Implications of Bone Metastases and the Benefits of Bone-Targeted Therapy

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Several cancers, including those originating in the breast, prostate, and lung, exhibit a propensity to metastasize to bone, resulting in debilitating skeletal complications. These sequelae, such as intractable pain, pathologic fractures, spinal compression, and hypercalcemia, greatly erode the patients’ quality of life. Bisphosphonates, a class of antiresorptive drugs, are now the mainstay of the treatment of skeletal-related events in myeloma bone disease and many solid cancers with bone metastases. Current evidence indicates that newer-generation nitrogen-containing bisphosphonates, particularly zoledronic acid, are potent inhibitors of bone resorption. In addition, increased understanding of the pathogenesis of bone metastasis has resulted in the development of several bone-targeted therapies including a monoclonal antibody targeting the receptor activator of nuclear factor (NF)-κB ligand (RANKL). In this review, clinical evidence regarding the efficacy and safety of currently available bone-targeted therapies including bisphosphonates and anti-RANKL monoclonal antibody in the treatment of bone metastasis due to breast cancer, prostate cancer, lung cancer, and multiple myeloma bone disease will be summarized.

Bone lesions due to metastatic disease undermine the structural integrity of the bone and are associated with substantial morbidity and debilitating complications. These sequelae, including severe bone pain, pathologic fractures, spinal cord compression, leukoerythroblastic anemia, bone deformity, and hypercalcemia of malignancy (HCM), have a devastating impact on quality of life and are associated with increased health care costs. The annual incidence of skeletal complications is 1.5–4.0 events per year in patients with bone metastasis.2,4

Hypercalcemia occurs in advanced stage disease, and is associated with dysfunction of the gastrointestinal tract, kidneys, and central nervous system that can reach potentially life-threatening proportions. In most instances, hypercalcemia is causally linked to increased osteoclastic bone resorption, either multifocal manifestations or as a generalized process, in response to tumor-derived growth factors and cytokines. Moreover, the loss of bone integrity due to metastasis results in rib fractures, vertebral collapse, and pathologic fractures. While the last is not as common as the other two, it is associated with the most incapacitating effects; sites of pathologic fractures commonly involve the hip and the proximal ends of the long bone and often require orthopedic surgery. Development of spinal cord compression is a catastrophic event that requires vigilant monitoring, early diagnosis, and urgent decompression interventions to allow neurologic recovery. Bone pain is a common cancer-related complication that can be intractable in severe cases, and is linked to the rate of bone resorption.

Several treatment strategies are currently employed in the management of bone metastasis, including surgery, radiation, chemotherapy, and treatment with a bisphosphonate class of antiresorptive drugs.4 While radiotherapy or surgery intervention are used with palliative intent and have been favorably associated with better quality of life and longer survival times, their curative potential is limited since they do not target the underlying pathobiology of the disease. Bisphosphonates are analogues of pyrophosphates that bind avidly to metabolizing bone and inhibit several components of the bone resorptive process, including induction of osteoclast apoptosis, inhibition of osteoclast formation, and recruitment. Based on their considerable clinical activity, bisphosphonates are now an integral part of the current armamentarium for the treatment of skeletal complications related to metastatic bone disease. There are several bisphosphonates currently available and they exhibit varying structures, mechanism of action, and potencies. The early-generation bisphospho-
nates such as clodronate do not contain nitrogen and are metabolized by osteoclasts. In contrast, later-generation bisphosphonates, such as pamidronate and zoledronic acid, are nitrogen-containing agents that are internalized by osteoclasts and lead to inhibition of farnesyl-diphosphonate (FPP) synthase that regulates activity of key guanosine triphosphatases (GTPases) required for osteoclast function. Of the nitrogen-containing bisphosphonates, current evidence indicates that zoledronic acid is the most potent in terms of FPP synthase inhibition and antiresorptive activity. Recent advances in understanding of the pathogenesis of bone metastasis in different cancer settings have led to the development of rational bone-targeted therapies. Several such emerging bone-targeted agents are currently being developed and are in varying stages of clinical testing. Considering the crucial role of the receptor activator of nuclear factor (NF)-κB ligand (RANKL) in osteoclastogenesis, a fully human monoclonal anti-RANKL antibody denosumab is being actively investigated in solid tumors and multiple myeloma. This review attempts to summarize the clinical data regarding the efficacy and safety of currently available bone-targeted therapies in the treatment of bone metastasis due to breast cancer, prostate cancer, lung cancer, and multiple myeloma bone disease.

**BREAST CANCER**

**Bisphosphonates in the Treatment of Bone Metastasis**

Randomized clinical trials have demonstrated that prolonged administration of oral or intravenous (IV) bisphosphonates significantly reduces the frequency of skeletal-related events (SREs) in patients with bone metastases from breast cancer. Although clodronate has demonstrated considerable activity in terms of reduction of SREs and palliation in the treatment of bone lesions of breast cancer, questions remain regarding the durability and survival effects. In a randomized placebo-controlled trial, clodronate therapy resulted in significant reduction of the total number of hypercalcemic episodes (28 events vs. 52 events; \( P < .01 \)), the rate of vertebral fractures (84 vs. 124 events per 100 patient-years; \( P < .025 \)), and the rate of vertebral deformity (168 vs. 252; \( P < .001 \)) compared with placebo. The combined event rate for all skeletal morbidity rate (SMR) was significantly reduced with clodronate therapy (218.6 vs. 304.8; \( P < .001 \)) (Table 1). However, these benefits did not translate into significant differences in survival. Considering that the statistical methods used to analyze differences in events per 100 patient-years between the clodronate and placebo groups might potentially overestimate treatment effects, the results of this study were later reanalyzed to measure the time to first SRE and survival; however, median survival time was still similar between the treatment groups. Kristensen et al reported that oral clodronate therapy in 100 patients with metastatic breast cancer led to significant reduction in the time to the first SRE and incidence of fractures compared to control (Table 1). However, these benefits were not durable and declined after 15 months of treatment. Another trial of 137 patients with osteolytic bone metastases from breast cancer demonstrated that addition of clodronate therapy to either chemotherapy or hormonal therapy resulted in a significant reduction in median time to first SRE (244 days vs. 180 days; \( P = .05 \)), pain intensity (\( P = .01 \)), and analgesic usage (\( P = .02 \)) compared to the control group. In these studies, no significant differences were observed in the incidence of adverse events between the two treatment groups.

