# Bone-Targeted Agents
## Preventing Skeletal Complications in Prostate Cancer

Alicia K. Morgans, MD*, Matthew R. Smith, MD, PhD

**KEYWORDS**

• Prostate cancer • Skeletal complications • Bone • Side effects of therapy • Skeletal related events • ADT

**KEY POINTS**

- Skeletal complications from metastases and androgen deprivation therapy are common in prostate cancer survivors.
- New pharmacologic approaches to preventing skeletal related events and other complications in this population are being employed.
- In addition to palliating pain caused by bone metastases in prostate cancer, the well-tolerated radiopharmaceutical Alpharadin appears to prolong life.

### NORMAL BONE PHYSIOLOGY

Healthy bone is perpetually in a state of turnover, striking a delicate balance between bone resorption by osteoclasts and bone formation by osteoblasts. Estrogen plays an important role in the regulation of this balance through estrogen receptors on osteoblasts and osteoclasts.[1] In low estrogen states, the balance favors bone resorption rather than formation. Low estrogen levels are likely one of the most significant contributors to the decline of bone mineral density (BMD) in hypogonadal states.

Additional regulatory signaling occurs via the receptor activator of nuclear factor-κB ligand (RANKL) system.[2] RANKL, a member of the tumor necrosis factor superfamily of proteins, is produced by osteoblasts and bone marrow stromal cells. It binds to RANK receptors on osteoclasts and osteoclast precursors to induce differentiation, activation, and survival of osteoclasts. The activation of RANK ultimately causes increased osteoclast activity and bone resorption. The action of osteoprotegerin (OPG), a protein produced by osteoblasts and other stromal tissues, decreases osteoclast activity by OPG binding RANKL, preventing the RANK/RANKL interaction. Relative levels of OPG and RANKL are thought to play a pivotal role in determining the degree to which bone resorption and formation occur.[3]

### PATHOPHYSIOLOGY OF BONE METASTASES

Bone lesions in prostate cancer appear osteoblastic radiographically, but both osteoblast and osteoclast activity is upregulated.[4–6] Osteoclast activity is enhanced by several mechanisms, including marrow stromal and tumor secretion of stimulatory proteins that act on nearby osteoclasts. Stromal cells produce RANKL and macrophage colony-stimulating factor (M-CSF) receptor, both of which stimulate osteoclast differentiation and activation.[7] Tumor cells also promote osteoclast activity by producing M-CSF and parathyroid hormone–related protein.[7] It has also been proposed that osteoclast activation may be explained almost entirely by the effect of androgen deprivation therapy (ADT), one of the most common treatments for recurrent or metastatic prostate cancer.[8] The mechanism of osteoblast activity promotion is

Department of Hematology/Oncology, Massachusetts General Hospital Cancer Center, 55 Fruit Street, Boston, MA 02114, USA
* Corresponding author.
*E-mail address:* alicia.morgans@vanderbilt.edu

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less well defined, but is presumed to be driven by stromal and tumor secretion of osteoblasts-stimulating factors, such as insulinlike growth factor, bone-morphogenic proteins, transforming growth factor-beta, fibroblast growth factors, and others.[9]

## CLINICAL COMPLICATIONS OF BONE METASTASES

The most common site of metastatic disease in advanced prostate cancer is bone, especially the bones of the axial skeleton, pelvis, and long bones. Spread to bone occurs via hematogenous dissemination. The biology of bone metastases is complex. Multiple factors appear to contribute to the bone tropism in prostate cancer, including blood flow in the bone marrow, expression of adhesive molecules on cancer cells that bind them to the bone matrix and stroma, and a rich supply of growth factors in the bone microenvironment.[10–12] There is also a significant amount of reciprocal signaling between osteoblasts, osteoclasts, fibroblasts, and other cells of the bone microenvironment and prostate cancer cells through the secretion of cytokines, proteases, and growth factors that promote prostate cancer cell survival and growth.[13]

Both pathologic fractures directly related to metastatic lesions and treatment-related benign osteoporotic fractures occur commonly in men with prostate cancer. Up to 22% of men with metastatic castrate-resistant prostate cancer (CRPC) experience pathologic fractures during the course of their disease because of weakened bone integrity in the area of metastasis.[14] Benign osteoporotic fractures occur owing to the treatment-related decline of BMD that can result in osteoporosis and increase an individual's risk of fracture.[15,16] Several large retrospective database analyses of men with nonmetastatic prostate cancer demonstrated that men treated with ADT have a significantly higher rate of fracture that those who were not, and the risk increases over time as BMD falls.[17,18]

Bone metastases are also associated with the development of additional skeletal complications. Both pain and weakness can develop from bone or nerve involvement with metastases. Hypocalcemia and subsequent secondary hyperparathyroidism occur owing to increased osteoblast activity in metastatic deposits.

## TREATMENT-RELATED OSTEOPOROSIS

ADT, via bilateral orchiectomies or through administration of gonadotropin-releasing hormone (GnRH) agonists or antagonists, is the cornerstone of systemic treatment for prostate cancer. The goal of ADT is to dramatically lower serum testosterone, typically lower than 20 ng/dL, or less than 5% of baseline values. Because of peripheral aromatization of testosterone to estradiol, reducing serum testosterone causes estradiol levels to fall. Estradiol levels decline to lower than 20% of baseline values, reaching levels as low as or lower than those of postmenopausal women.

