use, guidelines recommend measuring serum creatinine levels prior to each infusion with long term renal monitoring.[62] These limitations do not apply to denosumab therapy which is administered subcutaneously and has no known impact on renal function and therefore no need for renal monitoring.[53,64]

Outlook

To date, there are no approved therapies for the prevention or delay of bone metastases in advanced prostate cancer patients without bone metastases. Although zoledronic acid has been shown to reduce SREs in CRPC patients with bone metastases, as a class, bisphosphonates have not been shown to prevent or delay bone metastases in advanced prostate cancer patients without bone metastases. In the late 1990s, the Medical Research Council (MRC) Pr04 trial enrolled 508 men with advanced prostate cancer and a negative bone scan.[65] Patients were randomized over five years to either oral clodronate (2,080 mg) or placebo. Over an average of 10 years of follow-up, there was no benefit for the prevention of bone metastases (HR=1.22; 95 % CI 0.88 1.68) or increase in overall survival (HR=1.02; 95 % CI 0.80 1.30; p=0.90). For a weaker bisphosphonate such as clodronate, these results suggest there were no benefits in the prevention of bone metastases. In a follow-on study, zoledronic acid (Zometa® 704 trial) was compared with placebo for time to development of first bone metastases in non-metastatic CRPC. The trial was delayed and eventually discontinued because of a low event rate. However, analysis of the partial cohorts of zoledronic acid and placebo revealed no significant differences in the time-to-first metastases.[66] Recently, a Phase 3 study evaluating the effects of altering the bone microenvironment utilizing denosumab was conducted in CRPC patients without bone metastases but at high risk for bone metastases.[67] Eligible patients were randomized to either denosumab (716 patients) or placebo (716 patient) and were stratified by PSA eligibility criteria and previous or ongoing chemotherapy for prostate cancer. The primary endpoint was bone metastasis-free survival which was a composite endpoint determined by time-to-first occurrence of either asymptomatic or symptomatic bone metastases or death of any cause. Denosumab significantly increased bone metastasis-free survival by a median of 4.2 months compared with placebo (p=0.028) and also delayed time to first bone metastasis (33.2 months versus 29.5 months, p=0.032).

Figure 2: Kaplan-Meier Estimates of Time to First On-study Skeletal-related Events

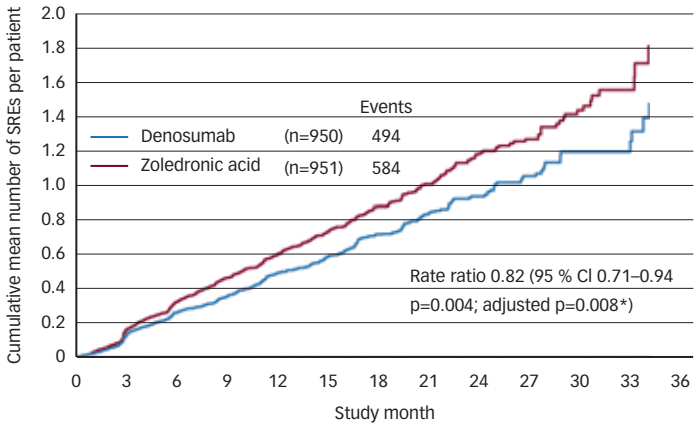


Patients at risk

Denosumab	950	758	582	472	361	259	168	115	70	39
Zoledronic acid	951	733	544	407	299	207	140	93	64	47

*Patients were assessed from baseline to the primary analysis cut-off date. HR=hazard ratio; SRE = skeletal-related events. *p values were adjusted for multiplicity.*
Source: Adapted from Fizazi et al., 2011.[55]

Figure 3: Time to First and Subsequent On-study Skeletal-related Events



*Events occurred at least 21 days apart. *Adjusted for multiplicity. SRE = skeletal-related events.*
Source: Reproduced from Fizazi et al., 2011.[55]

Emerging Therapies

Until recently, bone treatment options for patients with CRPC were limited. With the advancements in understanding of tumor derived factors, host factors, and bone microenvironments, emerging cancer therapeutics have targeted hormonal signaling pathways, bone derived factors, cell-cycle checkpoints, and activated tyrosine kinases.