Several trials have evaluated the safety and efficacy of pamidronate in the treatment of bone metastases in patients with breast cancer. Early clinical trials, albeit small nonrandomized trials, indicated the clinical benefit of pamidronate in terms of progression of bone disease and improvement in bone pain in patients with advanced breast cancer and osteolytic lesions. Subsequently, a randomized study of patients with bone metastases from breast cancer demonstrated that addition of pamidronate to chemotherapy resulted in significant prolongation of median time to progression (249 days vs. 168 days; \( P = .02 \)) and significant reduction in pain (44% vs. 30%; \( P = .025 \)) compared to those that received chemotherapy alone (Table 1).

The clinical benefit of pamidronate was confirmed in a randomized, multicenter trial (Protocol 19 Aredia Breast Cancer Study Group) initiated by Hortobagyi et al to evaluate the long-term effectiveness and safety of infrequent intravenous pamidronate therapy over a period of 2 years in 382 patients with metastatic breast cancer and osteolytic bone lesions (Table 1). Landmark analysis of the trial showed that monthly infusions of pamidronate therapy resulted in significant reductions in the proportion of patients with SRE compared to placebo at 15, 18, 21, and 24 months (\( P < .001 \)), which were consistent with data at end of 1 year. The median time to first SRE was also significantly increased with pamidronate therapy compared to placebo (13.9 months vs. 7 months; \( P < .001 \)). However, there was no difference in survival between the two groups. Moreover, long-term treatment did not have any adverse effects. These findings showed that long-term treatment with bisphosphonates was safe and effective as adjunct therapy with standard chemotherapy in the palliative management of metastatic breast cancer.

Subsequently, Hultborn et al demonstrated that pamidronate therapy in 404 women with skeletal metastases from breast cancer resulted in significantly fewer SREs (\( P < .01 \)) and significantly increased time to progression of pain (\( P < .01 \)) and hypercalcemic events.
## Table 1. Bone-Targeted Therapy in Patients With Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Results</th>
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<tbody>
<tr>
<td>Clodronate therapy</td>
<td>Placebo v oral clodronate (1,600 mg/d)</td>
<td>↓ terminal hypercalcemic episodes (17 v 7; P &lt; .05); ↓ vertebral fractures (124 events v 84 events per 100 patient years; P &lt; .025); ↓ rate of vertebral deformity (252 v 168; P &lt; .001); ↓ SMR (304.8 to 218.6; P &lt; .001); ↑ time to first SRE (4.9 months v 9.9 months; P = .022); No change in survival time</td>
</tr>
<tr>
<td>Kristensen et al</td>
<td>No treatment v oral clodronate (1,600 mg/d)</td>
<td>↑ time to first SRE (P &lt; .015); ↓ occurrence of fractures (P &lt; .023); SRE effects are not durable</td>
</tr>
<tr>
<td>Tubiana-Hulin et al</td>
<td>Placebo v oral clodronate (1,600 mg/d)</td>
<td>↑ time to first SRE (180 days v 244 days; P = .05); ↓ pain intensity (P = .01); ↓ analgesic usage (P = .02)</td>
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<tr>
<td>Pamidronate therapy</td>
<td>Placebo v pamidronate (45 mg IV every 3 weeks)</td>
<td>↑ time to progression of disease (168 days v 249 days; P = .02; ↑ by 48%); ↑ pain relief (30% v 44% of patients; P = .025)</td>
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<tr>
<td>Conte et al</td>
<td>Placebo v pamidronate (90 mg IV every 3–4 weeks; for 2 years)</td>
<td>↓ patients with SRE at 15, 18, 21, and 24 months (P &lt; .001); ↑ time to first SRE (7.0 months v 13.9 months; P &lt; .001); No change in survival</td>
</tr>
<tr>
<td>Hortobagyi et al</td>
<td>Placebo v pamidronate (60 mg IV every 4 weeks)</td>
<td>↓ time to progression of pain (P &lt; .01); ↑ time to hypercalcemic events (P &lt; .05); ↑ PS scores (P &lt; .05); No change in fracture or paralysis due to vertebral compression</td>
</tr>
<tr>
<td>Theriault et al</td>
<td>Placebo v pamidronate (90 mg IV every 4 weeks; for 2 years)</td>
<td>↓ SMR at 12 months (P = .028), 18 months (P = .023) and 24 months (P = .008); ↓ skeletal complications (67% v 56%; P = .027)</td>
</tr>
<tr>
<td>Lipton et al</td>
<td>Pooled analysis of the Hortobagyi et al and Theriault et al trials</td>
<td>↓ in skeletal complications (64% v 51%; P &lt; .001); ↓ mean SMR (3.7 v 2.4; P &lt; .001)</td>
</tr>
<tr>
<td>Ibandronate therapy</td>
<td>Placebo v ibandronate (6 mg IV every 3–4 weeks; 2 years)</td>
<td>↓ SMPR (↓ by 20%; 1.48 events v 1.19 events per patient year; P = .004); ↓ time to first SRE (33.1 weeks v 50.6 weeks; P = .018); ↓ number of new bone events (↓ by 38%)</td>
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Comparison of pamidronate and zoledronic acid therapy for skeletal-related events (SREs) in patients with breast cancer treated with hormone therapy. Table 1. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Results</th>
</tr>
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<tr>
<td>Body et al\textsuperscript{16}</td>
<td>Placebo v ibandronate (50 mg/day; oral; 96 weeks)</td>
<td>↓ mean SMPR (1.18 vs 0.95; ( P = .004 )); ↓ risk of SRE (HR = 0.62; ( P = .0001 )); No significant difference in percentage of patients with SRE or time to SRE</td>
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<tr>
<td>Zoledronic acid therapy</td>
<td>Placebo v zoledronic acid (4 mg IV every 4 weeks for 1 year)</td>
<td>↓ SRE (( P = .027 )); ↓ in percentage of patients with ≥ SRE (49.6% vs 29.8%; ( P = .003 )); delayed time to first SRE (364 days vs median not reached; ( P = .007 )); ↓ risk of SRE (↓ by 41%; RR = 0.59; ( P = .019 )); ↓ bone pain (45% vs 32% of patients)</td>
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<tr>
<td>Pamidronate v zoledronic acid therapy</td>
<td>Pamidronate (90 mg IV) v zoledronic acid (4 mg IV) every 3–4 weeks</td>
<td>Prolonged time to first SRE (174 days vs 310 days; ( P = .013 )); ↓ risk of skeletal events (↓ by 20%; HR = 0.801; ( P = .037 )); ↓ risk of skeletal events in patients with osteolytic lesions (↓ by 30%; HR = 0.704; ( P = .010 ))</td>
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<tr>
<td>Denosumab therapy</td>
<td>Pamidronate (90 mg IV) v denosumab (0.1, 0.3, 1.0 or 3.0 mg/kg SC) in patients with multiple myeloma or breast cancer</td>
<td>Sustained ↓ in urinary and serum NTX in denosumab treated patients</td>
</tr>
<tr>
<td>Body et al\textsuperscript{19}</td>
<td>Zoledronic acid (4 mg IV) v denosumab (120 mg SC) every 4 weeks</td>
<td>Delayed time to first on-study SRE (HR = 0.82; ( P &lt; .0001 ) noninferiority; ( P = .01 ) superiority); delayed time to first and subsequent on-study SRE (rate ratio 0.77; ( P = .001 )); delayed time to first radiation to bone (HR = 0.74; ( P = .01 )); delayed time to first on-study SRE or HCM (HR = 0.82; ( P = .007 )); ↓ mean SMR (0.58 vs 0.45, respectively; ( P = .004 )); ↓ patients experiencing ≥1 on-study SRE (denosumab: 30.7% [95% CI, 27.9%, 33.5%]; zoledronic acid: 36.5% [95% CI, 33.5%, 39.4%]).</td>
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Abbreviations: IV, intravenous; SC, subcutaneous; PS, performance status; SRE, skeletal-related event; SMPR, skeletal morbidity period rate; SMR, skeletal morbidity rate; HR, hazard ratio; RR, risk ratio; NTX, N-telopeptide levels; HCM, hypercalcemia of malignancy; CI, confidence interval.