ADT is widely used, both in subgroups of men with prostate cancer who clearly have improved overall survival with ADT, and in those in whom a survival benefit has not been demonstrated. One group that appears to benefit from treatment with ADT is men with metastatic disease who have an improved overall survival and quality of life with treatment. Men undergoing treatment with radiation for high-risk localized disease or locally advanced prostate cancer experience prolonged survival with the addition of ADT.[19] Finally, there is evidence that men who have positive lymph nodes after radical prostatectomy have improved overall survival when treated with ADT.[20] Although there is no evidence of improved overall survival in men with a prostate-specific antigen (PSA)-only relapse, this population is frequently treated with ADT alone or in combination with salvage radiation.[19]

The major causes of osteoporosis in men are use of steroids, alcohol use, or hypogonadism.[21] The intended therapeutic effect of ADT is marked hypogonadism. Consistent with the important role of gonadal steroids in normal bone metabolism in men, ADT decreases BMD and is associated with greater fracture risk. Within 6 to 9 months of initiating ADT, BMD falls.[22–24] BMD continues to decline during treatment at a rate of 2% to 3% per year.[22–25] This is substantially faster than typical age-related decline in men of 0.5% to 1.0%.

ADT is also associated with an increased fracture rate.[17,18] Within 5 years of initiating therapy with ADT, the incidence of fracture approaches 20%.[17] Several large retrospective analyses found that men treated with ADT experience a 21% to 45% relative increase in fracture risk as compared with men not treated with ADT.[17,18,26] Additionally, a Surveillance Epidemiology and End Results (SEER) Medicare analysis of more than 50,000 men with prostate cancer found a fracture rate of 19.4% in men treated with ADT, whereas the rate of fracture in men not undergoing treatment was 12.6% ($P<.001$).[17] A second analysis of Medicare data from the same year included 4000 men with nonmetastatic prostate cancer and reported a relative risk of fracture of 1.21 among men treated with ADT as compared with those who were not (95% confidence interval [CI], 1.14–1.29, $P<.01$).[18]

## MECHANISMS OF TREATMENT-RELATED BONE LOSS

ADT decreases BMD through several mechanisms. Both testosterone and estrogen are important for maintaining normal bone homeostasis, and ADT causes a significant decline in both testosterone and estrogen. When serum testosterone is low, less testosterone is available to undergo peripheral aromatization to estradiol. Low estrogen states are associated with increased bone resorption. In healthy men, studies demonstrate a decline in BMD when estradiol levels are low, and an inverse relationship between fracture risk and estradiol levels.[27–29]

ADT also affects the rate of bone turnover and skeletal sensitivity to parathyroid hormone. Serum markers of osteoblast activity, like bone-specific alkaline phosphatase and osteocalcin, and markers of osteoclast activity, such as N-telopeptide, increase in men treated with ADT.[24] These markers generally increase within 6 to 12 weeks of initiating therapy with ADT, and plateau approximately 6 months after starting therapy. ADT also increases skeletal sensitivity to parathyroid hormone.[30]

## OSTEOCLAST-TARGETED THERAPY

Two osteoclast-targeted therapies have been studied in men with prostate cancer. Bisphosphonates are used to prevent skeletal-related events (SREs) in metastatic CRPC. SREs are a group of skeletal complications associated with malignancy. The term typically encompasses the following outcomes: pathologic fractures, cord compression, and the use of surgery or radiation to treat unstable or painful metastatic lesions in bone. Some studies also include the development of hypercalcemia or hypocalcemia in the definition. Denosumab, a fully humanized monoclonal antibody targeting RANKL, has been approved to prevent SREs in metastatic solid tumors, including CRPC, and to increase BMD in men at risk for ADT-associated bone loss.

### *Bisphosphonates*

Bisphosphonates prevent bone resorption through several mechanisms, including decreased osteoclast differentiation and survival and increased osteoblast survival.[31] Bisphosphonate molecules are structurally similar to native pyrophosphate molecules that normally adhere to hydroxyapatite crystal-binding sites. The molecules attach to binding sites located in areas of bone resorption, reducing osteoclast activity by preventing their adherence to the bone surface and the formation of the ruffled border. Bisphosphonates impair osteoclast progenitor differentiation and survival via their effects on osteoblasts.[31]

Bisphosphonates vary by the R2 group attached to their common structural backbone. The R2 group determines the potency of the molecule, with nitrogen-containing bisphosphonates like pamidronate, alendronate, and zoledronic acid being significantly more potent than simple bisphosphonates like clodronate and etidronate, which are non-nitrogenous. Among the nitrogen-containing bisphosphonates, those that contain secondary or tertiary amino groups, such as zoledronic acid, are significantly more potent than other compounds.[32] Zoledronic acid is estimated to be at least 100 times more potent than pamidronate and more than 1000 times as potent as etidronate in vitro.[32]

