Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology–Cancer Care Ontario Focused Guideline Update


ABSTRACT

Purpose
To update, in collaboration with Cancer Care Ontario (CCO), key recommendations of the American Society of Clinical Oncology (ASCO) guideline on the role of bone-modifying agents (BMAs) in metastatic breast cancer. This focused update addressed the new data on intervals between dosing and the role of BMAs in control of bone pain.

Methods
A joint ASCO-CCO Update Committee conducted targeted systematic literature reviews to identify relevant studies.

Results
The Update Committee reviewed three phase III noninferiority trials of dosing intervals, one systematic review and meta-analysis of studies of de-escalation of BMAs, and two randomized trials of BMAs in control of pain secondary to bone metastases.

Recommendations
Patients with breast cancer who have evidence of bone metastases should be treated with BMAs. Options include denosumab, 120 mg subcutaneously, every 4 weeks; pamidronate, 90 mg intravenously, every 3 to 4 weeks; or zoledronic acid, 4 mg intravenously every 12 weeks or every 3 to 4 weeks. The analgesic effects of BMAs are modest, and they should not be used alone for bone pain. The Update Committee recommends that the current standard of care for support care and pain management—analgesia, adjunct therapies, radiotherapy, surgery, systemic anticaner therapy, and referral to supportive care and pain management—be applied.

Evidence is insufficient to support the use of one BMA over another. Additional information is available at www.asco.org/breast-cancer-guidelines and www.asco.org/guidelineswiki.

INTRODUCTION

The American Society of Clinical Oncology (ASCO) has published a series of guidelines on the role of bone-modifying agents (BMAs) in metastatic breast cancer since 2000.1-3 ASCO updates its guidelines at intervals determined by an Update Committee of the original Expert Panel. The recent publications of phase III studies of breast cancer and dosing intervals for zoledronic acid4-6 prompted this update. This focused update of the 2011 guideline, completed in collaboration with Cancer Care Ontario (CCO), provides recommendations for the intervals between dosing and the role of zoledronic acid in the control of bone pain. The guideline also provides a discussion of cost considerations in the use of available BMAs for this population. The remaining recommendations from the 2011 ASCO guideline are unchanged because there were no new data to support substantive revisions.

FOCUSED GUIDELINE UPDATE QUESTIONS

1. What are the best intervals between dosing of zoledronic acid?
2. What is the role of BMAs in control of pain secondary to bone metastases?
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**Intervention**
Bone-modifying agents (BMAs).

**Target Audience**
Medical oncologists, radiation oncologists, surgical oncologists, oncology nurses, advanced practice providers, patients, patient advocates, caregivers, and oncology pharmacists.

**Key Recommendations**

**Recommendation updated for 2017 guideline.** As recommended in the 2011 version of the ASCO BMAs guideline, patients with breast cancer who have evidence of bone metastases should be treated with BMAs. One BMA is not recommended over another. If patients are treated with zoledronic acid, 4 mg intravenously administered over no less than 15 minutes, dosing options are every 12 weeks or every 3 to 4 weeks (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

**Recommendation updated for 2017 guideline.** The analgesic effects of BMAs (denosumab, pamidronate, or zoledronic acid) are modest, and they should not be used alone for bone pain. The Panel recommends that the current standard of care for supportive care and pain management be applied. This can include analgesia, adjunct therapies, radiotherapy, surgery, systemic anticancer therapy, and referral to supportive care and pain management. Evidence of a clinically meaningful benefit is insufficient to support the use of one BMA over another. Further research is needed on this clinical question. (Type: evidence based; benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak).

**Recommendations Unchanged From 2011 Guideline Update**
BMAs are recommended for patients with metastatic breast cancer with evidence of bone destruction. One BMA is not recommended over another.

Mechanism of action, as well as the potential benefits and harms, should be taken into account when considering long-term use of BMAs.

In patients with creatinine clearance > 60 mL/min, no change in dosage, infusion time, or interval is required; monitor creatinine level with each intravenous bisphosphonate dose.

In patients with creatinine clearance < 30 mL/min or on dialysis who may be treated with denosumab, close monitoring for hypocalcemia is recommended.

All patients should have a dental examination and preventive dentistry before using a BMA.

Use of biochemical markers to monitor BMA use is not recommended for routine care.

**Methods**
A joint ASCO-CCO Update Committee conducted targeted systematic literature reviews to identify relevant studies. The Panel reviewed three phase III noninferiority trials of dosing intervals, one systematic review and meta-analysis of studies of de-escalation of BMAs, and two randomized trials of BMAs in control of pain secondary to bone metastases. No cost-effectiveness analysis publications meeting the literature search and review inclusion criteria provided evidence to inform the cost considerations special commentary.

