Bisphosphonates in oncology: evidence for the prevention of skeletal events in patients with bone metastases

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Abstract: Bone metastases frequently occur in patients with advanced solid tumors, particularly breast and prostate cancers, and nearly all patients with multiple myeloma have some degree of skeletal involvement. The strides made in treating these primary tumors have extended median survival times and thereby increased patient risk for skeletal-related events (SREs), including pathologic fractures, spinal cord compression, need for palliative radiation therapy or surgery to bone, and hypercalcemia. Bisphosphonates, inhibitors of osteoclastic bone resorption that were first established as treatment of osteoporosis, have been shown to prevent and/or delay SREs related to malignancy. The results of a large, randomized phase 3 study comparing zoledronic acid and pamidronate in breast cancer or multiple myeloma patients with osteolytic lesions showed that the incidence of SREs, time to first SRE, and risk of developing a SRE were similar between treatment groups. However, in patients with solid tumors (excluding breast or prostate cancer) metastatic to the bone, only zoledronic acid has demonstrated clinical efficacy. Although bone turnover marker levels, such as N-telopeptide of type I collagen, have been shown to correlate with clinical response, additional studies are needed to validate their ability to predict response to bisphosphonate therapy.

Keywords: bisphosphonates, prevention, skeletal-related events, bone metastases, cancer

Introduction
Osteoporosis, a skeletal condition common in postmenopausal women and aging men, is characterized by low bone mass, destruction of bone microarchitecture, and increased bone turnover resulting in decreased bone strength and consequent susceptibility to fractures.1,2 Osteoporotic fractures, such as fractures of the hip, vertebral body, and distal forearm, may lead to decreased quality of life (QOL), disability, and possibly death. In the last decade, bisphosphonates, compounds that inhibit osteoclastic bone resorption, have been the most significant contribution to the advancement in osteoporosis treatment; clinical trials have demonstrated a reduction in vertebral fractures of 40% to 50% and nonvertebral fractures (including hip fractures) of 20% to 40%.1,3 Bisphosphonates approved by the United States Food and Drug Administration (FDA) for the prevention and/or treatment of osteoporosis include alendronate, alendronate plus vitamin D, ibandronate, risedronate, risedronate with calcium, and zoledronic acid.4–10 Because their bioavailability is quite low, oral agents usually require daily or weekly administration (with the exception of ibandronate, which may be administered monthly) that can contribute to low patient compliance rates.6,9 Intravenous (IV) bisphosphonates may be administered less frequently (eg, on a monthly, quarterly, or yearly basis).6,10–12 In general, patient compliance rates with prescribed IV bisphosphonate regimens are higher than with oral bisphosphonates.
In addition to osteoporosis, bisphosphonates have been used to prevent and/or treat cancer-related bone complications.\textsuperscript{3,13} Patients who develop bone metastases are at increased risk for developing skeletal-related events (SREs), such as intractable bone pain requiring opioid analgesics or palliative radiation therapy, pathologic fractures, spinal cord compression, a need for surgery, and hypercalcemia of malignancy (HCM).\textsuperscript{14} SREs are a consequence of excessive bone metabolism, primarily bone resorption, which characterizes malignant bone lesions.\textsuperscript{3} Local bone pain requiring radiation therapy and pathologic fractures are the most commonly reported SREs.\textsuperscript{3}

As a result of advancements in the primary treatment of several solid tumors and hematologic malignancies, patients are surviving longer, placing them at an increased risk for developing bone metastasis and SREs that may complicate their clinical course, adversely affect QOL, and increase medical costs.\textsuperscript{14–16} Bone metastases are particularly prevalent in patients with advanced metastatic breast or prostate cancers, affecting approximately 70% of patients.\textsuperscript{3} Although observed less frequently, bone metastases also occur in patients with lung, kidney, and thyroid tumors.\textsuperscript{17} Nearly all patients with advanced multiple myeloma (MM) develop bone involvement during the course of their disease since this malignancy colonizes in the bone marrow.\textsuperscript{14,18}

### Metastatic bone disease

Under normal circumstances, bone homeostasis is achieved through balanced resorption of old bone by osteoclasts and formation of new bone by osteoblasts.\textsuperscript{19} Metastatic bone disease alters the normal bone remodeling process by causing osteolytic bone destruction and abnormal osteoblastic bone formation, often with one process more dominant than the other, resulting in an imbalance in normal bone homeostasis.\textsuperscript{18–20} Although historically bone metastases from breast cancer or MM have been characterized as osteolytic lesions and prostate cancer bone metastases have been primarily osteoblastic in nature, recent evidence suggest that both bone processes are present in many patients.\textsuperscript{18,20} Without bisphosphonate treatment, it is estimated that patients with bone metastases from advanced cancer will experience, on average, 2 to 4 SREs per year.\textsuperscript{15} Thus, bone complications of cancer are a considerable clinical concern, and preventing or delaying the occurrence of such events is an important treatment objective. Although palliation has traditionally been the primary goal of therapy, the introduction of bisphosphonates has afforded oncologists with an effective therapeutic option for preventing and/or treating SREs associated with bone metastases.