Several bisphosphonates are currently used in patients with cancer. Indications include hypercalcemia, low BMD, and metastatic lesions in bone. As early as the 1990s, evidence demonstrated that pamidronate decreased the risk of skeletal complications in individuals with metastatic breast cancer and multiple myeloma.[33,34] Pamidronate was subsequently approved for use in these populations in 1995. Zoledronic acid was approved to prevent skeletal complications in multiple myeloma and in any solid tumor with bone metastases in 2002.[14,35,36] The study that specifically led to its approval in metastatic prostate cancer, Zometa 039, demonstrated a reduction in SRE as compared with placebo.[14]

### *Denosumab*

As described previously, bone exists in state of continuous remodeling, striking a balance between osteoclast resorption and osteoblast formation of new bone. The RANKL/RANK system plays a key role in achieving this balance. Currently, the only available therapy that targets this system is denosumab, a fully human monoclonal antibody directed at RANKL. The drug mimics the action of OPG by binding RANKL and reducing osteoclast action. It has a half-life of more than 30 days, does not accumulate in bone, like bisphosphonates, and can be used in patients with renal insufficiency.[37] Similar to bisphosphonates, treatment with denosumab carries a small risk of developing osteonecrosis of the jaw.[38]

Denosumab has been studied to prevent the development of osteoporosis and reduce the risk of fracture in postmenopausal women.[39,40] In the fracture-prevention trial, 7868 postmenopausal women with osteoporosis were randomized to receive placebo or twice-yearly denosumab. Women in the denosumab group developed fewer new vertebral fractures, nonvertebral fractures, and hip fractures than those in the placebo group

during the 36-month follow-up period (relative decreased risk of vertebral fractures 68%, nonvertebral fractures 20%, and hip fractures 40%).[41] Denosumab was approved by the Food and Drug Administration (FDA) to treat postmenopausal women with osteoporosis based on this study.

Denosumab was also studied in women with breast cancer who were being treated with aromatase inhibitors.[42] Aromatase inhibitors are associated with a decline in BMD in women owing to the inhibition of peripheral tissue estrogen production. A recent study demonstrated that denosumab prevents the loss of BMD at the lumbar spine in women with breast cancer being treated with aromatase inhibitors as compared with placebo (BMD increased by 5.5% and 7.6% at 12 and 24 months, respectively [$P$<.0001 at both time points]).

## CLINICAL USES OF OSTEOCLAST-TARGETED THERAPIES IN PROSTATE CANCER

### *Prevention of Therapy-related Fragility Fractures*

Several medications have been evaluated for prevention of fragility fractures, the most clinically relevant end point in this population (**Table 1**). Denosumab, the fully human monoclonal antibody against RANKL, has been approved to prevent treatment-related fragility fractures in men treated with ADT.[43] Toremifene, a selective estrogen receptor modulator (SERM) has been studied in this setting, but has not been approved for use because of an unacceptable risk-benefit ratio.[44] Multiple bisphosphonates, including alendronate, pamidronate, zoledronic acid, and neridronate, have been evaluated to prevent a decline in BMD, but those studies were not powered to evaluate fracture prevention.[15,45–49]

The National Comprehensive Cancer Network and National Osteoporosis Foundation (NOF) created guidelines for the treatment of secondary osteoporosis associated with ADT and fracture prevention. These guidelines suggest that all men older than 50 years who are being treated with ADT should be treated with calcium (1200 mg per day) and vitamin D (1000 IU per day). They also recommend additional pharmacologic therapy for fracture prevention for any individual with a 10-year probability of hip fracture of 3% or more or a 20-year probability of major osteoporotic fracture of 20% or more.

An individual's 10-year probability of fracture depends on multiple factors besides BMD.[50,51] BMD is routinely used as a surrogate end point for fracture in clinical trials, but most fractures occur in men whose BMD is not in the osteoporotic range. A man's risk of fracture increases by approximately 30-fold between the ages of 50 and 90, and the decline of BMD with age accounts for only a 4-fold increase in risk of fracture.[50] To address this,

**Table 1**
**Bone-targeted therapies evaluated for the prevention of therapy-related fragility fractures**

| Study | N | Study Population | Arms | Outcome |
|---|---|---|---|---|
| Denosumab Halt 138[43] | 1468 | Men with nonmetastatic prostate cancer being treated with a GnRH agonist and at high risk of fracture. | Denosumab 60 mg subcutaneously every 6 mo vs placebo for 3 y | Denosumab was associated with a significant increase in BMD ($P$<.001) and a decrease in the incidence of vertebral fractures (RR 0.38 as compared with placebo, $P$ = .006). |
| Toremifene protocol G300203[44] | 1294 | Men with nonmetastatic prostate cancer being treated with ADT who were at high risk of fracture. | Toremifene 80 mg orally daily vs placebo | Toremifene was associated with a 50% reduction in the relative risk of new vertebral fracture and an increase in bone mineral density ($P$ = .05). Elevated risk of thromboembolic events in the toremifene arm. |

*Abbreviations:* ADT, androgen deprivation therapy; BMD, bone mineral density; GnRH, gonadotropin-releasing hormone; RR, relative risk.

the NOF recommends using the World Health Organization (WHO)/Fracture Risk Assessment (FRAX) computer-based tool to calculate the 10-year probability of hip or major osteoporotic fracture.[52] This population-specific assessment is based on various easily obtained clinical factors in addition to BMD, and it can be calculated without BMD data if that is not available.