**Additional Resources**
Additional Information including data supplements, evidence tables, and clinical tools and resources can be found at [www.asco.org/breast-cancer-guidelines](http://www.asco.org/breast-cancer-guidelines) and [www.asco.org/guidelineswiki](http://www.asco.org/guidelineswiki). Patient information is available there and at [www.cancer.net](http://www.cancer.net). Visit [www.asco.org/guidelineswiki](http://www.asco.org/guidelineswiki) to provide comments on the guideline or to submit new evidence.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.
METHODS

**Guideline Update Process**

ASCO uses a signals approach to facilitate guideline updating. This approach identifies new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted literature searching and the expertise of ASCO guideline panel members to identify signals.

For this focused update, a set of three phase III randomized non-inferiority trials addressing dosing interval of zoledronic acid provided the signal. Primarily on the basis of this signal, the ASCO Breast Cancer Advisory Group ranked updating the guideline on BMAs in metastatic breast cancer among its highest priorities. To that end, ASCO and CCO convened a joint Update Committee (Appendix Table A1, online only) to review the evidence and to formulate updated recommendations for practice. With the approval of the ASCO Breast Cancer Guideline Advisory Group, the Update Committee expanded the guideline scope to include a commentary on cost considerations in the use of BMAs in patients with metastatic breast cancer.

The Update Committee conducted a search of the PubMed database to identify systematic reviews, meta-analyses, and randomized controlled trials (RCTs) that addressed the role of BMAs in the management of metastatic breast cancer. The review of the yield from this search focused on publications that reported on 4-week and 12-week intervals between the dosing of zoledronic acid and the role of BMAs in control of pain secondary to bone metastases.

To inform the special commentary on cost considerations, the Update Committee conducted an additional targeted PubMed literature search to identify articles reporting on the results of cost-effectiveness analyses of BMAs. This search was limited to non–industry-supported studies.

Additional information about the results of the updated literature search and search strategy strings and results, as well as a discussion of ASCO’s signals approach to guideline updating, are available at www.asco.org/breast-cancer-guidelines in the Data Supplement and Methodology Supplement, respectively. The Data Supplement also includes QUORUM diagrams of the updated search and the Clinical Questions.

The entire Update Committee contributed to the development of the guideline, provided critical review, and finalized the guideline recommendations. The ASCO Clinical Practice Guidelines Committee reviews and approves all ASCO guidelines. In addition, the Cancer Care Ontario Report Approval Panel reviewed this focused update manuscript. All funding for the administration of the project was provided by ASCO.

**Guideline Disclaimer**

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This is the most recent information as of the publication date. For the most recent information, and to submit new evidence, please visit www.asco.org/breast-cancer-guidelines and the ASCO Guidelines Wiki (www.asco.org/guidelineswiki).

**Guideline and Conflicts of Interest**

The Expert Panel was assembled in accordance with ASCO’s Conflict of Interest Management Procedures for Clinical Practice Guidelines (“Procedures,” summarized at http://www.asco.org/rwc). Members of the Panel completed ASCO’s disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial effect as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker’s bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Procedures, the majority of the members of the Panel did not disclose any such relationships.

RESULTS

The PubMed search (from January 2011 to March 2017) conducted to identify publications that reported on studies of the optimal intervals between BMA dosing and studies addressing the role of BMAs in control of pain secondary to bone metastases yielded 273 records. After review of the identified abstracts, six full-text articles—three phase III noninferiority trials of dosing intervals, one systematic review and meta-analysis of studies of de-escalation of BMAs, and two RCTs of the role of BMAs in control of pain secondary to bone metastases—were selected for review by the Update Committee.

The PubMed literature search (2003 to July 2016) performed to identify articles reporting on the results of cost-effectiveness analyses of BMAs yielded 32 records; however, none of the publications provided new evidence to inform the special commentary on cost considerations. A bibliography of the results of the cost-effectiveness literature search is provided in Data Supplement 3.

UPDATED RECOMMENDATIONS

**Clinical Question 1**

What are the best intervals between dosing of zoledronic acid?