\( P < .05 \) compared with placebo.\textsuperscript{12} However, no significant difference in pathologic fractures of long bones or pelvis, or paralysis due to vertebral compression was observed between the two groups. In another confirmatory trial (Protocol 18 Aredia Breast Cancer Study Group), Theriault et al demonstrated that pamidronate therapy in 372 patients with at least one osteolytic bone lesion from breast cancer treated with hormone therapy significantly reduced the primary endpoint of SMR at 12 cycles (\( P < .028 \)), 18 cycles (\( P < .023 \)), and
ibandronate significantly reduced the SMPR (hazard ratio [HR] = 0.95; P = .004) compared to placebo (0.95 v 1.18; P = .004).10 Oral ibandronate significantly decreased the risk of SRE by 38% compared to placebo (hazard ratio [HR] = 0.62; P < .0001). However, oral ibandronate did not significantly decrease the percentage of patients with SREs (45% v 52%; P = .122) or the time to the first SRE (median 21 months v 15 months; P = .089). In another pooled analysis that included both IV ibandronate and oral ibandronate trials, Tripathy et al showed that both IV ibandronate and oral ibandronate significantly reduced the SMPR (P = .004) compared with placebo, and reduced bone pain. In a multivariate analysis, the mean reduction in the relative risk of new bone events were comparable between intravenous and oral administration.20 Due to the lack of unequivocal demonstrations of clinical activity with ibandronate therapy, its clinical use is limited in breast cancer.

The third-generation bisphosphonate, zoledronic acid, is considered to be a more potent bisphosphonate compared to pamidronate, as evidenced from preclinical data, and requires a relatively short infusion time. Based on these favorable features, a large randomized phase III trial was undertaken to directly compare zoledronic acid (4 mg IV 15-minute infusion every 3–4 weeks) to the then standard pamidronate therapy (90 mg IV 2-hour infusion every 3–4 weeks) in 1,150 patients with breast cancer who had bone metastasis including osteolytic, mixed, or osteoblastic18 (Table 1). In the total breast cancer population, both zoledronic acid and pamidronate reduced the overall proportion of patients with an SRE (43% v 45%) to a similar extent. However, in the subset of patients with at least one osteolytic lesion, treatment with zoledronic acid reduced the proportion of patients with an SRE compared to pamidronate (48% v 58%), although this trend did not reach statistical significance (P = .058). Moreover, significant reduction in the time to first SRE was achieved with zoledronic acid compared to pamidronate (median, 310 days v 174 days; P = .013). Multiple event analysis, which is proposed to provide a comprehensive assessment of skeletal morbidity, demonstrated a 20% reduction in the risk of skeletal events (HR = 0.801; P = .037) with zoledronic acid compared to pamidronate in all patients, with an even greater reduction the lytic subgroup (HR = 0.70; P = .010). These results suggested that zoledronic acid was superior to pamidronate in treatment of patients with bone metastases from breast cancer. Moreover, in an exploratory analysis of this trial, 68% of the patients who had experienced at least one SRE prior to study entry were associated with an increased risk for the development of an on-study SRE compared to patients with no prior SREs (58% v 32%), implying that early initiation of bisphosphonate therapy might be beneficial and must not be reserved till occurrence of first SRE.