In clinical practice, more individuals meet criteria for pharmacologic management of therapy-related osteoporosis than would be expected based on the WHO definition of osteoporosis alone (T-score of <–2.5 alone). One recent study applied FRAX to 363 patients with nonmetastatic prostate cancer being treated with ADT in an academic practice.[53] In that cohort, 51.2% met criteria for pharmacologic treatment. Age played a major role in the risk stratification, with 3.3% of men younger than 70 years and 99.8% of men 80 years or older meeting criteria.[53]

### *Denosumab HALT 138*

Denosumab was studied in a phase 3, multicenter, double-blind, randomized-controlled trial evaluating whether it could prevent osteoporosis and reduce the rate of fracture in men treated with ADT (see **Table 1**).[43] Men in the study were treated with a GnRH agonist for nonmetastatic hormone-sensitive prostate cancer, and were at high risk of fracture based on low baseline BMD, age older than 70 years, or previous fragility fracture. A total of 1468 subjects were randomized to receive denosumab or placebo subcutaneously every 6 months, and BMD was evaluated at 24 and 36 months. The primary end point in the study was the change in lumbar spine BMD, and incidence of new vertebral fracture was included as a secondary end point.

The trial found that there was both an increase in BMD and a decrease in the rate of clinical fracture in men treated with denosumab as compared with placebo.[43] At 24 months, there was a 5.6% increase in lumbar spine BMD in the group treated with denosumab as compared with a 1.0% decrease in BMD in the placebo group ($P<.001$). Significant differences in BMD were evident in some patients as soon as 1 month after treatment. At 36 months, the denosumab group had significantly fewer vertebral fractures, with an incidence of 1.5% in the denosumab group and 3.9% in the placebo group (relative risk 0.38, $P = .006$).

Subgroup analyses revealed that denosumab improved BMD at all skeletal sites in all subgroups.[54] The men with the most pronounced improvement in BMD were those with the highest markers of bone turnover (serum C-telopeptide and tartrate-resistant alkaline phosphatase). Adverse events were not significantly different between the 2 groups.

Based on the results of this trial, denosumab was recently approved by the FDA for fracture prevention in men receiving ADT.

### *Toremifene Protocol G300203*

Selective estrogen receptor modulators (SERMs), including raloxifene and toremifene, have been studied to prevent therapy-related fragility fractures in men treated with ADT, but are not approved for use in men with prostate cancer.[44,55]

Toremifene was evaluated in a recently reported multicenter, international phase III study of 1294 men with nonmetastatic prostate cancer who were being treated with ADT (see **Table 1**).[44] Men were at high risk of fracture owing to low BMD or age older than 70 years. Subjects were randomized to receive oral toremifene daily or placebo, and they were followed for 2 years. The primary end point in the study was development of new vertebral fractures, and BMD was assessed as a secondary end point. This study revealed that toremifene was associated with a relative risk reduction of 50.0% in the incidence of new vertebral fractures, with a fracture incidence of 2.5% in the toremifene group versus 4.9% in the placebo group (95% CI −1.5 to 75.0, $P = .05$). Notably, toremifene was also associated with a higher rate of venous thromboembolic events than placebo, and has not been approved for fracture prevention in men receiving ADT (2.6% vs 1.1%, respectively).[44]

## METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

There have been 3 contemporary randomized controlled trials of bisphosphonates to prevent skeletal complications in patients with CRPC and bone metastases (**Table 2**). Zoledronic acid is the only bisphosphonate approved to prevent skeletal-related events in men with metastatic prostate cancer. In a recent global randomized-controlled trial, denosumab was superior to zoledronic acid for prevention of SREs in men with CRPC and bone metastases and is approved to prevent SREs in this setting.

### *Zometa 039*

The Zometa 039 trial provided the basis for the FDA approval of zoledronic acid for the prevention of SRE in CRPC with bone metastases. The study included 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases (see **Table 2**).[14] Subjects were randomized to receive