Radiopharmaceuticals

Alpha-emitting pharmaceuticals deliver high-energy, systemic radiation with the ability to induce double stranded DNA breaks and cell death in a very localized area.[68] Alpharadin (radium-223 [^{223}Ra] chloride), an investigational pharmaceutical containing an alpha-particle emitting nuclide,[69] has been recently evaluated in the Alpharadin in symptomatic prostate cancer (ALSYMPCA) trial, a Phase 3, randomized, double-blind, placebo-controlled international study of Alpharadin plus current standard of care (SOC) versus placebo plus SOC in CRPC patients with symptomatic bone metastases. The primary endpoint was overall survival and secondary endpoints included time to occurrence of SREs, changes and time to progression in PSA, and QOL. The results of the Phase 3 trial were presented at the 2011 European Multidisciplinary Cancer Congress (EMCC) and Alpharadin was shown to significantly improve overall survival (OS) in CRPC patients with symptomatic bone metastases. The median OS was 14.0 months versus 11.2 months (HR=0.695; 95 % CI 0.552 0.875, p=0.0018) with an OS benefit of 2.8 months. The safety and tolerability profile of Alpharadin were comparable to the earlier Phase 1 and 2 trials.

SRC inhibitor

The proto-oncogene tyrosine kinase SRC has established roles in pathogenesis of visceral and bone metastases[70,71] and regulation of normal osteoclast function.[72–74] Dasatinib, a potent SRC inhibitor with pre-clinical antineoclast and antitumor activity, has demonstrated inhibitory activity against bone regulatory mechanisms including osteoclastogenesis, prostate cancer cell-induced osteoclast differentiation and activity, and osteoblast proliferation.[75–78] In a Phase 2 trial in patients with chemotherapy-naive CRPC and increasing PSA levels, single agent dasatinib (100 mg, once daily) decreased uNTx levels (51 % patients had a >40 % decrease) and BAP levels (59 % of patients) in the majority of patients. The most common treatment associated adverse event were fatigue, nausea, and diarrhea while 13 % of the patients had grade 3 to 4 side effects.[79]

c-MET and VEGFR2 inhibitor

Metastases of prostate cancer have been associated with overexpression of hepatocyte growth factor receptor (c-MET) and hepatocyte growth factor (HGF).[80] In pre-clinical studies, androgen ablation upregulated MET signaling and promoted tumor growth and metastases.[81] In a randomized Phase 2 discontinuation trial in CRPC patients, the c-MET- and VEGFR2-inhibitor cabozantinib was associated with normalization of radionuclide bone scans in 86 % of patients, bone pain improvements in 64 % of patients, and a decline in bone turnover marker levels.[82,83] A pair of Phase 3 trials are planned for the indication of palliation of pain and improvement in overall survival in CRPC patients.[82]

Conclusions

Advanced prostate cancer patients require long-term disease management where maintenance of overall bone health is an essential component of a comprehensive treatment program during all stages of prostate cancer. Cancer progression in bone can lead to detrimental bone destruction and loss of skeletal integrity despite the predominance of osteoblastic appearances on plain radiographs, which may lead to fractures, pain, and adversely impact QOL. Moreover, SREs from bone metastases in CRPC patients are associated with increased morbidity and place considerable pressure on the resources of health care systems. Therefore, SREs resulting from bone metastases represent a crucial target for pharmacotherapy and clinical intervention. Although IV zoledronic acid has been shown to reduce the incidence of SREs in CRPC patients with bone metastases, treatment has been associated with increased incidences of APRs and significant potential to cause both short and long-term renal impairment. Recently, denosumab was successfully developed for the treatment of CRPC patients with bone metastases. Based on the principles of the RANKL/RANK/OPG pathway, denosumab was designed as a treatment to prevent skeletal complications due to cancer. To date, many clinical trials have demonstrated that denosumab is effective in inhibiting bone resorption. In a large Phase 3 trial of CRPC patients with bone metastases, efficacy results demonstrated superiority of denosumab to zoledronic acid in delaying time to first on-study SREs. Denosumab also significantly delayed time to first and subsequent on-study SREs compared to zoledronic acid. Updated NCCN guidelines[84] now include denosumab as an option for the prevention of SREs such as fractures and pain. Overall, the use of bone modifying agents for the reduction of SREs in CRPC patients with bone metastases yields both clinical and economic benefits, including a meaningful improvement in patient QOL and lowering of the financial burden on the healthcare system. ■