Subsequently, a registrational, randomized, placebo-controlled trial of zoledronic acid in Japan in 228 women with breast cancer bone metastases showed that zoledronic acid led to a significant 39% reduction in the rate of SRE compared to placebo (risk ratio [RR] = 0.61; P = .027), and a 40% decrease in the percentage of patients with at least one SRE (29.8% v 49.6%; P = .003)17 (Table 1). Placebo was deemed an appropriate comparator since no other bisphosphonates were approved in Japan in this disease and patient setting. Zoledronic acid also significantly decreased the time to first SRE (median not reached v 364 days; P = .007). A significant reduction in the risk of SREs was associated with zoledronic acid in this study compared to placebo (RR = 0.59; P = .019). Zoledronic acid also reduced bone pain (32% v 45%), with only 6% of patients in the zoledronic acid group experiencing grade 3 or 4 bone pain compared to 20% of patients in the placebo group. While cautioning the hazards of cross-trial interpretations, it must be noted that the magnitude of clinical benefit from treatment with zoledronic acid in this trial appeared to be higher than that from pamidronate and ibandronate treatment.11,13
Novel Targeted Agents in the Treatment of Bone Metastasis

The investigational bone-targeted human anti-RANKL monoclonal antibody denosumab is the furthest along in clinical testing. It was initially compared to pamidronate in patients with multiple myeloma (N = 25) or breast cancer (N = 29) with radiologically confirmed bone lesions, where patients either received denosumab (0.1, 0.3, 1.0, or 3.0 mg/kg subcutaneously [SC]) or pamidronate (90 mg IV), and the effect on bone metabolism was assessed using changes in bone markers urinary and serum N-telopeptide levels (NTX). In this study, a significant reduction in median urinary NTX was observed after 1 day of both denosumab and pamidronate. While this decrease was sustained with higher doses of denosumab until 84 days of follow-up, it was not durable in the pamidronate group. These results suggested that denosumab conferred a much longer inhibitory activity on bone resorption compared to standard doses of pamidronate.

A prospective large placebo-controlled randomized trial was initiated to compare the effects of denosumab to zoledronic acid in delaying or preventing bone metastases in 2,046 patients with breast cancer and bone metastases that had not been previously treated with bisphosphonates. Patients were randomized to receive either denosumab (120 mg SC) plus placebo (IV), or placebo (SC) plus zoledronic acid (4 mg IV) every 4 weeks (Table 1). Denosumab significantly delayed the primary endpoint of time to first on-study SRE compared to zoledronic acid (HR = 0.82; P < .0001 noninferiority; P = .01 superiority) and the time to first and subsequent on-study SRE (rate ratio = 0.77; P = .001). Denosumab therapy also demonstrated a significant delay in the time to first radiation on bone (HR 0.74; P = .01) and time to first on-study SRE or HCM (HR = 0.82; P = .007) compared to zoledronic acid therapy. Moreover, denosumab therapy reduced the mean SMR compared to zoledronic acid (0.45 v 0.58; P = .04). At the time of analysis of the primary data, the proportion of patients experiencing at least one on-study SRE was lower in the denosumab arm (30.7% v 36.5%) compared to zoledronic acid. Acute-phase reactions during the initial 3 days of the study were reported by 10% of the patients on denosumab treatment and 27% of patients on zoledronic acid. Based on these study results, denosumab appears to be more effective than zoledronic acid in delaying the first on-study SRE, and in reducing SMR, time to first radiation to bone, and the proportion of patients with SREs.

PROSTATE CANCER

Bisphosphonates in the Treatment of Prostate Cancer

Although prostate cancers are predominantly sclerotic or osteoblastic, they also have an osteolytic component that might be responsive to bisphosphonates. Consequently, several trials have investigated clodronate, pamidronate, and zoledronic acid in patients with prostate cancer. While several early clinical trials indicated that intravenous clodronate might have analgesic effects in patients with bone pain associated with metastatic bone disease from prostate cancer, subsequent trials failed to show convincing clinical activity in preventing skeletal complications, delaying symptomatic bone progression, or in palliative responses in prostate cancer, which might be attributable to differences in patient populations, dosage used, and baseline pain levels. In the placebo-controlled, randomized PR05 trial in 311 men with bone metastases from prostate cancer who were either commencing or responding to first-line hormone therapy, oral clodronate 2,080 mg/d therapy for 3 years resulted in a 21% reduction in risk of bone progression-free survival (BPFS; HR = 0.79; P = .006) and a 20% reduction in risk of death (HR = 0.80; P = .082) compared with placebo; however, both were not statistically significant (Table 2). However, clodronate therapy significantly lowered the risk of worsened World Health Organization (WHO) performance scores compared to those treated with placebo (HR = 0.71; P = .008). Nonetheless, patients in the clodronate group exhibited an elevated risk for adverse events, with high levels of gastrointestinal toxicities and increased lactate dehydrogenase levels. Based on the bulk of current evidence, the role of clodronate therapy in prostate cancer is uncertain.

Two multicenter, randomized, placebo-controlled trials evaluated the effect of pamidronate in the treatment of bone metastases in 378 patients with hormone-refractory prostate cancer (HRPC). Pooled analysis of these two trials showed no statistically or clinically significant differences in pain scores compared with placebo at 9 or 27 weeks in the total population (Table 2). Although a subset of patients with stable or decreasing analgesic use achieved significant pain relief at 9 weeks, this was no longer significant at 27 weeks of treatment. Moreover, pamidronate also had no effect on the proportion of patients with SRE at 9 weeks and 27 weeks. Pamidronate was generally well tolerated; the most common adverse events in both groups included bone pain, nausea, anorexia, and fatigue.

In contrast to the disappointing data with clodronate and pamidronate in prostate cancer, zoledronic acid has demonstrated efficacy in terms of analgesic effects and reduction in SREs. In a randomized, placebo-controlled trial conducted to test the efficacy of zoledronic acid in reducing the incidence of SREs in men with metastatic HRPC, patients were randomized to receive either zoledronic acid (4 mg IV every 3 weeks for 15 months) or placebo (Table 2). After 24 months on the study, a significantly lower percentage of patients who received zoledronic acid treatment had at least one SRE compared to those that received pla-
cebo (38% v 49%; difference = −11%; 95% confidence interval [CI], −20.2% to −1.3%; P = .028). Consistently, the annual incidence of SREs was lower in the zoledronic acid group compared to placebo (0.77 v 1.47; P = .005). A significant prolongation in the median time to first SRE was achieved in the zoledronic acid treatment group (488 days v 321 days; P = .009) compared to placebo. Treatment with zoledronic acid also significantly decreased the risk of developing a skeletal complication by 36% compared to placebo (RR = 0.64; P = .002). Moreover, zoledronic acid treatment significantly decreased bone pain compared to placebo. Zoledronic acid was well tolerated with mild to moderate adverse effects including mild-to-moderate fatigue, myalgia, and fever. These results represent the first compelling demonstrations of durable activity with any bisphosphonate therapy in prostate cancer.