**Table 2**
**Randomized-controlled trials of bone-targeted therapies in prostate cancer with bone metastases**

| Study | N | Study Population | Arms | Outcome |
|---|---|---|---|---|
| Zometa 039[14] | 643 | Men with CRPC and symptomatic or minimally symptomatic bone metastases | Zoledronic acid 4 mg IV every 3 wk vs Placebo | Zoledronic acid was associated with significantly fewer SRE (33.2% vs 44.2%) and a trend toward improved overall survival. |
| CGP 032/INT 05[57] | 350 | Men with CRPC and symptomatic bone metastases | Pamidronate 90 mg IV every 3 wk or placebo | No difference in self-reported pain score, analgesic use, or SREs. |
| NCIC CTG PR.6[58] | 209 | Men with CRPC and symptomatic bone metastases | Clodronate 1500 mg IV every 3 wk or placebo | No difference in palliative response, overall quality of life, overall survival, duration of response, or symptomatic disease progression. |
| Denosumab protocol 20050103[38] | 1901 | Men with CRPC | Denosumab 120 mg subcutaneously or zoledronic acid 4 mg IV every 4 wk | Denosumab prolonged the median time to first on-study SRE by 3.6 mo (met both noninferior and superiority end points). No difference in overall survival or adverse events (including osteonecrosis of the jaw). |
| MRC PR05[59,60] | 311 | Men with castration-sensitive prostate cancer with bone metastases | Clodronate 2080 mg orally daily vs placebo | Trend toward improved progression-free and overall survival with clodronate on initial analysis, and significantly prolonged overall survival at 8-y analysis. |
| CALGB/CTSU | 680[a] | Men with castration-sensitive prostate cancer with bone metastases | Zoledronic acid 4 mg IV every 4 weeks or placebo | Endpoints are SRE and prostate cancer death. Study is ongoing. |

*Abbreviations:* CRPC, castrate-resistant prostate cancer; IV, intravenous; SRE, skeletal-related event.
[a] Target accrual.

4 mg intravenous (IV) zoledronic acid, 8 mg IV zoledronic acid, or placebo every 3 weeks for 15 months, in addition to treatment with ADT and any other therapy provided by their treating physician. The primary end point was the proportion of patients having at least 1 SRE, defined as pathologic bone fracture, spinal cord compression, surgery to bone, radiation to bone, or change in antineoplastic therapy to treat bone pain.

Because of an unacceptable number of grade 3 elevations in creatinine in the 8-mg zoledronic acid arm, changes were made in zoledronic acid dosing and administration. All participants in the 8-mg zoledronic acid group were switched to 4-mg dosing for the remainder of the trial, and creatinine was assessed before each dose. In addition, the infusion period of zoledronic acid was lengthened from 5 minutes to 15 minutes. Following these

changes, the frequency of adverse renal events was similar between the zoledronic acid and placebo arms. At the conclusion of the study, only the 4-mg zoledronic acid and placebo data were compared in the primary efficacy analysis.

At the study's conclusion, a significantly smaller proportion of men in the 4-mg zoledronic acid arm experienced SRE than in the placebo arm (33.2% vs 44.2%; $P = .021$).[56] The median time to first SRE was shorter in the placebo arm than in the 4-mg zoledronic acid arm (321 day vs not reached; $P = .009$). Urinary markers of bone resorption were lower in the zoledronic acid arms than the placebo arm ($P = .011$ for both doses of zoledronic acid vs placebo). There was no significant difference in overall survival between the zoledronic acid and placebo groups.

### *CGP 032 and INT 05*

*CGP 032* and *INT 05* evaluated the effectiveness of IV pamidronate for pain reduction in men with CRPC and symptomatic bone metastases (see **Table 2**).[57] Both trials were similarly designed multicenter, randomized, placebo-controlled trials, which allowed their results to be pooled and reported together. Between the 2 trials, 350 men with CRPC and painful bone metastases were randomized to receive pamidronate (90 mg IV) or placebo every 3 weeks for 27 weeks. The primary end point was change from baseline self-reported pain score, and secondary end points included analgesic use and the proportion of patients with an SRE (defined as pathologic fracture, radiation or surgery to bone, spinal cord compression, or hypercalcemia). Serum and urinary markers of bone turnover were also assessed.

At the conclusion of the studies, the pooled results were unable to demonstrate a difference between the pamidronate and placebo arms in self-reported pain score, analgesic use, proportion of patients with an SRE, or overall survival.[57] Urinary markers of bone turnover were significantly lower in the pamidronate group.

There are several possible reasons for the lack of apparent efficacy of pamidronate in these studies while zoledronic acid demonstrated efficacy in SRE prevention. First, pamidronate is significantly less potent than zoledronic acid, being approximately 100 times less potent than zoledronic acid in vitro. In vivo pamidronate decreases urinary N-teleopeptide, a marker of bone turnover, by approximately 50%, whereas zoledronic acid decreases biomarkers of osteoclast activity by 70% to 80%.[14] Additional reasons for the difference in outcome between these studies and the Zometa 039 trial include a patient population with more advanced disease (symptomatic bone metastases vs asymptomatic metastases) and less precise study end points.

### *National Cancer Institute of Canada Clinical Trials Group PR.6*

Clodronate was evaluated in National Cancer Institute of Canada Clinical Trials Group PR.6 study to determine its ability to palliate bone pain in men with CRPC and symptomatic bone metastases (see **Table 2**).[58] The study included 209 men treated with mitoxantrone (12 mg/m$^2$ IV every 3 weeks) and prednisone (5 mg orally twice daily) who were randomized to receive clodronate 1500 mg IV or placebo every 3 weeks. The primary end point was palliative response determined by a reduction in patient-reported pain intensity index to zero or by 2 points, or a decrease in analgesic use by 50%, without an increase in either. Secondary end points included duration of response, symptomatic disease progression-free survival, and overall quality of life.