### Mechanism of action of bisphosphonates

Because of their ability to diminish bone resorption and subsequently normalize calcium levels, prevent development of new osteolytic lesions, and reduce the risk of fractures, bisphosphonates are the treatment of choice for skeletal complications of malignancy.\textsuperscript{21} Bisphosphonates are pyrophosphate analogs that preferentially bind to bone at sites of active metabolism, are released from the bone matrix during bone resorption, and inhibit osteoclast activity and survival.\textsuperscript{3,21} Variable side chains determine the potency and side effect profile of each agent.\textsuperscript{21} These compounds can be grouped into two classes according to their chemical structure and molecular mechanism of action (Figure 1).\textsuperscript{22} The newer nitrogen (N)-containing, second- or third-generation compounds, including alendronate, ibandronate, pamidronate, risedronate, and zoledronic acid, inhibit the enzyme farnesyl diphosphate synthase in the cholesterol mevalonate pathway and thereby suppress osteoclast-mediated bone resorption, whereas the non–N-containing, first-generation bisphosphonates, such as clodronate, etidronate, and tiludronate, induce osteoclast apoptosis via metabolism into cytotoxic analogues of adenosine 5'-triphosphate.\textsuperscript{21,23,24} The N-containing agents are more potent than the non–N-containing bisphosphonates, inhibiting bone resorption at micromolar concentrations.\textsuperscript{3} Only IV zoledronic acid and IV pamidronate are approved by the FDA for cancer-related indications.\textsuperscript{25,26} In Europe, oral clodronate, IV pamidronate, and oral and IV ibandronate have received regulatory approval for patients with bone metastases secondary to breast cancer.\textsuperscript{3,27} Only zoledronic acid has received US and European approval for the treatment of bone metastases independent of the primary tumor type.\textsuperscript{25,28}

### Evaluating efficacy of bisphosphonates

Developing composite end points of similar clinical significance may be appropriate when the clinical benefit of a drug is multifaceted as is the case with bisphosphonates.\textsuperscript{29} Using a SRE as a quantifiable clinical end point was first applied to studies assessing pamidronate for prevention of SREs. This end point included one or more of the following: pathologic fracture, radiation therapy for local pain, surgery to stabilize near-fractures, or spinal cord compression. Subsequently, SREs were used as the primary end points for most of the trials assessing a bisphosphonate for this indication. However, the definition or names for SREs have differed slightly between studies (see Tables 1–4), sometimes being
referred to as skeletal complications or bone events. Furthermore, HCM has been excluded from the definition of a SRE in some trials because bisphosphonates have been shown to be effective for the treatment of HCM before studies investigating bisphosphonates as preventive therapy for SREs were developed.

Several clinical studies designed to evaluate bisphosphonates to prevent skeletal complications have demonstrated clinical benefit. This article reviews the results of clinical studies assessing bisphosphonates as prevention and/or treatment for cancer-related bone complications in a variety of tumor types.