1. Siegel R, Naishadham D, Jemal A, Cancer statistics, 2012, *CA Cancer J Clin,* 2012;62:10–29.
2. Huggins C, Hodges CV, Studies on prostatic cancer. I. The effects of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate, *Cancer Research,* 1941;1:293–97.
3. Chen Y, Clegg NJ, Scher HI, Anti-androgens and androgen-depleting therapies in prostate cancer: new agents for an established target, *Lancet Oncol,* 2009;10:981–91.
4. Scher HI, Halabi S, Tannock I, et al., Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group, *J Clin Oncol,* 2008;26:1148–59.
5. Kirby M, Hirst C, Crawford ED, Characterising the castration-resistant prostate cancer population: a systematic review, *Int J Clin Pract,* 2011;65:1180–92.
6. Norgaard M, Jensen AO, Jacobsen JB, et al., Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007), *J Urol,* 2010;184:162–7.
7. Keller ET, Brown J, Prostate cancer bone metastases promote both osteolytic and osteoblastic activity, *J Cell Biochem,* 2004;91:718–29.
8. Lee RJ, Saylor PJ, Smith MR, Treatment and prevention of bone complications from prostate cancer, *Bone,* 2011;48:88–95.
9. Shiozawa Y, Havens AM, Pienta KJ, et al., The bone marrow niche: habitat to hematopoietic and mesenchymal stem cells, and unwitting host to molecular parasites, *Leukemia,* 2008;22:941–50.
10. Paget S, The distribution of secondary growths in cancer of the breast, *Lancet,* 1889;1:571–3.
11. Batson OV, The Function of the Vertebral Veins and Their Role in the Spread of Metastases, *Ann Surg,* 1940;112:138–49.
12. Aaron AD, The management of cancer metastatic to bone, *JAMA,* 1994;272:1206–9.
13. Mundy GR, Metastasis to bone: causes, consequences and therapeutic opportunities, *Nat Rev Cancer,* 2002;2:584–93.
14. Brown JE, Cook RJ, Major P, et al., Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors, *J Natl Cancer Inst,* 2005;97:59–69.
15. Coleman RE, Major P, Lipton A, et al., Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid, *J Clin Oncol,* 2005;23:4925–35.
16. Kanis JA, McCloskey EV, Taube T, et al., Rationale for the use of bisphosphonates in bone metastases, *Bone,* 1991;12 (Suppl. 1):S13–8.
17. Demers LM, Costa L, Chinchilli VM, et al., Biochemical markers of bone turnover in patients with metastatic bone disease, *Clin Chem,* 1995;41:1489–94.
18. Christenson RH, Biochemical markers of bone metabolism: an overview, *Clin Biochem,* 1997;30:573–93.
19. Jung K, Lein M, Stephan C, et al., Comparison of 10 serum bone turnover markers in prostate carcinoma patients with bone metastatic spread: diagnostic and prognostic implications, *Int J Cancer,* 2004;111:783–91.
20. Brown JE, Thomson CS, Ellis SP, et al., Bone resorption predicts for skeletal complications in metastatic bone disease, *Br J Cancer,* 2003;89:2031–7.
21. Hirsh V, Major PP, Lipton A, et al., Zoledronic acid and survival in patients with metastatic bone disease from lung cancer and elevated markers of osteoclast activity, *J Thorac Oncol,* 2008;3:228-36.
22. Kantoff PW, Schuetz TJ, Blumenstein BA, et al., Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer, *J Clin Oncol,* 2010;28:1099–105.
23. Coleman RE, Metastatic bone disease: clinical features, pathophysiology and treatment strategies, *Cancer Treat Rev,* 2001;27:165–76.
24. Saad F, Pantel K, The current role of circulating tumor cells in the diagnosis and management of bone metastases in advanced prostate cancer, *Future Oncol,* 2012;8:321–31.