Clodronate did not increase the palliative response of men with CRPC and symptomatic metastatic bone lesions when compared with placebo (46% response vs 39% response in clodronate and placebo, respectively; $P = .54$). When compared with placebo, clodronate was equivalent in its effect on overall quality of life, overall survival, duration of response, and symptomatic disease progression-free survival. A subgroup analysis indicated that clodronate may provide some benefit as compared with placebo for pain palliation in men with severe pain, but the investigators note that additional evidence will be necessary to confirm this conclusion.

### *Denosumab Protocol 20050103*

Denosumab was compared with zoledronic acid in an international, phase III, randomized, controlled trial to evaluate its ability to prevent SRE in men with CRPC (see **Table 2**).[38] The trial included 1901 men who were randomized to receive denosumab (120 mg subcutaneously every 4 weeks) or zoledronic acid (4 mg IV every 4 weeks). The primary end point was time to first on-study SRE, defined as pathologic fracture, radiation to bone, surgery to bone, or spinal cord compression. The study aimed to demonstrate noninferiority of denosumab as compared with zoledronic acid. Secondary objectives were to assess for superiority of denosumab and compare drug safety profiles.

After a median follow-up of 12.2 months for men treated with denosumab and 11.2 months for men receiving zoledronic acid, denosumab prolonged

the median time to first on-study SRE by 3.6 months as compared with zoledronic acid (hazard ratio [HR] 0.82, 95% CI 0.71–0.95; $P = .0002$ for noninferiority; $P = .008$ for superiority).[38] Overall survival was similar between the denosumab and zoledronic acid groups. The safety profiles were also similar. Compared with zoledronic acid, denosumab was associated with similar rates of osteonecrosis of the jaw (1% vs 2%; $P = .09$) and higher rates of hypocalcemia (6% vs 13%; $P<.001$). Denosumab was approved by the FDA for use in individuals with metastatic solid tumors, including prostate cancer, for the prevention of SREs.

## METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

### *Bisphosphonates*

Several studies have evaluated the use of bisphosphonates in men with hormonally sensitive metastatic prostate cancer. Initial data from one study evaluating clodronate for the prevention of symptomatic skeletal disease progression or prostate cancer death was negative. Long-term data from that study demonstrating an improved overall survival with clodronate has not yet been incorporated into widespread clinical practice. A second study in this population, CALGB/CTSU (cancer and leukemia group B/cancer trials support unit) 90202, is investigating the use of zoledronic acid in this setting and is ongoing.

#### *Medical Research Council PR05*

The Medical Research Council (MRC) PR05 study evaluated clodronate in men with metastatic prostate cancer who were initiating or continued to be responsive to initial treatment with ADT (see **Table 2**). In the study, 311 men were randomized to clodronate (2080 mg orally daily) or placebo in addition to continuing treatment with primary ADT.[59] The primary study end point was bone progression-free survival defined as time to either symptomatic disease progression or prostate cancer death. Compared with placebo, clodronate did not significantly improve bone progression-free survival (HR 0.79; 95% CI 0.61–1.02; $P = .066$). Treatment with clodronate was associated with longer overall survival, a secondary end point of the study (8-year overall survival, 22% vs 14%; HR 0.77; 95% CI 0.60–0.98; $P = .032$).[60]

#### *CALGB/CTSU 90202*

A second study investigating the use of bisphosphonates in men with hormonally responsive metastatic prostate cancer is the ongoing CALGB/CTSU 90202 (NCT00079001) trial (see **Table 2**). The study aims to randomize 680 men with castrate-sensitive disease and skeletal metastases to receive zoledronic acid (4 mg IV every 4 weeks) or placebo. End points include SRE and prostate cancer death. Because it is FDA approved for prevention of SRE in metastatic castrate-resistant disease, patients cross over to zoledronic acid when they develop castrate-resistant disease or experience an SRE. This study remains open to enrollment.

## PREVENTION OF BONE METASTASES

Several osteoclast-targeted therapies have been evaluated to prevent metastases in men with high-risk or locally advanced disease. Two bisphosphonates, clodronate and zoledronic acid, were studied in randomized, placebo-controlled trials. In MRC PR04, clodronate failed to significantly prolong bone-metastasis–free survival. A trial evaluating the ability of zoledronic acid to prolong time to first metastasis, Zometa 704, did not reach its accrual goal and was therefore not evaluable. The Zometa European Study (ZEUS) is an ongoing European randomized-controlled trial evaluating the efficacy of zoledronic acid in metastasis prevention in men with high-risk prostate cancer. In contrast, a recently reported randomized, placebo-controlled, phase III trial demonstrated that denosumab prolonged bone-metastasis–free survival when compared with placebo.