**Clinical studies**

**Breast cancer**

Clinical trial results show that bisphosphonates reduce the occurrence of skeletal complications in patients with breast cancer and bone metastases (Table 1). Based on the results of two randomized, placebo-controlled clinical studies in patients with osteolytic bone metastases from breast cancer being treated with either chemotherapy or hormonal therapy, IV pamidronate was approved by the FDA for preventing SREs. Pamidronate (90 mg administered IV over 2–4 hours q 3–4 weeks) significantly prolonged the time to the first SRE and reduced the overall incidence of SREs for up to 2 years (see Table 1). In another placebo-controlled trial of breast cancer patients with at least one osteolytic lesion, zoledronic acid significantly lowered the risk of SREs by 39% (p = 0.027), reduced the proportion of patients experiencing a SRE at 1 year by 20% (29.8% vs 49.6%, p = 0.003), and significantly prolonged the time to first SRE excluding HCM (median not reached vs 364 days, p = 0.007). Only one study has directly compared zoledronic acid with pamidronate (see Table 1). This large, randomized phase 3 study was designed to demonstrate the equivalence of zoledronic acid and pamidronate in reducing the incidence of SREs in patients with breast cancer or MM. Among the breast carcinoma stratum, the overall incidence of SREs other than HCM was comparable between the two study groups. The median time to first SRE was also similar; however, in patients receiving hormonal therapy for breast cancer, zoledronic acid 4 mg IV significantly delayed the time to first SRE (415 vs 370 days; p = 0.047). Oral and IV ibandronate have also been evaluated in breast cancer patients with metastatic bone disease; compared with placebo, both formulations of ibandronate (6 mg IV and 50 mg oral) have significantly reduced the
Table 1  Efficacy of bisphosphonates in patients with bone metastases secondary to breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Drug</th>
<th>Primary endpoint</th>
<th>Efficacy results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen et al 2001</td>
<td>MC, R, DB</td>
<td>ZOL 4 mg or 8 mg IV every 3–4 wk × 24 mo versus PAM 90 mg IV every 3–4 wk × 24 mo</td>
<td>Proportion with ≥1 SRE at 13 mo and 25 mo</td>
<td>13-mo analysis (includes all patients except where noted):</td>
<td>Stage IV breast carcinoma and multiple myeloma patients</td>
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<td>(N = 1643)</td>
<td></td>
<td></td>
<td></td>
<td>• Proportion of patients with a SRE was similar between treatment groups</td>
<td>Noninferiority trial</td>
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<td>• Proportion requiring radiation therapy to bone was significantly lower in ZOL 4 mg versus PAM overall (15% vs 20%, p = 0.031) and in MBC (16% vs 25%, p = 0.022)</td>
<td>Patients stratified prospectively by tumor type</td>
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<td>25-mo analysis (includes all patients except where noted):</td>
<td>Protocol amendment reduced dose of ZOL from 8 mg to 4 mg due to renal toxicity</td>
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<td>• Proportion requiring radiation therapy to bone was significantly lower in ZOL 4 mg versus PAM (19% vs 24%, p = 0.037)</td>
<td>Included patients with osteolytic and/or osteoblastic bone lesions</td>
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<td></td>
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<td>• ZOL 4 mg reduced risk of skeletal complications by 16% compared to PAM (RR = 0.841 (95% CI, 0.719–0.983, p = 0.030)</td>
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<td>• Risk of developing SRE comparable between ZOL 4 mg and PAM in MBC (RR, 0.955; p = 0.749)</td>
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<tr>
<td>Rosen et al 2003</td>
<td>MC, R, DB</td>
<td>ZOL 4 mg or 8 mg IV every 3–4 wk × 12 mo versus PAM 90 mg IV every 3–4 wk × 12 mo</td>
<td>Proportion with ≥1 SRE at 13 mo</td>
<td>• Among all patients with MBC, proportion with ≥1 SRE was comparable (43% ZOL 4 mg vs 45% PAM)</td>
<td>Analysis of MBC stratum of phase 3 trial (Rosen et al 2001, Rosen et al 2003)</td>
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<td>(N = 1648)</td>
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<td>• In patients with only osteolytic lesions, ZOL 4 mg reduced proportion with ≥1 SRE (48% vs 58%, p = 0.058) and significantly prolonged time to first SRE (p = 0.013)</td>
<td>Patients stratified based on ≥1 osteolytic lesion versus nonosteolytic lesion at study entry</td>
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<td>• 30% experienced ≥1 SRE (22% only experienced 1 SRE)</td>
<td>~60% experienced an SRE before study entry</td>
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<td>• Median time to first SRE was not reached</td>
<td>Japanese patients with MBC</td>
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<td>• Mean SMR (up to wk 52), 0.9 ± 3.8</td>
<td>Median time from diagnosis of bone metastases to study treatment was short (3.9 mo)</td>
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<td></td>
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<td>• Mean SRE (up to wk 52), 0.9 ± 3.8</td>
<td>Patients with ≥1 osteolytic lesion</td>
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<td>• Pathologic fracture and bone irradiation were the most common SREs</td>
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<td>• Diagnosed with bone metastases ≤6 wk before first visit and no prior bisphosphonate therapy</td>
<td>Included patients with osteolytic and/or osteoblastic bone lesions</td>
</tr>
<tr>
<td>Kohno et al 2005</td>
<td>MC, R, DB, PC</td>
<td>ZOL 4 mg IV every 4 wk × 1 yr versus placebo</td>
<td>SRE rate ratio</td>
<td>• SRE rate (events/yr) 0.63 ZOL versus 1.10 placebo (SRE rate ratio 0.57, p = 0.016) when not adjusted for prior fracture</td>
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<td>(N = 228)</td>
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<td>• ZOL reduced proportion with ≥1 SRE by 20% (p = 0.003) and prolonged time to first SRE (p = 0.007)</td>
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<tr>
<td>Carteni et al 2006</td>
<td>MC, OL</td>
<td>ZOL 4 mg IV every 3–4 wk × 12 infusions</td>
<td>Proportion with ≥1 SRE; time to first SRE; SMR</td>
<td>• 30% experienced ≥1 SRE (22% only experienced 1 SRE)</td>
<td>Diagnosed with bone metastases ≤6 wk before first visit and no prior bisphosphonate therapy</td>
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<tr>
<td>(N = 312)</td>
<td></td>
<td></td>
<td></td>
<td>• Median time to first SRE was not reached</td>
<td>Included patients with osteolytic and/or osteoblastic bone lesions</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment</td>
<td>Description</td>
<td>Endpoint 1</td>
<td>Endpoint 2</td>
<td>Comments</td>
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</table>
| Hortobagyi et al 1996<sup>a</sup> | PAM 90 mg IV q 4 wk × 12 cycles versus placebo  | Proportion with any skeletal complication<sup>1</sup> at 12 mo and 24 mo | 12-mo analysis: | • Proportion with any skeletal complication significantly less with PAM (p = 0.005)  
• PAM did not reduce incidence of pathologic vertebral fractures (p = 0.49) | Patients receiving concurrent cytotoxic chemotherapy  
• Effects of PAM on skeletal complications more apparent with each successive treatment  
• Primarily osteolytic lesions  
• Time from diagnosis of bone metastases to study entry  
• Treatment effect did not diminish with extended duration of therapy  
• Patients receiving concurrent hormonal therapy  
• Primarily osteolytic lesions |
| Hortobagyi et al 1998<sup>b</sup> (N = 382) | | | | | Long-term follow-up of 2 randomized, controlled trials (Hortobagyi et al 1998<sup>b</sup>; Theriault et al 1999<sup>c</sup>)  
Only treatment at study entry varied between the 2 groups (hormonal vs cytotoxic therapy)  
• 58% of IBA (6 mg) and 45% of placebo groups completed 60 wk of study  
• IBA 6 mg maintained bone pain below baseline throughout the study  
No evidence of renal toxicity in IBA-treated patients  
• Pooled results of 2 phase 3 clinical trials  
• Only results of IBA 50 mg arm reported because this is the dose used in clinical practice  
• 42% of IBA (50 mg) and 38% of placebo groups completed 96 wk of study  
• 26% were not compliant with oral therapy  
• Toxicities similar between CLO and placebo arms; withdrawal due to difficulty swallowing capsules did occur |
| Theriault et al 1999<sup>d</sup> (N = 372) | PAM 90 mg IV every 4 wk × 24 cycles versus placebo  | SMR<sup>4</sup> (end of phase I); OS rate (end of phase II) | 24-mo analysis: | • Only 82/382 patients (21%) had data available at 24 mo  
• Proportion with any skeletal complication significantly less with PAM (p = 0.001)  
• PAM significantly decreased overall SMR at 12, 18, and 24 mo (p = 0.028, p = 0.023, p = 0.008)  
• Proportion with any SRE<sup>5</sup> significantly lower in PAM at 24 mo (72 vs 83, p = 0.049)  
• OS rate did not significantly vary (p = 0.685) | Primarily osteolytic lesions |
| Lipton et al 2000<sup>e</sup> (N = 751) | PAM 90 mg IV every 3–4 wk × 24 cycles versus placebo  | SMR<sup>4</sup> | 24-mo analysis: | • PAM significantly decreased overall SMR at 12, 18, and 24 mo (p = 0.028, p = 0.023, p = 0.008)  
• Proportion with any SRE<sup>5</sup> significantly lower in PAM at 24 mo (72 vs 83, p = 0.049)  
• OS rate did not significantly vary (p = 0.685) | Long-term follow-up of 2 randomized, controlled trials (Hortobagyi et al 1998<sup>b</sup>; Theriault et al 1999<sup>c</sup>)  
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| Body et al 2003<sup>f</sup> (N = 466) | IBA 2 mg or 6 mg IV every 3–4 wk × 60–96 wk versus placebo  | SMPR<sup>6</sup> | | • IBA 6 mg significantly reduced SMPR for all new bone events<sup>6</sup> compared with placebo (p = 0.004)  
• IBA 6 mg significantly reduced new bone events<sup>6</sup> patient (p = 0.032) and increased time to first bone event (p = 0.018) | No evidence of renal toxicity in IBA-treated patients  
• Pooled results of 2 phase 3 clinical trials  
• Only results of IBA 50 mg arm reported because this is the dose used in clinical practice  
• 42% of IBA (50 mg) and 38% of placebo groups completed 96 wk of study  
• 26% were not compliant with oral therapy  
• Toxicities similar between CLO and placebo arms; withdrawal due to difficulty swallowing capsules did occur |
| Body et al 2004<sup>g</sup> (N = 564) | IBA 20 mg or 50 mg PO daily up to 96 wk versus placebo  | SMPR<sup>6</sup> | | • IBA 50 mg significantly reduced mean SMPR for all new bone events<sup>6</sup> (p = 0.004), primarily a result of a significant reduction in radiation therapy and surgery to bone | |
| Paterson et al 1993<sup>h</sup> (N = 173) | CLO 1,600 mg PO daily × 3 yr versus placebo  | Number of hypercalcemic episodes, vertebral and nonvertebral fractures, patients requiring radiation therapy to bone  | | • Significantly fewer hypercalcemic events occurred with CLO (52 vs 28; p < 0.01))  
• CLO significantly reduced cumulative incidence of vertebral fractures (p = 0.025) and overall incidence of morbid skeletal events per 100 patient-yr (218.6 vs 304.8, p < 0.001)  
• Trends favoring CLO for nonvertebral fractures and radiation therapy requirements observed | |
Table 1 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Drug</th>
<th>Primary endpoint</th>
<th>Efficacy results</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Kristensen et al 1999 @</td>
<td>SC, R, OL</td>
<td>CLO 1600 mg PO daily x maximum of 2 yr versus placebo</td>
<td>Skeletal events b</td>
<td>• All skeletal events occurred less frequently in CLO arm (14 vs 21)</td>
<td>• Most skeletal events in control arm occurred within 3–5 mo of randomization, whereas events in CLO arm occurred within 15–20 mo</td>
</tr>
</tbody>
</table>