**Other Bone-Targeted Therapies in Prostate Cancer**

Besides bisphosphonates, several bone-specific agents, including denosumab, atrasentan, and ZD4054 (zibotentan), are either being evaluated or rationally de-

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**Table 2. Clinical Trial Data of Bone-Targeted Therapy in Prostate Cancer**

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<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Results</th>
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<tbody>
<tr>
<td>Clodronate therapy</td>
<td>Ernst et al27</td>
<td>Men with advanced prostate cancer with bone pain</td>
<td>Placebo v clodronate (600 mg or 1,500 mg IV) for 2 weeks and switched to alternate treatment for 2 weeks</td>
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<td></td>
<td>Dearnaley et al28 (PR05 trial)</td>
<td>Men with bone metastases from prostate cancer on first-line hormone therapy</td>
<td>Placebo (n = 156 patients) v clodronate (2,080 mg/d; oral; 3 years; n = 155 patients)</td>
</tr>
<tr>
<td></td>
<td>Ernst et al31</td>
<td>Patients with HRPC treated with mitoxantrone and prednisone (MP)</td>
<td>Placebo v clodronate (1,500 mg IV) every 3 weeks</td>
</tr>
<tr>
<td>Pamidronate therapy</td>
<td>Small et al33</td>
<td>Patients with HRPC</td>
<td>Placebo or pamidronate (90 mg IV every 3 weeks)</td>
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<tr>
<td>Zoledronic acid therapy</td>
<td>Saad et al34</td>
<td>Patients with HRPC</td>
<td>Placebo or zoledronic acid (4 mg IV every 3 weeks) for 15 months</td>
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<td>Denosumab therapy</td>
<td>Fizazi et al35</td>
<td>Patients with bone metastases from prostate cancer, multiple myeloma and other solid tumors</td>
<td>IV bisphosphonate every 4 weeks v 180 mg denosumab SC every 4 or 12 weeks</td>
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<td>Atrasentan therapy</td>
<td>Carducci et al36 (phase II trial)</td>
<td>Men with metastatic HRPC</td>
<td>Placebo or atrasentan (2.5 mg; oral) or atrasentan (10 mg; oral)</td>
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<tr>
<td></td>
<td>Carducci et al37</td>
<td>Patients with metastatic HRPC</td>
<td>Placebo or atrasentan (10 mg; oral)</td>
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<td></td>
<td>Nelson et al38</td>
<td>Patients with nonmetastatic HRPC</td>
<td>Placebo or atrasentan (10 mg; oral)</td>
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<td></td>
<td>James et al39</td>
<td>Men with metastatic HRPC</td>
<td>Placebo or ZD4054 (10 mg; oral; daily) or ZD4054 (15 mg; oral; daily)</td>
</tr>
</tbody>
</table>

Abbreviations: SRE, skeletal-related event; RR, risk ratio; uNTX, urinary N-telopeptide levels; WHO PS, World Health Organization performance status; OS, overall survival; PFS, progression-free survival; TTP, time to progression; TTPSA, time to prostate-specific antigen; PSA, prostate-specific antigen; BALP, bone-specific alkaline phosphatase; SC, subcutaneous; IV, intravenous.
signed for the treatment of bone lesions due to metastatic prostate cancer. In a randomized phase II trial, 111 patients with bone metastases from prostate cancer, other solid tumors, or multiple myeloma and high urinary NTX values were treated with IV bisphosphonates every 4 weeks or subcutaneous denosumab 180 mg every 4 weeks or 12 weeks (Table 2). Of the entire study group, 45% represented patients with prostate cancer, all of whom had received prior treatment with zoledronic acid. After 13 weeks of treatment, 69% of patients who received denosumab therapy achieved the primary endpoint of urinary NTX levels <50 compared to 19% of patients that received IV bisphosphonate; this trend was sustained even at week 25. The median time to reduction of urinary NTX values to <50 was 10 days in the denosumab group vs. 88 days in the IV bisphosphonate group (P <.001). A lower proportion of patients with prostate cancer who received denosumab experienced an on-study SRE compared to patients receiving IV bisphosphonate (3% vs. 19%). Only one grade 4 adverse event of asymptomatic reversible hypophosphatemia was reported in patients receiving denosumab therapy. Several ongoing phase III studies are further evaluating the role of denosumab in patients with prostate cancer who have not been previously treated with bisphosphonates, or in patients with castration-resistant prostate cancer and bone metastases.

Based on preclinical evidence, endothelin-1 receptor blockade with atrasentan or ZD4054 may represent an attractive treatment option for osteoblastic bone disease in prostate cancer metastases. A placebo-controlled, randomized phase II trial demonstrated that atrasentan had favorable tolerability and delayed time to progression of disease in 288 asymptomatic patients with HRPC compared to placebo (Table 2). Although the primary endpoint of median time to progression (TTP) was not significantly prolonged in the intent-to-treat (ITT) population, it was found to be significantly increased in the assessable population with both drug doses (10 mg and 2.5 mg). Median time to prostate-specific antigen (PSA) progression in the 10-mg atrasentan group was twice that of the placebo group in both the ITT and the assessable populations (155 days vs. 71 days; P = .002). Primary adverse events included headache, rhinitis, and peripheral edema in the atrasentan group. Based on these encouraging results, Carducci et al. conducted a phase III placebo-controlled trial to evaluate the efficacy and safety of atrasentan 10 mg in patients with metastatic HRPC. Disappointingly, atrasentan did not decrease TTP (HR = 0.89; P = .136), time to PSA progression (HR = 0.84; P = .366), or overall survival (OS) (HR = 0.97; P = .775) compared with placebo. In another placebo-controlled, international phase III trial, reported by Nelson et al., in 941 patients with nonmetastatic HRPC who had adequate androgen suppression, and no evidence of metastatic progression but increasing PSA levels, atrasentan 10 mg resulted in a nonsignificant prolongation of median TTP (764 days vs. 671 days; P = .288) and median time to initial diagnosis of skeletal metastases (1,008 days vs. 757 days; P = .035) compared to placebo. There was no difference in OS between the treatment arms. However, atrasentan therapy resulted in significant reductions in PSA doubling time (P = .031) and was significantly slowed rise in bone-specific alkaline phosphatase (BALP) (P = .001). An ongoing phase III trial by the Southwest Oncology Group (SWOG-0421) is evaluating atrasentan in combination with docetaxel in patients with metastatic HRPC.