#### *MRC PR04*

Clodronate was evaluated in a randomized, double-blind, placebo-controlled trial for the prevention of symptomatic bone metastases in the MRC PR04 study (**Table 3**). The trial enrolled 508 men with locally advanced prostate cancer (T2-T4, N0, N+, or NX, M0) who were considered to be at high risk of developing metastases.[61] Men were randomized to 5 years of treatment with clodronate (2080 mg orally per day) or placebo, and most received treatment of their prostate cancer consistent with standard of care at the time (external beam radiation, external beam radiation and hormonal therapy, or primary hormonal therapy). The primary end point was bone-metastasis–free survival, a composite end point that included development of symptomatic bone metastasis or death from prostate cancer. After median follow-up of 118 months and 148 primary end point events, there was no difference in bone-metastasis–free survival or overall survival between the 2 groups. There was a trend toward men in the placebo arm experiencing fewer events than those in the clodronate arm, although this

**Table 3**
**Bone-targeted therapies evaluated for metastasis prevention in nonmetastatic prostate cancer**

| Study | N | Study Population | Arms | Outcome |
|---|---|---|---|---|
| MRC PR04[61] | 508 | Men with locally advanced prostate cancer at high risk of developing metastases. | Clodronate 2080 mg orally daily vs placebo for 5 y | No difference in bone-metastasis–free survival or overall survival. |
| Zometa 704[62] | 398 | Men with CRPC and rising PSA without radiographic evidence of metastatic disease. | Zoledronic acid 4 mg IV every 4 wk vs placebo | Poor accrual and low event rate caused early closure of the trial and impairs analysis of study results. |
| ZEUS[63] | 1300 | Men with high-risk localized castrate-sensitive prostate cancer | Zoledronic acid 4 mg IV every 3 mo or placebo for 48 mo | Target accrual complete, data acquisition and analysis ongoing. |
| Denosumab protocol 20050147[64] | 1435 | Men with nonmetastatic CRPC at high risk of developing metastatic disease | Denosumab 120 mg subcutaneously every 4 wk vs placebo. | Denosumab prolonged median bone-metastasis–free survival by 4.2 mo as compared with placebo. No difference in overall survival between groups. |

*Abbreviations:* CRPC, castrate-resistant prostate cancer; IV, intravenous; PSA, prostate-specific antigen.

did not reach significance (HR 1.22, 95% CI 0.88–1.68; $P = .23$). Excluding PSA level, after 226 events, men in the clodronate arm had shorter time to disease progression than those in the placebo arm (HR 1.31, 95% CI 1.01–1.70; $P = .041$). Overall survival at 5 years was similar between the 2 groups at 78%. Despite evidence of a survival advantage in the castrate-sensitive metastatic setting after long-term follow-up, there was no difference in overall survival after long-term follow-up in this population with locally advanced castrate-sensitive disease.[60]

### *Zometa 704*

Zometa 704 was a randomized-controlled trial evaluating the ability of zoledronic acid to prolong time to first metastasis in men with CRPC and a rising PSA but no radiographic evidence of metastatic disease (see **Table 3**).[62] Men were randomized to receive zoledronic acid (4 mg IV every 4 weeks) or placebo. The primary end point was time to first metastatic bone lesion, and subjects were evaluated by bone scan every 4 months.

Although planned accrual was 991, the trial was closed after only 398 men had enrolled owing to a low event rate. Analysis of the available data found no difference in time to first metastasis between zoledronic acid and placebo, although the low event rate and early study termination precludes reliable conclusions about efficacy of zoledronic acid in this setting.

### *ZEUS*

ZEUS is an ongoing randomized, controlled, open-label study evaluating the ability of zoledronic acid to prevent bone metastases in a high-risk population (see **Table 3**).[63] Subjects have high-risk localized castrate-sensitive prostate cancer, defined by having one of the following disease characteristics: PSA of 20 ng/mL or higher, lymph-node–positive disease, or Gleason score of 8 to 10. Subjects were randomized to receive zoledronic acid (4 mg IV every 3 months for 48 months) or placebo, and additional treatment was delivered per standard of care. The primary end point is the proportion of men who develop at least 1 bone metastasis during a 48-month study period. Target accrual of 1300 men has been met and the study is ongoing.

### *Denosumab Protocol 20050147*

Denosumab has been evaluated for its activity in metastasis prevention in a recently reported international, phase III, double-blind, randomized-controlled trial, Denosumab Protocol 20050147 (see **Table 3**). This study randomized 1435

men with nonmetastatic CRPC at high risk of developing metastatic disease to receive denosumab (120 mg subcutaneously every 4 weeks) or placebo.[64,65] High risk was defined as PSA of 8.0 μg/L or higher, PSA doubling time of 10 months or less, or both. The primary end point of the trial was bone-metastasis–free survival, which included time to first bone metastasis (symptomatic or asymptomatic) or death from any cause. Overall survival was a secondary end point.

Denosumab prolonged median bone-metastasis–free survival by 4.2 months as compared with placebo (29.5 months [95% CI 25.4–33.3] versus 25.2 months [95% CI 22.2–29.5], respectively).[64] Additionally, denosumab delayed time to first bone metastasis when compared with placebo (median 33.2 months [95% CI 29.5–38.0] vs 29.5 months [95% CI 22.4–33.1], respectively). Overall survival was equivalent between groups (median overall survival of 43.9 months with denosumab and 44.8 months with placebo [HR 1.01, 95% CI 0.85–1.20; $P = .91$]). Notable adverse events included hypocalcemia and osteonecrosis of the jaw in 2% and 5% of men receiving denosumab, respectively. Hypocalcemia occurred in fewer than 1% of men receiving placebo, and there were no episodes of osteonecrosis of the jaw.