Updated recommendation. As recommended in the 2011 version of the ASCO BMAs guideline, patients with breast cancer who have evidence of bone metastases should be treated with BMAs. One BMA is not recommended over another. If patients are treated with zoledronic acid, 4 mg intravenously administered
over no less than 15 minutes, dosing options are every 12 weeks or every 3 to 4 weeks (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

**Literature review and analysis.** The dosing interval recommendation has been updated from 2011 for zoledronic acid. Table 1 presents the dose, route of administration, and dosing intervals for denosumab, pamidronate, and zoledronic acid. The literature review for this guideline update identified three RCTs (Table 2) investigating zoledronic acid dosed every 4 weeks versus every 12 weeks and a meta-analysis (Fig 1) of dose de-escalation of BMAs. In each of the three RCTs, the comparisons between dosing the BMAs every 4 weeks or every 12 weeks showed a similar rate of skeletal complications as measured by proportion of skeletal-related events (SREs) or skeletal morbidity rates (SMRs) between the 4-week and 12-week dosing study arms. SREs are defined as fracture, radiation, or surgery to bone or spinal cord compression. ZOOM also included hypercalcemia as an SRE. SMR is defined as the number of SREs over time. Both ZOOM and OPTIMIZE 2 were industry-sponsored studies, while the CALGB (Alliance) study was National Institutes of Health sponsored. ZOOM and OPTIMIZE 2 both enrolled participants who had a least nine prior doses of intravenous bisphosphonate therapy for metastatic bone disease. The CALGB (Alliance) study enrolled bisphosphonate-naïve participants.

Himelstein et al3 reported on the CALGB (Alliance) protocol 70604, an open-label, noninferiority study. CALGB 70604 enrolled 1,822 patients with breast cancer (n = 855), prostate cancer (n = 689), or multiple myeloma (n = 278) who had at least one site of bone involvement from cancer and no prior intravenous bisphosphonate exposure. Participants were randomly assigned to either zoledronic acid once every 4 weeks or zoledronic acid once every 12 weeks for 2 years. The primary end point was the proportion of participants with at least one SRE at 2 years. Seven hundred ninety-five participants (43%) completed the 2 years of study. Of the 855 participants with breast cancer, 390 (45%) completed 2 years of follow-up. The most common reasons for discontinuing the study were withdrawal or refusal, disease progression, and death. With a median follow-up of 1.2 years, CALGB 70604 demonstrated noninferiority between the two study arms, with the SRE rate of 29.5% in the 4-week arm and 28.6% in the 12-week arm. The proportional difference was 0 (one-sided 95% CI, −0.04 to infinity; P < .001) and 0.01 (one-sided 95% CI, −0.03 to infinity; P < .001) for the intention-to-treat analysis and sensitivity analysis, respectively. In a planned disease-site analysis, in patients with breast cancer, the between-group difference was −0.02 (99.9% CI, −0.13 to 0.09; P = .50).

The probability of at least one SRE occurring within 2 years of randomization was consistent across breast cancer, prostate cancer, and multiple myeloma groups and was not statistically different between the 4-week and 12-week arms. There was no statistically significant difference between the treatment arms in Eastern Cooperative Oncology Group performance status or in any measures of the mean pain scores. The SMR (0.4) was equal in both arms. There were numerically more cases of osteonecrosis of the jaw (ONJ) in the 4-week dosing arm (18 participants; 2.0%) than in the 12-week dosing arm (9 participants; 1.0%); however, the difference was not statistically significant (two-sided Cochran-Mantel-Haenszel P = .10). Grade 3 or grade 4 kidney dysfunction occurred in 10 participants (1.2%) in the 4-week arm and in four participants (0.5%) in the 12-week arm. This difference was not statistically significant. A post hoc analysis evaluated the risk of significant increases in creatinine level, defined as an increase of ≥ 0.5 mg/dL when the baseline creatinine level was ≤ 1.4 mg/dL or an increase of ≥ 1 mg/dL when the baseline creatinine was > 1.4 mg/dL. In this post hoc analysis, 19.9% of participants in the 4-week dosing arm and 15.5% of participants in the 12-week dosing arm experienced elevations in serum creatinine (Cochran-Mantel-Haenszel P = .02). Grade 4 hypocalcemia (< 6 mg/dL) occurred in eight patients (0.9%) in the 4-week dosing arm and in five patients (0.6%) in the 12-week dosing arm (two-sided χ² P = .61). There was no statistical difference in hypocalcemia between the two arms. The percentage of patients experiencing grade 4 hypocalcemia is particularly notable given that the CALGB 70604 protocol advised participants on daily intake of calcium and vitamin D.

The biochemical marker of bone resorption, C-terminal telopeptide, was serially measured in 553 study participants. In both treatment arms, the C-terminal telopeptide values were lowered from baseline and suppressed during the course of the study. Note that this ASCO guideline update does not alter the prior recommendation (No. 7) that the use of the biochemical markers to monitor BMA use is not recommended for routine care.