Preliminary investigations of safety and efficacy of two doses of oral ZD4054 (10 mg or 15 mg) from a placebo-controlled, randomized multicenter phase II study in 312 patients with metastatic HRPC were recently presented (Table 2). At the time of primary analysis, the median TTP was not significantly different between the treatment groups. However, a clear statistically significant survival benefit emerged in subsequent analysis with 10 mg ZD4054 therapy compared to placebo (HR = 0.55; P = .008), but the differences in TTP remained insignificant. Adverse events were as expected for an endothelin-A receptor (ETAR) antagonist including peripheral edema, headaches, and nasal congestion.

MULTIPLE MYELOMA

Bisphosphonates in the Treatment of Myeloma Bone Disease

Clodronate therapy has demonstrated particular clinical efficacy in myeloma bone disease. In the Finnish Leukemia Study Group placebo-controlled randomized trial in patients with multiple myeloma, 350 patients were treated with either placebo or clodronate 2,400 mg/d in addition to melphalan/prednisolone for 2 years; only 68 of these patients did not present with overt skeletal disease (Table 3). A significantly lower proportion of patients showed increased progression of osteolytic bone lesions in the clodronate treatment group compared to placebo (12% vs. 24%, P = .026). While there was no significant difference in the incidence of vertebral fractures between the two groups (30% vs. 40%), significantly greater pain relief was experienced with clodronate therapy compared to placebo (54% vs. 24%; P <.001). In the randomized Medical Research Council (MRC) trial reported by McCloskey et al., the use of clodronate 1,600 mg daily in addition to chemotherapy was separately evaluated in newly diagnosed patients with and without overt skeletal disease at study entry (Table 3). An approximately 50% decrease in the proportion of patients with severe hypercalcemia (5.1% vs. 10.1%; P = .06) or non-vertebral fractures (6.8% vs. 13.2%; P = .04) were
achieved with clodronate therapy. Additionally, clodronate treatment decreased the frequency of back pain (10.9% vs 19.9%, \( P = .05 \)) and height loss (2.0 cm vs 3.4 cm, \( P = .01 \)) compared to placebo at 24 months. While OS was similar between clodronate and placebo therapy at a median follow-up of 8.6 years, it appeared that baseline absence of vertebral fractures might be associated with better survival.\(^{43}\) These results suggested that long-term usage of oral clodronate may slow the progression of skeletal disease in multiple myeloma.

Berenson et al demonstrated that monthly infusions of pamidronate 90 mg in patients with advanced multiple myeloma and at least one osteolytic lesion who had responded to last chemotherapy significantly reduced incidence of vertebral and nonvertebral fractures (21 months vs 10 months, \( P < .0001 \)) compared to placebo. While OS was similar between the two treatment groups in the total population, a subset analysis

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Abbreviations: SRE, skeletal-related event; SMR, skeletal morbidity rate; HR, hazard ratio; NTX, N-telopeptide levels; OS, overall survival; BALP, bone-specific alkaline phosphatase; Hb, hemoglobin; SC, subcutaneous; IV, intravenous.
found that a survival advantage was derived by patients who had failed to respond to prior chemotherapy compared to those for which this was first-line chemotherapy (21 months vs 14 months, $P = .041$). It is unknown if a similar benefit could not be detected in the MRC clodronate study since all patients received first-line chemotherapy in that trial. Overall, pamidronate was safe and well tolerated during the duration of treatment. These results suggest that the benefits of pamidronate were predominantly restricted to reductions in skeletal complications. In contrast, Brincker et al reported no difference in skeletal morbidity in terms of bone fracture, related surgery, vertebral collapse, or increase in number and/or size of bone lesions with oral pamidronate plus conventional intermittent melphalan/prednisalone in 300 patients with newly diagnosed multiple myeloma\(\textsuperscript{45}\) (Table 3).\(\textsuperscript{19,41-50}\) Treatment with pamidronate also had no effect on patient survival or hypercalcemia. However, pamidronate treatment appeared to have a palliative effect on severe pain ($P = .02$) and decreased reduction of body height ($P = .02$) compared to placebo. The overall negative result of the study was attributed to the low absorption of orally administered bisphosphonates in general.

Based on the encouraging results of a randomized phase II trial that showed similar antiresorptive effects compared to pamidronate, a phase III randomized trial was conducted to compare the long-term safety and efficacy of zoledronic acid (4 mg or 8 mg) with pamidronate for 2 years in 1,648 patients with multiple myeloma or breast cancer with osteolytic lesions\(\textsuperscript{46,51}\) (Table 3).\(\textsuperscript{19}\) Zoledronic acid was similar to pamidronate in the reduction of the overall proportion of patients with at least one SRE other than HCM, ($47\%$ vs $51\%$) and reduction of SMR ($1.04$ events per year vs $1.39$ events per year; $P = .084$). Zoledronic acid was also comparable to pamidronate in the reduction of the time to first SRE in the multiple myeloma stratum (380 days vs 286 days, $P = .538$). The most common adverse events included bone pain, nausea, fatigue, pyrexia, and emesis and there was no difference in the renal safety profiles between the 4-mg zoledronic acid and pamidronate treatment groups. Based on these two randomized trials, zoledronic acid is considered to be clearly noninferior to pamidronate in terms of long-term safety and skeletal effects.