## RADIOISOTOPES

Both alpha-emitting and beta-emitting radioisotopes have been studied for pain palliation in men with prostate cancer and painful bone metastases. Two beta-emitting radioisotopes, Strontium-89 and Samarium-153, have been approved for bone metastasis pain palliation in men with prostate cancer. Radium-223, an alpha-emitting radioisotope, has also been studied for palliation of bone pain in men with metastatic prostate cancer. In a recently reported international, phase III, randomized, placebo-controlled trial, radium-223 prolonged overall survival in men with CRPC and painful bone metastases.

### *Strontium-89 and Samarium-153*

Strontium-89 and Samarium-153 are beta-emitting radioisotopes that have been approved for use in men with CRPC and painful bone metastases. They act by honing to tissues surrounding osteoblastic lesions to deliver high-energy radiation therapy locally. They are especially useful for treating multifocal lesions that are not easily targeted in a single radiation field or for the palliation of tissues that have previously received maximum doses of external beam radiation.

Several clinical trials have evaluated the efficacy of strontium-89 for pain palliation in men with CRPC and bone metastases. A British study included 284 men treated with strontium-89 or conventional focal or hemibody external beam radiation therapy.[65] Pain control was similar between the groups at 3 months, although bone marrow suppression was more common in the strontium-89 group. A phase III, randomized, controlled Canadian trial included 126 men with hormone-resistant prostate cancer and painful bone metastases who were randomized to receive strontium-89 or placebo after initial treatment with focal external beam radiation.[66] Overall survival was similar between the 2 groups, but men treated with strontium-89 had improved quality-of-life scores and more frequently discontinued pain medications at 3 months than those treated with placebo. In contrast, a European Organization for Research and Treatment of Cancer study randomized 203 men to receive local field external beam radiation or strontium-89.[67] There was no difference between the groups in pain relief, but overall survival was significantly higher in the external beam group (median overall survival 11 vs 7 months, $P = .046$).

Samarium-153 has also been studied in phase III, randomized, placebo-controlled studies in men with prostate cancer. In the first, 118 individuals with bone metastases from various solid tumors were randomized to 0.5 mCi/kg or 1.0 mCi/kg of samarium-153 or placebo.[68] Patients with prostate cancer made up 68% of the group. During the first 4 weeks of the study, the high dose of samarium-153 was associated with significantly less pain than placebo. There was no difference between groups in overall survival. A second study randomized 152 men with CRPC to receive samarium-153 or placebo.[69] Men receiving samarium-153 had significantly lower analgesic use at 3 and 4 weeks during the study.

Complications from beta radioisotopes occur because of the effects of radiation on the tissue surrounding metastatic lesions. The most common adverse effect is myelosuppression, and blood counts should be monitored at least once every 2 weeks during treatment. Additional complications include severe pain flare in fewer than 10% of men, and acute leukemia has rarely been associated with strontium-89.[70,71]

### *Alpharadin in Symptomatic Prostate Cancer*

Radium-223 is an alpha-emitting radioisotope that is currently being evaluated in the Alpharadin in Symptomatic Prostate Cancer trial, an international, randomized, controlled, phase III study. The trial included 922 men with CRPC and 2 or more symptomatic bone metastases but no

visceral metastases who had received docetaxel or were unfit to receive it.[72] They were randomized to radium-223 (50 kBq/kg) or placebo. The primary end point of the study was overall survival, and secondary end points included time to first SRE, time to PSA progression, and total alkaline phosphatase normalization.

After 314 events from 809 randomized patients were collected, a planned interim analysis was performed. Because radium-223 was associated with a significant improvement in overall survival as compared with placebo, the trial was closed immediately (median survival 14.0 vs 11.2 months, HR 0.695, $P = .002$).[72] Radium-223 also prolonged time to first SRE (13.6 months vs 8.4 months for radium-223 and placebo, respectively). The most common complications associated with radium-223 versus placebo include anemia (27% vs 27%), bone pain (43% vs 58%), and nausea (34% vs 32%). This medication is not yet approved for use in men with CRPC and symptomatic bone metastases in the United States.

## SUMMARY

In prostate cancer, both metastatic lesions and the effects of hormonal therapy can have negative effects on the skeletal system. Multiple therapies have been developed to target bone-related complications for men at various stages of the disease. Evidence supports the use of osteoclast-inhibiting therapies in men treated with ADT to prevent therapy-related fragility fractures. There is also evidence that osteoclast-inhibiting therapies are beneficial in preventing SREs in men with CRPC. More recently, phase III data demonstrate that using denosumab in men with CRPC can prevent the development of metastases. Finally, radium-223 prolongs overall survival in men with CRPC and skeletal metastases after treatment with docetaxel. The spectrum of bone-targeted therapies for the skeletal complications of prostate cancer continues to evolve, providing numerous novel options in our arsenal against bone complications in this disease.

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