aDefined as pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone, excluding HCM.
bDefined as total number of SREs divided by total number of years on study.
cDefined as pathologic fracture, radiation therapy to bone, surgery to bone, spinal cord compression, and HCM.
dNumber of SREs per patient per year.
eDefined as the ratio of the number of skeletal complications experienced by patient divided by the time on trial; skeletal complication defined as pathologic fractures, irradiation of or surgery on bone, spinal cord compression, or HCM.
fDefined as number of 12-wk periods with new skeletal complications divided by total observation time; skeletal complications included vertebral or pathologic nonvertebral fractures, radiation therapy to bone, or surgery to bone.
gDefined as hypercalcemia, courses of radiotherapy for bone pain, and vertebral and nonvertebral fracture.
hDefined as hypercalcemia with serum ionized calcium level > 1.40 mmol L−1, a new fracture, or radiotherapy to a bone metastasis.

Abbreviations: Chemo, chemotherapy; CI, confidence interval; CLO, clodronate; DB, double blind; HCM, hypercalcemia of malignancy; IBA, ibandronate; IV, intravenous; MC, multicenter; MBC, metastatic breast cancer; OL, open-label; OS, overall survival; PAM, pamidronate; PC, placebo-controlled; PO, oral; R, randomized; RR, risk ratio; SC, single center; SRE, skeletal-related event; SMR, skeletal morbidity rate; SMPR, skeletal morbidity period rate; ZOL, zoledronic acid.