**Emerging Therapies in the Treatment of Bone Metastasis**

In early-phase clinical studies, the investigational agent denosumab substantially diminished the levels of bone turnover markers in heavily pretreated patients with multiple myeloma.\(\textsuperscript{19,52}\) In a randomized trial, denosumab resulted in immediate and more sustained dose-dependent decrease in bone turnover markers compared to pamidronate.\(\textsuperscript{19}\) Subsequently, a double-blind, phase III study compared denosumab with zoledronic acid among 1,776 bisphosphonate-naïve patients experiencing bone metastases from solid tumors (excluding breast and prostate cancers) or multiple myeloma\(\textsuperscript{47}\) (Table 3). In the initial report, denosumab was similar to zoledronic acid in terms of the median time to first on-study SRE (20.6 months vs 16.5 months; $P = .06$), time to first-and-subsequent SRE (HR = 0.90; $P = .14$), and OS (HR = 0.95; $P = .43$). Subsequent analysis demonstrated that time to first SRE or HCM was significantly longer with denosumab therapy compared to zoledronic acid (HR = 0.83; $P=.02$) as well as the time to first radiation to bone (HR = 0.78; $P = .03$). Patients that received denosumab also experienced a significant delay in pain worsening compared to those that received zoledronic acid (median 169 days vs 143 days for; HR = 0.85; $P = .02$).\(\textsuperscript{49}\) While these results are encouraging, longer follow-up results are needed to determine if these differences are durable.

A number of promising novel targeted agents with therapeutic potential in multiple myeloma bone disease are being investigated in clinical trials, and are in early stages of clinical testing (Table 3). ACE-011 is a fully human soluble fusion protein that blocks activin A signaling, which is implicated in modulation of bone remodeling. Clinically, Ruckle et al showed that ACE-011 increased biomarkers of bone formation and concomitantly decreased biomarkers of bone resorption in healthy volunteers.\(\textsuperscript{53}\) In addition, ACE-011 treatment resulted in a significant increase in hemoglobin, red blood cell levels, and bone mineral density.\(\textsuperscript{54}\) A randomized, placebo-controlled study in patients with multiple myeloma and evidence of bone disease demonstrated that addition of ACE-011 (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg) to a regimen of melphalan/prednisolone/thalidomide (MPT) resulted in a dose-dependent and significant increase in biomarkers of bone formation, improvement in pain reduction and bone metastases, and significant hematologic activity.\(\textsuperscript{50}\) BHQ880, a fully human anti-DKK1 monoclonal antibody, in combination with zoledronic acid increased bone mineral density by up to 6% in relapsed and/or refractory multiple myeloma.\(\textsuperscript{55}\)

**LUNG CANCER**

Current clinical evidence with clodronate therapy in the treatment of bone metastasis from lung cancer is sparse and shows ambivalence in terms of analgesic effects. In an early small retrospective study in patients with non-small cell lung cancer (NSCLC), Caristi et al showed that clodronate in addition to radiation therapy decreased occurrence of pain worsening and increased complete pain relief compared with radiation therapy alone\(\textsuperscript{56}\) (Table 4).\(\textsuperscript{56-61}\) In contrast, Piga et al, in an assessment of clodronate therapy in 66 patients with
bone metastases from poorly chemoresponsive tumors, such as NSCLC, bladder cancer, gastrointestinal cancers, kidney cancer, and melanoma, showed no significant difference in worsening of pain between control and clodronate therapy. However, analgesic requirement appeared to be significantly higher in the placebo group (P = .042). The primary drawback of both the studies was the sample size and the low number of patients available for follow-up. More encouragingly, pamidronate therapy has demonstrated significant improvement in OS compared to untreated patients (15.4 months vs. 2.1 months; P < .001), albeit in a retrospective analysis of 41 patients with bone metastases from NSCLC.56

In contrast, more robust clinical evidence exists for the role of zoledronic acid in reducing skeletal complications in lung cancer. Rosen et al performed a randomized, placebo-controlled trial in 773 patients with bone metastases secondary to lung carcinoma and other solid tumors (except carcinomas of the breast and prostate), of which 378 patients had NSCLC. They reported that IV zoledronic acid significantly delayed the median time to first SRE (236 days vs. 155 days; P = .009) and decreased the annual incidence of SREs (1.74 per year vs. 2.71 per year; P = .012)59 (Table 4). Patients in the zoledronic acid treatment group also demonstrated a 31% reduction in the risk of developing a skeletal event (HR = 0.693; P = .003). Zoledronic acid was well tolerated over the course of the treatment and the most common adverse events, in all treatment groups, were bone pain and acute phase reactions of nausea, anemia and emesis.

Further, a retrospective analysis of patients with bone metastases from NSCLC demonstrated statistically significant improvement in OS with zoledronic acid in 507 patients with bone metastasis secondary to lung cancer or other solid tumors60 (Table 4). Among patients with an SRE before study entry, zoledronic acid reduced the risk of SREs (P = .009), reduced the mean skeletal morbidity rate (1.96 vs. 2.81 SREs per year; P = .030), and prolonged the median time to first SRE by nearly 4 months (215 days vs. 106 days for placebo; P = .011). In a retrospective exploratory analysis of 382 patients of this trial, Hirsh et al demonstrated significant correlations between baseline NTX levels and clinical outcomes with zoledronic acid.61 In both placebo-treated patients and zoledronic acid–treated patients, high baseline NTX significantly correlated with increased SRE risk. While high baseline NTX levels correlated with more than a twofold increased risk of bone lesion progression (P = .039) and death (P = .001) compared to normal NTX levels in the placebo group, these correlations were not apparent in the zoledronic acid group. Importantly, zoledronic acid significantly decreased the RR of death by 35% in patients with high baseline NTX (P = .024), underscoring the importance of treating bone metastasis in patients with high-risk disease. Recently, Zarogoulidis et al demonstrated that addition of zoledronic acid to docetaxel and carboplatin chemotherapy in 144 patients with stage IV lung cancer and evidence of bone metastases led to significant prolongation of survival compared to those who received chemotherapy alone62 (Table 4). A positive correlation was also observed between the number of treatment cycles with zoledronic acid and patient survival (P < .01) and time to progression (P < .01).