25. Saad F, Gleason DM, Murray R, et al., Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer, *J Natl Cancer Inst,* 2004;96:879–82.
26. Kantoff PW, Higano CS, Shore ND, et al., Sipuleucel-T immunotherapy for castration-resistant prostate cancer, *N Engl J Med,* 2010;363:411–22.
27. Weinfurt KP, Li Y, Castel LD, et al., The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer, *Ann Oncol,* 2005;16:579-584.
28. Namer M, Clinical consequences of osteolytic bone metastases, *Bone,* 1991;12 Suppl 1:S7.
29. Berruti A, Dogliotti L, Bitossi R, et al., Incidence of skeletal complications in patients with bone metastatic prostate cancer and hormone refractory disease: predictive role of bone resorption and formation markers evaluated at baseline, *J Urol,* 2000;164:1248–53.
30. Brown J, Cleeland CS, Fallowfield LJ, et al., Pain outcomes in patients with bone metastases from castrate-resistant prostate cancer: Results from a phase 3 trial of denosumab vs. zoledronic acid, *Eur Urol,* 2011;10:336.
31. Halabi S, Vogelzang NJ, Kornblith AB, et al., Pain predicts overall survival in men with metastatic castration-refractory prostate cancer, *J Clin Oncol,* 2008;26:2544–9.
32. Hamerman D, Aging and the musculoskeletal system, *Ann Rheum Dis*, 1997;56:578–85.
33. Lage MJ, Barber BL, Harrison DJ, et al., The cost of treating skeletal-related events in patients with prostate cancer, *Am J Manag Care,* 2008;14:317–22.
34. Russell RG, Bisphosphonates: mode of action and pharmacology, *Pediatrics*, 2007;119 (Suppl. 2):S150–62.
35. Roelofs AJ, Thompson K, Gordon S, et al., Molecular mechanisms of action of bisphosphonates: current status, *Clin Cancer Res,* 2006;12:6222s–30s.
36. Hortobagyi GN, Theriault RL, Porter L, et al., Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group, *N Engl J Med,* 1996;335:1785–91.
37. Berenson JR, Lichtenstein A, Porter L, et al., Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group, *N Engl J Med,* 1996;334:488–93.
38. Major PP, Lipton A, Berenson J, et al., Oral bisphosphonates: A review of clinical use in patients with bone metastases, *Cancer,* 2000;88:6–14.
39. Small EJ, Smith MR, Seaman JJ, et al., Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer, *J Clin Oncol,* 2003;21:4277–84.
40. Lahtinen R, Laakso M, Palva I, et al., Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group, *Lancet,* 1992;340:1049–52.
41. Saylor PJ, Smith MR, Bone health and prostate cancer, *Prostate Cancer Prostatic Dis*, 2010;13:20–7.
42. Rosen LS, Gordon D, Kaminski M, et al., Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial, *Cancer J,* 2001;7:377–87.
43. Rosen LS, Gordon D, Tchekmedyian S, et al., Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial--the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group, *J Clin Oncol,* 2003;21:3150–7.
44. Saad F, Gleason DM, Murray R, 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.
45. Schwarz EM, Ritchlin CT, Clinical development of anti-RANKL therapy, *Arthritis Res Ther,* 2007;9 (Suppl. 1):S7.
46. Fuller K, Owens JM, Chambers TJ, Induction of osteoclast formation by parathyroid hormone depends on an action on stromal cells, *J Endocrinol,* 1998;158:341–50.
47. Lacey DL, Tan HL, Lu J, et al., Osteoprotegerin ligand modulates murine osteoclast survival in vitro and in vivo, *Am J Pathol,* 2000;157:435–48.
48. Gao YH, Shinki T, Yuasa T, et al., Potential role of cbfa1, an essential transcriptional factor for osteoblast differentiation, in osteoclastogenesis: regulation of mRNA expression of osteoclast differentiation factor (ODF), *Biochem Biophys Res Commun,* 1998;252:697–702.
49. Vidal NO, Brandstrom H, Jonsson KB, et al., Osteoprotegerin mRNA is expressed in primary human osteoblast-like cells: down-regulation by glucocorticoids, *J Endocrinol*, 1998;159:191–5.
50. Simonet WS, Lacey DL, Dunstan CR, et al., Osteoprotegerin: a novel secreted protein involved in the regulation of bone density, *Cell,* 1997;89:309–19.
51. Bucay N, Sarosi I, Dunstan CR, et al., osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification, *Genes Dev,* 1998;12:1260–8.
52. Body JJ, Facon T, Coleman RE, et al., A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer, *Clin Cancer Res,* 2006;12:1221–8.
53. Lipton A, Steger GG, Figueroa J, et al., Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases, *J Clin Oncol*, 2007;25:4431–7.