Prostate cancer

Although prostate cancer is most commonly associated with osteoblastic lesions, increased osteoclastic activity also disrupts normal bone metabolism when prostate cancer invades the skeleton. This inhibition of bone metabolism can be beneficial for osteoblastic metastases. Several bisphosphonates have been evaluated in patients with hormone-refractory prostate cancer (HRPC) who were treated with SREs (Table 2). In a randomized study, patients with disease recurrence at least one SRE (38% vs 49%, 95% CI, −20.2% to −1.3%, p = 0.0026) and prolonged the time to the first SRE by bisphosphonates. The NCCN guidelines suggest that bisphosphonates may be beneficial for osteoblastic metastases from breast cancer. The American Society of Clinical Oncology (ASCO) recommends either IV zoledronic acid or IV pamidronate for patients with bone metastases secondary to breast cancer. The Cochrane Breast Cancer Review Group has reported the results of their meta-analysis of 21 randomized trials evaluating bisphosphonates in 9 studies. However, the ASCO panel concluded that there is insufficient evidence to recommend one bisphosphonate over the other. Evidence to recommend one bisphosphonate over the other is not commercially available in the US, and the FDA has not approved zoledronic acid for osteosclerotic metastases from breast cancer. The NCCN guidelines suggest that zoledronic acid may be superior to pamidronate therapy for treating osteosclerotic metastases from breast cancer. Neither zoledronic acid nor pamidronate were recommended for patients with bone metastases from hormone-refractory prostate cancer. However, the ASCO panel concluded that there is insufficient evidence to recommend one bisphosphonate over the other. Evidence to recommend one bisphosphonate over the other is not commercially available in the US, and the FDA has not approved zoledronic acid for osteosclerotic metastases from breast cancer. The NCCN guidelines suggest that zoledronic acid may be superior to pamidronate therapy for treating osteosclerotic metastases from breast cancer.
<table>
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</tr>
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<tbody>
<tr>
<td>Saad et al 2002</td>
<td>MC, R, DB, PC</td>
<td>ZOL 4 mg or 8 mg IV</td>
<td>Proportion</td>
<td>15-mo analysis:</td>
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<tr>
<td>(N = 643)</td>
<td></td>
<td>every 3 wk × 24 mo</td>
<td>with ≥ 1 SREa</td>
<td>• Urinary markers of bone resorption significantly decreased in patients receiving ZOL (p = 0.001)</td>
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<td>• ZOL significantly reduced SRE (44.2% vs 33.2%, p = 0.021) and SMRb (p = 0.006), and increased median time to first SRE (p = 0.011)</td>
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<td>24-mo analysis:</td>
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<td>• ZOL significantly reduced SREs (38% vs 49%, p = 0.028) and increased median time to first SRE (p = 0.009)</td>
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<td>• ZOL 4 mg produced 36% reduction in ongoing risk of SREs (p = 0.002)</td>
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<td>Protocol amendment reduced dose of ZOL from 8 mg to 4 mg due to renal toxicity</td>
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<td></td>
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<td>Only 122 patients completed total 24 mo of study</td>
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<tr>
<td>Small et al 2003</td>
<td>MC, R, DB, PC</td>
<td>PAM 90 mg IV every</td>
<td>Reduction in bone</td>
<td>• No significant change from baseline pain scores</td>
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<tr>
<td>(N = 378)</td>
<td></td>
<td>3 wk × 27 wk</td>
<td>pain or analgesic use</td>
<td>36% patients able to decrease or stabilize analgesic use</td>
</tr>
<tr>
<td>Dearnaley et al 2003</td>
<td>MC, R, DB, PC</td>
<td>CLO 2080 mg PO daily ×</td>
<td>Symptomatic BPFSc</td>
<td>• Patients receiving CLO had longer symptomatic BPFS times (HR 0.79, 95% CI, 0.61–1.02, p = 0.066)</td>
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<td>(N = 311)</td>
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<td>maximum 3 yr</td>
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<td>Patients were starting or responding to hormonal therapy</td>
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<td>PSA levels were lower among patients receiving CLO (p = 0.053)</td>
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</table>

**Table 2 Efficacy of bisphosphonates in randomized, placebo-controlled trials of prostate cancer patients with bone metastases**

<table>
<thead>
<tr>
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<td>MC, R, DB, PC</td>
<td>ZOL 4 mg or 8 mg IV every 3 wk × 24 mo</td>
<td>Proportion with ≥ 1 SREa</td>
<td>15-mo analysis:</td>
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<td>• Urinary markers of bone resorption significantly decreased in patients receiving ZOL (p = 0.001)</td>
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<td>• ZOL significantly reduced SRE (44.2% vs 33.2%, p = 0.021) and SMRb (p = 0.006), and increased median time to first SRE (p = 0.011)</td>
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<td>24-mo analysis:</td>
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<td>• ZOL significantly reduced SREs (38% vs 49%, p = 0.028) and increased median time to first SRE (p = 0.009)</td>
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<td>• ZOL 4 mg produced 36% reduction in ongoing risk of SREs (p = 0.002)</td>
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<td>Protocol amendment reduced dose of ZOL from 8 mg to 4 mg due to renal toxicity</td>
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<td>Only 122 patients completed total 24 mo of study</td>
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<tr>
<td>Small et al 2003</td>
<td>MC, R, DB, PC</td>
<td>PAM 90 mg IV every 3 wk × 27 wk</td>
<td>Reduction in bone pain or analgesic use</td>
<td>• No significant change from baseline pain scores</td>
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<td>36% patients able to decrease or stabilize analgesic use</td>
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<tr>
<td>Dearnaley et al 2003</td>
<td>MC, R, DB, PC</td>
<td>CLO 2080 mg PO daily × maximum 3 yr</td>
<td>Symptomatic BPFSc</td>
<td>• Patients receiving CLO had longer symptomatic BPFS times (HR 0.79, 95% CI, 0.61–1.02, p = 0.066)</td>
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<td>Patients were starting or responding to hormonal therapy</td>
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<td>PSA levels were lower among patients receiving CLO (p = 0.053)</td>
</tr>
</tbody>
</table>