SAFETY OF BONE-TARGETED THERAPY

Oral bisphosphonates are commonly associated with gastrointestinal adverse events such as epigastric pain and esophagitis.63 IV bisphosphonates are often associated with typical infusion-related side effects such as injection site reactions, flu-like syndromes, and sometimes renal issues. The most commonly reported adverse events reported in the pivotal trial comparing zoledronic acid and pamidronate reported by Rosen et al were bone pain, nausea, fatigue, emesis, and fever. Renal complications with intravenous bisphosphonates are of some clinical concern. In the Rosen et al study, renal toxicities occurred at a frequency of about 10% and were not found to be different between zoledronic acid and pamidronate. In particular, change from baseline of serum creatinine of at least 2 times baseline value was 7.7% for patients treated with 4 mg zoledronic acid compared to 6.0% with pamidronate therapy. Due to these renal toxicity concerns, regular monitoring of renal function and dose adjustment according to creatinine clearance is advocated with zoledronic acid use. Recently, it was revealed that long-term bisphosphonate therapy might be associated with a rare incidence of osteonecrosis of the jaw (ONJ), with an estimated frequency of about 1%. Its incidence has been correlated with dental extraction procedures and corticosteroid therapy. The incidence of ONJ was similar between zoledronic acid and the investigational agent denosumab (1.4% vs 2.0%). Although the incidence of adverse events (all grades) and serious adverse events was similar between the two treatment groups, Stopeck et al reported a lower rate of acute phase reactions with denosumab therapy compared to zoledronic acid (10.4% vs 27.3%). Taken together, while there might be some class effect toxicities with bone-targeted therapies that require vigilant monitoring and management, the benefits of bone-targeted therapy far outweigh any toxicities, particularly in light of the debilitating symptoms of skeletal disease that these patients would otherwise experience.

CURRENT TREATMENT GUIDELINES

According to the American Society of Clinical Oncology (ASCO), infusional bisphosphonates pamidr-
Clodronate therapy
Caristi et al56
Patients with metastatic osteolysis from breast cancer and NSCLC who received RT
Clodronate for at least 3 days from the beginning of radiation therapy or no clodronate
↓ pain worsening (33.3% v 41.9%);
↑ pain relief with clodronate at end of RT (40.7% v 20.9%) and 4–6 weeks after therapy (70.3% v 53.7%)

Piga et al57
Patients with poorly responsive tumors such as NSCLC, bladder cancer, gastrointestinal cancers, kidney cancer, melanoma and metastatic carcinoma of unknown origin
Placebo or clodronate (1,600 mg/d; oral; 1 year)
No difference in pain palliation with clodronate;
↓ analgesic requirement (P = .042)

Pamidronate therapy
Spizzo et al58
Patients with bone metastases from NSCLC
Pamidronate treatment (90 mg IV; every 4 weeks) or untreated
↑ median OS (15.4 months v 2.1 months; P < .001).

Zoledronic acid
Rosen et al59
Patients with bone metastases secondary to lung carcinoma and other solid tumors (except carcinomas of the breast and prostate)
Placebo or zoledronic acid (4 mg IV every 3 weeks for 21 months)
↑ time to first SRE (236 days v 155 days; P = .009);
↓ annual incidence of SREs (1.74 v 2.71 per year; P = .012);
31% ↓ in the risk of developing a skeletal event (HR = 0.693; P = .003)

Hirsh et al61,62
Patients with bone metastases secondary to lung carcinoma
Placebo or zoledronic acid (4 mg IV every 3 weeks for 21 months)
↓ risk of death in patients with high baseline NTX (P = .024).

Zarogoulidis et al62
Patients with stage IV lung cancer with evidence of metastasis
Zoledronic acid (4 mg IV every 21 days) or no treatment in combination with docetaxel and carboplatin
↑ survival (P < .01) and ↑ time to progression (P < .01);
No difference in pain palliation

Abbreviations: NSCLC, non-small cell lung cancer; SRE, skeletal-related event; HR, hazard ratio; NTX, N-telopeptide levels; OS, overall survival; RT, radiotherapy; IV, intravenous.

Donate 90 mg (delivered over 2 hours) or zoledronic acid (4 mg over 15 minutes every 3 to 4 weeks) are recommended for management of bone-related metastases in women with breast cancer who show evidence of bone destruction by plain radiography.65 However, the presence or absence of bone pain is not considered a determinant of initiation of bisphosphonate therapy. In patients with bone metastasis from lung cancer, regardless of presence of symptoms, initiation of zoledronic acid and continuation of therapy as long as it is well
tolerated is indicated in patients with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. For palliative purposes, initiation of zoledronic acid is also suggested in patients with compromised performance status. In multiple myeloma, pamidronate and zoledronic acid are the current standard treatments for skeletal complications resulting from osteolytic bone disease. While guidelines recommend monthly treatment for up to 2 years, alternative dosing schedules are currently being evaluated, as are the benefits of treatment beyond 2 years.

CONCLUSIONS

The natural history of bone metastases due to solid tumors or myeloma bone disease shows dismal prognosis. Skeletal complications due to bone metastasis are strong determinants of quality of life and survival in these patients. Based on solid evidence, treatment with bisphosphonates, particularly pamidronate and zoledronic acid, is deeply entrenched in the treatment paradigm of management of bone disease. In contrast to analgesics or radiation therapy, bone-targeted therapy is not only used with palliative intent but also in the prevention of future SREs. While patients with a history of SREs are more prone to developing subsequent SREs, zoledronic acid appeared to be effective in reducing skeletal morbidity regardless of prior SRE history. Looking forward, based on convincing evidence that profound survival benefits are achieved in patients with less advanced bone lesions, it is increasingly being speculated that initiation of bisphosphonate therapy early during the course of the disease might be an optimal management strategy. Several prospective studies are ongoing to evaluate the efficacy of bisphosphonates in delaying or preventing bone metastasis in many cancer types. Outcomes of these studies will provide further insights into the role of bone-targeted therapies in the management of bone metastases.

STATEMENT OF CONFLICT OF INTEREST

A. Lipton discloses the following potential conflicts of interest: Consulting fees: Amgen Inc; Cephalon, Inc; Novartis Pharmaceuticals Corporation; and Thar Pharmaceuticals. Speaker’s bureau: Amgen Inc, Genentech, and Novartis Pharmaceuticals Corporation. Contracted research: Monogram Biosciences, Oncogene Science/Siemens HealthCare Diagnostics, Novartis Pharmaceuticals Corporation. Expert testimony: Novartis Pharmaceutical Corporation.

Acknowledgment

The author wishes to thank Nathan Kelly, PhD, and Trudy Grenon Stoddert, ELS, for their assistance in preparing the manuscript for publication.

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