54. Fizazi K, Lipton A, Mariette X, et al., Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates, *J Clin Oncol,* 2009;27:1564–71.
55. Fizazi K, Carducci M, Smith M, 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.
56. Lewiecki EM, Bilezikian JP, Denosumab for the treatment of osteoporosis and cancer-related conditions, *Clin Pharmacol Ther,* 2012;91:123–33.
57. VA Pharmacy Benefits Management Services MAP, and VISN Pharmacist Executives, *Denosumab (XGEVA) National Drug Monograph,* 2011.
58. Zojer N, Keck AV, Pecherstorfer M, Comparative tolerability of drug therapies for hypercalcaemia of malignancy, *Drug Saf,* 1999;21:389–406.
59. Green J, Bisphosphonates and the kidney. In: Broe ME, Porter GA, Bennett WM, Deray G (eds), *Clinical Nephrotoxins,* Springer: US, 2008:547–66.
60. Bounameaux HM, Schifferli J, Montani JP, et al., Renal failure associated with intravenous diphosphonates, *Lancet,* 1983;1:471.
61. Chang JT, Green L, Beitz J, Renal failure with the use of zoledronic acid, *N Engl J Med,* 2003;349:1676–9
62. Novartis, Zometa (zoledronic acid) [prescribing information], East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2003.
63. Novartis, Aredia (pamidronate disodium) [prescribing information], East Hanover, NJ: Novartis Pharmaceuticals Corporation, 1997.
64. Smith MR, Egerdie B, Hernandez Toriz N, et al., Denosumab in men receiving androgen-deprivation therapy for prostate cancer, *N Engl J Med,* 2009;361:745–55.
65. Mason MD, Sydes MR, Glaholm J, et al., Oral sodium clodronate for nonmetastatic prostate cancer--results of a randomized double-blind placebo-controlled trial: Medical Research Council PR04 (ISRCTN61384873), *J Natl Cancer Inst,* 2007;99:765–76.
66. Michaelson MD, Smith MR, Bisphosphonates for treatment and prevention of bone metastases, *J Clin Oncol,* 2005;23:8219–24.
67. Smith MR, Saad F, Coleman R, et al., Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial, *Lancet,* 2012;379:39–46.
68. Ritter MA, Cleaver JE, Tobias CA, High-LET radiations induce a large proportion of non-rejoining DNA breaks, *Nature,* 1977;266:653–5.
69. Nilsson S, Franzen L, Parker C, et al., Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study, *Lancet Oncol,* 2007;8:587–94.
70. Kim LC, Song L, Haura EB, Src kinases as therapeutic targets for cancer, *Nat Rev Clin Oncol,* 2009;6:587–95.
71. Summy JM, Gallick GE, Src family kinases in tumor progression and metastasis, *Cancer Metastasis Rev*, 2003;22:337–58.
72. Edwards J, Src kinase inhibitors: an emerging therapeutic treatment option for prostate cancer, *Expert Opin Investig Drugs,* 2010;19:605–14.
73. Fizazi K, The role of Src in prostate cancer, *Ann Oncol,* 2007;18:1765–73.
74. Miyazaki T, Sanjay A, Neff L, et al., Src kinase activity is essential for osteoclast function, *J Biol Chem,* 2004;279:17660–6.
75. Araujo JC, Poblenz A, Corn P, et al., Dasatinib inhibits both osteoclast activation and prostate cancer PC-3-cell-induced osteoclast formation, *Cancer Biol Ther*, 2009;8:2153–9.
76. Brownlow N, Mol C, Hayford C, et al., Dasatinib is a potent inhibitor of tumour-associated macrophages, osteoclasts and the FMS receptor, *Leukemia,* 2009;23:590–4.
77. Lee YC, Huang CF, Murshed M, et al., Src family kinase/abl inhibitor dasatinib suppresses proliferation and enhances differentiation of osteoblasts, *Oncogene,* 2010;29:3196–207.
78. Vandyke K, Dewar AL, Farrugia AN, et al., Therapeutic concentrations of dasatinib inhibit in vitro osteoclastogenesis, *Leukemia*, 2009;23:994–7.
79. Yu EY, Massard C, Gross ME, et al., Once-daily dasatinib: expansion of phase II study evaluating safety and efficacy of dasatinib in patients with metastatic castration-resistant prostate cancer, *Urology,* 2011;77:1166–71.
80. Dai Y, Siemann DW, BMS-777607, a small-molecule met kinase inhibitor, suppresses hepatocyte growth factor-stimulated prostate cancer metastatic phenotype in vitro, *Mol Cancer Ther,* 2010;9:1554–61.
81. Christensen JG, Burrows J, Salgia R, c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention, *Cancer Lett,* 2005;225:1–26.
82. Chen Y, Scher HI, Prostate cancer in 2011: Hitting old targets better and identifying new targets, *Nat Rev Clin Oncol*, 2012;9:70–2.
83. Hussain M, Smith MR, Sweeney C, et al., Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial, *J Clin Oncol,* 2011;29.
84. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Prostate Cancer; Version 3, 2012.