*Defined as pathologic bone fractures (vertebral or nonvertebral), spinal cord compression, surgery to bone, radiation therapy to bone (including the use of radioisotopes), or a change of antineoplastic therapy to treat bone pain.
*Number of SREs divided by the time at risk in years.
*Defined as the time from randomization to the development of symptomatic bone metastases (i.e., the need to initiate further treatment) or to death from prostate cancer.

**Abbreviations:** BPFS, bone progression-free survival; CI, confidence interval; CLO, clodronate; DB, double blind; HR, hazard ratio; IV, intravenous; MC, multicenter; PAM, pamidronate; PC, placebo-controlled; PO, oral; PSA, prostate specific antigen; R, randomized; SMR, skeletal morbidity rate; SRE, skeletal-related event; ZOL, zoledronic acid.
### Table 3 Efficacy of bisphosphonates in randomized, placebo-controlled trials of patients with bone metastases secondary to lung cancer or other solid tumors

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Drug</th>
<th>Primary endpoint</th>
<th>Efficacy results</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Rosen et al 2003<sup>47</sup> | MC, R, DB, PC | ZOL 4 mg or 8 mg IV every 3 wk × 21 mo | Proportion with ≥ 1 SRE<sup>a</sup> | 9-mo analysis:  
• ZOL 8/4 mg (p = 0.023), but not ZOL 4 mg (p = 0.127), reduced proportion with ≥ 1 SRE  
• When HCM was included, both ZOL groups significantly reduced SRE  
• ZOL 4 mg significantly extended time to first SRE (2.30 vs 1.63 d, p = 0.023) | • Various solid tumors (approximately 50% NSCLC, 10% RCC, 10% SCLC)  
• Protocol amendment reduced dose of ZOL from 8 mg to 4 mg due to renal toxicity  
• Long-term (21 mo) follow-up confirms results demonstrated at 9 mo |
| Rosen et al 2004<sup>48</sup> (N = 773) | | | | | |
| Heras et al 2007<sup>49</sup> (N = 73) | R, PC | IBA 6 mg IV every 4 wk × 9 mo | Proportion with SRE<sup>b</sup> | • IBA significantly reduced proportion with SREs (39% vs 78%, p = 0.019)  
• Delayed time to first SRE by 6 mo (p = 0.009) | • Patients with metastatic bone disease from CRC |
| Piga et al 1998<sup>50</sup> (N = 50) | R, DB, PC | CLO 1600 mg PO daily × 1 yr | Symptom control, prevention of skeletal complications, and evolution of bone metastases | • CLO did not significantly lower mean pain scores  
• Patients receiving CLO had significantly lower analgesic requirement (p = 0.042) | • Various poorly responsive solid tumors  
• Short survival of most patients did not allow for adequate follow-up of bone lesions |

<sup>a</sup>Defined as pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone, excluding HCM.

<sup>b</sup>Defined as pathologic fracture, spinal cord compression, radiation therapy to bone, change in antineoplastic therapy, or surgery to bone.

**Abbreviations:** CLO, clodronate; CRC, colorectal cancer; DB, double-blind; HCM, hypercalcemia of malignancy; IBA, ibandronate; IV, intravenous; MC, multicenter; NSCLC, non–small cell lung cancer; PC, placebo-controlled; PO, oral; R, randomized; RCC, renal cell carcinoma; SCLC, small cell lung cancer; SRE, skeletal-related event; ZOL, zoledronic acid.
Lung cancer and other solid tumors

Only zoledronic acid 4 mg has demonstrated significant long-term clinical benefits in patients with bone metastases from a broad range of solid tumors (Table 3). In a randomized, placebo-controlled, phase 3 study assessing patients with lung cancer or other solid tumors (excluding breast or prostate cancer), zoledronic acid 4 mg significantly reduced the proportion of patients developing at least one SRE, including HCM at 21 months (39% vs 48%, p = 0.039) and delayed the onset of skeletal complications (236 vs 155 d, p = 0.009). Moreover, when HCM was included, zoledronic acid 4 mg reduced the risk of developing a SRE, including HCM, by 31% (hazard ratio, 0.693; p = 0.003) compared with placebo. Non–small cell lung cancer, renal cell carcinoma, and small cell lung cancer were the most common diagnoses of enrolled patients. Oral clodronate (1600 mg/day for 1 year) was also evaluated in patients with bone metastases from solid tumors poorly responsive to chemotherapy; clodronate did not significantly reduce mean pain scores compared with placebo but significantly reduced use of analgesics (p = 0.042). Ibandronate 6 mg IV, administered every 4 weeks for 9 months to patients with metastatic bone disease from colorectal cancer, significantly reduced the proportion of patients who experienced SREs (39% vs 78%, p = 0.019) and delayed time to the first SRE by at least 6 months (>279 vs 93 days, p = 0.009) compared with placebo. Ibandronate has not been evaluated in other solid tumors. For bone metastases related to solid tumors other than breast or prostate cancer, zoledronic acid is the only bisphosphonate that has received worldwide regulatory approval. Consensus guidelines for the use of bisphosphonates for patients with lung cancer or other solid tumors (except breast and prostate cancer) are not available.

Multiple myeloma

The long-term efficacy and safety of bisphosphonate therapy for prevention of SREs in patients with advanced MM and osteolytic lesions is well established (Table 4). In a randomized, placebo-controlled trial, pamidronate (90 mg IV administered over 4 hours q 4 weeks) significantly delayed the onset (p = 0.016) and reduced the incidence of skeletal complications (p = 0.016) for up to 21 months. Consequently, a large, international, randomized, phase 3 trial was designed to demonstrate equivalence (defined as difference in SRE rate of less than 8%) between either 4 or 8 mg zoledronic acid and standard-dose pamidronate (90 mg). Because of renal safety concerns, the protocol was amended to reduce zoledronic acid from 8 mg to 4 mg. After 25 months of follow-up, the percentage of MM patients who developed a SRE excluding HCM (47%, 4 mg zoledronic acid vs 51%, pamidronate), the median time to first SRE including HCM (380 vs 286 days, p = 0.538), and the risk of developing a skeletal complication (RR, 0.932; p = 0.593) were similar between the treatment groups. Most of these studies assessed zoledronic acid administered every 3 to 4 weeks; however, because of its long half-life and evidence supporting the use of longer dosing intervals for other indications, less frequent dosing (every 12 wk) is being evaluated. Furthermore, oral clodronate (1600 mg daily) has established its ability to significantly reduce the incidence of nonvertebral and vertebral fractures compared with placebo in MM patients. Long-term follow-up indicates that clodronate treatment may also prolong survival time in patients without overt vertebral fractures at diagnosis. Ibandronate has not been shown to reduce skeletal complications in this patient population.

ASCO recently released an update to their clinical practice guidelines for the role of bisphosphonates in MM. For MM patients who have radiographic evidence of osteolytic bone destruction or spinal compression, ASCO recommends treatment with either pamidronate 90 mg IV delivered over
<table>
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<tr>
<th>Study</th>
<th>Study design</th>
<th>Drug</th>
<th>Primary endpoint</th>
<th>Efficacy results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen et al 2001&lt;sup&gt;30&lt;/sup&gt;</td>
<td>MC, R, DB</td>
<td>ZOL 4 mg or 8 mg IV every</td>
<td>Proportion with $\geq 1$ SRE$^a$ at 13 mo and 25 mo</td>
<td>13-mo analysis (includes all patients except where noted):</td>
<td>• Durie-Salmon Stage III MM and stage IV breast cancer</td>
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<tr>
<td>Rosen et al 2003&lt;sup&gt;31&lt;/sup&gt;</td>
<td></td>
<td>3–4 wk × 24 mo</td>
<td></td>
<td>• Similar proportion of patients with $\geq 1$ SRE$^a$ among treatment groups (ZOL 4 mg, 47%; ZOL 8/4 mg, 49%; PAM, 49%)</td>
<td>• Noninferiority trial</td>
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<tr>
<td>(N = 1643)</td>
<td></td>
<td>versus</td>
<td></td>
<td>• Proportion requiring radiation therapy to bone was significantly lower in ZOL 4 mg overall (15% vs 20%, p = 0.031)</td>
<td>• Protocol amendment reduced dose of ZOL from 8 mg to 4 mg due to renal toxicity</td>
</tr>
<tr>
<td>Berenson et al 1998&lt;sup&gt;32&lt;/sup&gt;</td>
<td>MC, R, DB, PC</td>
<td>PAM 90 mg IV every 4 wk × 21</td>
<td>Time to first SRE$^a$</td>
<td>9-mo analysis:</td>
<td>• Durie-Salmon Stage III MM</td>
</tr>
<tr>
<td>(N = 377)</td>
<td></td>
<td>cycles</td>
<td></td>
<td>• PAM significantly increased time to first SRE (p = 0.001)</td>
<td>• Patients stratified into 2 stratum based on line of chemotherapy</td>
</tr>
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<td>Berenson et al 1996&lt;sup&gt;31&lt;/sup&gt;</td>
<td></td>
<td>versus</td>
<td></td>
<td>• Time to first pathologic fracture (p = 0.006) and first radiation treatment to bone (p = 0.05) were significantly longer with PAM</td>
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<tr>
<td>Menssen et al 2002&lt;sup&gt;33&lt;/sup&gt;</td>
<td>MC, R, DB, PC</td>
<td>IBA 2 mg IV monthly × 12–24 mo</td>
<td>Number of 3-mo periods with new bone complication$^b$</td>
<td>21-mo analysis:</td>
<td>• Durie-Salmon Stage II or III MM</td>
</tr>
<tr>
<td>(N = 214)</td>
<td></td>
<td>versus</td>
<td></td>
<td>• Time to first SRE significantly longer with PAM (p = 0.016)</td>
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<td></td>
<td></td>
<td>placebo</td>
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<td>• Proportion of patients with SREs remained lower with PAM at each time point up to 21 mo (p = 0.016)</td>
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<td></td>
<td></td>
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<td>• Number of 3-mo periods with new bone complications, time to first SRE, and SRE/patient-yr were similar between the 2 groups</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• OS time was not statistically different between the 2 groups</td>
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</table>

<sup>1</sup> Drug Design, Development and Therapy downloaded from https://www.dovepress.com/ by 54.70.40.11 on 01-May-2019
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Powered by TCPDF (www.tcpdf.org)

<sup>a</sup> SRE: skeletal-related event

<sup>b</sup> New bone complication
McCloskey et al 1998\textsuperscript{54} (N = 536)
McCloskey et al 2001\textsuperscript{55} (N = 535)

MC, R, DB, PC

CLO 1600 mg PO daily until disease progression or toxicities versus placebo

Minimum follow-up of 2 yr

- CLO significantly reduced pathologic vertebral (p = 0.01) and nonvertebral fractures (p = 0.04)
- Lower incidence of hypercalcemia with CLO (39\% vs 48\%)
- Significantly lower incidence of back pain (p = 0.05) and poor performance status with CLO (p = 0.03)
- No difference in OS time (p = 0.74)

Minimum follow-up of 5 yr

- No significant difference in OS time between 2 groups (p = 0.38)
- Patients receiving CLO with no skeletal fracture at study entry had significant survival advantage (p = 0.006)

\textsuperscript{1}Defined as pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone, excluding HCM.

\textsuperscript{2}Defined as peripheral pathologic fracture, significant vertebral reduction (>25\%), hypercalcemic event (albumin-corrected serum calcium level of >2.8 mmol/L), severe bone pain (requiring opiate treatment), radiation therapy to bone, or surgery to bone.

\textbf{Abbreviations:}\ CI, confidence interval; CLO, clodronate; DB, double-blind; HCM, hypercalcemia of malignancy; IBA, ibandronate; IV, intravenous; MC, multicenter; MM, multiple myeloma; OS, overall survival; PAM, pamidronate; PC, placebo-controlled; PO, oral; R, randomized; RR, risk ratio; SRE, skeletal-related event; ZOL, zoledronic acid.
at least 2 hours or zoledronic acid 4 mg IV delivered over 15 minutes every 3 to 4 weeks for a period of 2 years. IV or oral clodronate is an alternative in other countries, but it is not commercially available in the United States.

**Duration of therapy**
A consensus has not been reached regarding the appropriate duration of bisphosphonate therapy. Most studies of bisphosphonates in cancer patients with bone metastases did not treat patients beyond 2 years. However, ASCO has tried to place some clarity on the issue in both their clinical practice guidelines for patients with breast cancer and MM. In patients with breast cancer metastatic to bone, ASCO advises to continue bisphosphonates until evidence of a progressive decline in performance status develops, even in the presence of SREs. No evidence addressing the consequences of discontinuing bisphosphonate therapy after developing a SRE in breast cancer patients exists. Among patients with osteolytic metastases secondary to MM, 2 years of bisphosphonate therapy is recommended. After 2 years, treating physicians should consider treatment discontinuation if the MM is responding to therapy or is stable. Guidelines addressing duration of therapy in other solid tumors are not available.

**Bone turnover markers**
Investigators frequently assess markers of bone turnover as secondary end points in bisphosphonate studies. Biochemical markers of bone metabolism are indicative of either bone formation or bone resorption and may help identify patients likely to respond to and benefit from bisphosphonate therapy. N-telopeptide of type I collagen (NTX) is of particular interest; patients with bone metastases and elevated NTX levels in urine have a significantly increased risk of SREs, disease progression, and death compared with patients with low NTX levels. In addition, urinary NTX normalization with pamidronate treatment has been linked with delays in bone lesion progression and a trend toward fewer fractures. Thus, NTX may be useful for monitoring therapeutic response to bisphosphonate therapy. However, because of the lack of sufficient, rigorous, prospective trials validating this approach, ASCO’s clinical practice guidelines recommend that the use of these markers be confined to research protocols; currently, they should not be used in routine clinical practice.

**Conclusion**
Skeletal complications are a major source of cancer-related morbidity. In patients with bone metastases, bisphosphonates have become the standard of care for preventing or delaying SREs. In patients with breast cancer or MM involving bone, zoledronic acid and pamidronate were comparable in their ability to decrease the incidence of SREs and delay the onset of skeletal events. In patients with solid tumors (except breast cancer) that metastasize to the bone, only zoledronic acid has been proven effective; ibandronate is effective in colorectal cancer. Despite their impressive efficacy in the prevention of skeletal complications associated with malignancy, several questions related to bisphosphonate use remain. Studies are ongoing to evaluate the appropriate duration of therapy, validate the usefulness of bone markers in predicting response to therapy, understand management of toxicities such as osteonecrosis of the jaw, and determine the most appropriate and cost-effective time to initiate bisphosphonate therapy.

**Acknowledgments**
The author thanks Kristin Hennenfent, PharmD, MBA, BCOP, and Terri Davidson, PharmD, BCOP, who assisted with writing and editorial services, respectively, and Novartis Pharmaceuticals Corporation, who sponsored development of this article.

**Disclosures**
The author has no conflicts of interest to disclose.

**References**