The randomized clinical trials ZOOM 4 and OPTIMIZE-2 each enrolled slightly over 400 women with metastatic breast cancer involving the bone. The trials are different, but they are relatively similar in that eligible patients had prior exposure to pamidronate or zoledronic acid for approximately 1 year or more, and study participants were randomly assigned to either 4 mg zoledronic acid intravenously every 4 weeks or 4 mg zoledronic acid every 12 weeks. ZOOM was open label, while OPTIMIZE-2 was double-blind and placebo-controlled. Initially, OPTIMIZE-2 included a placebo arm, but this was subsequently discontinued. Both ZOOM and OPTIMIZE-2 followed patients for about 1 year. In ZOOM, 68% of participants completed the study. SMR was the primary end point and was 0.22 (95% CI, 0.14 to 0.29) in the 4-week group and 0.26 (95% CI, 0.15 to 0.37) in the 12-week group.

### Table 1. Route of Administration, Dose, and Schedule for BMAs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
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<tbody>
<tr>
<td>Bisphosphonates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Intravenous</td>
<td>90 mg</td>
<td>Delivered over no less than 2 hours every 3 or 4 weeks</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Intravenous</td>
<td>4 mg</td>
<td>Delivered over no less than 15 minutes every 12 weeks or every 3 to 4 weeks</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Subcutaneous injection</td>
<td>120 mg</td>
<td>Every 4 weeks</td>
</tr>
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Abbreviation: BMA, bone-modifying agent.
group. The between-group difference of 0.04 and the upper limit of the one-tailed 97.5% CI was 0.17, indicating noninferiority of the 12-week schedule. The negative binomial model for the SMR ratio of the 4-week versus 12-week schedule was 97% (95% CI, 0.60 to 1.57; \( P = .896 \)). In both arms, 15% of participants experienced on-study SREs \( (P = .898) \). The Anderson–Gill multiple event analysis did not demonstrate a statistically significant difference between the 4-week and 12-week dosing arms. The median time to first SRE on study was not calculated due to a low event rate. Pain scores and analgesic use did not differ between the two arms. Renal adverse events and ONJ were deemed adverse events related to zoledronic acid. Renal adverse events occurred in 1% of participants in the 4-week dosing arm and in \(< 1\%\) in the 12-week dosing arm. Post hoc analysis of deterioration of renal function did not demonstrate clinically meaningful difference between treatment groups. ONJ occurred in 1% of participants in the 4-week dosing arm \( (n = 3) \) and in 2% of the 12-week dosing arm \( (n = 4) \). The median change from baseline in the biochemical marker of bone resorption, N-telopeptide, was statistically significantly lower in the 4-week dosing arm than in the 12-week dosing arm at 6, 9, and 12 months.

In OPTIMIZE-2, the primary end point was the SRE rate. Between 53% and 63% of OPTIMIZE-2 participants completed the study. Twenty-two percent of the OPTIMIZE-2 participants in the 4-week group and 23.2% of participants in the 12-week group experienced one or more SREs. The proportional difference of 1.2% had a one-sided 97.3% CI bound that was less than the noninferiority threshold \( (P = .02) \), and the 12-week dosing arm was noninferior to the 4-week dosing arm. The time to first SRE, time to multiple SRE events, SMR, and SRE-free survival were not significantly different between the 4-week and 12-week arms. Likewise, the patient-reported pain scores and analgesic consumption were not statistically different between the two arms. The most common treatment-emergent adverse event was a rise in serum creatinine leading to discontinuation of the study drug occurring in six patients in the 4-week arm and one in the 12-week arm. Renal adverse events occurred at similar rates between the two arms. ONJ occurred in two participants in the 4-week dosing arm; no cases of ONJ occurred in the 12-week dosing arm. Atypical femur fractures were not observed. A statistically significant difference in the mean change from baseline of the biochemical bone resorption marker N-telopeptide was seen at 36 weeks only \( (P = .01) \), and there was no statistically significant mean change in the biochemical marker of bone formation bone-specific alkaline phosphatase.

The systematic review and meta-analysis by Ibrahim et al\(^8\) identified five studies comparing 4-weekly versus 12-weekly dosing of denosumab, pamidronate, or zoledronic acid. Analysis of on-study SRE demonstrated that these bisphosphonates and denosumab

### Table 2. Dosing Interval Noninferiority Trials

<table>
<thead>
<tr>
<th>Study and Dosing Interval</th>
<th>No. of Patients Completing Study (%)</th>
<th>Prior IV BMA</th>
<th>% With SRE at Baseline</th>
<th>Median Time to First SRE (months)</th>
<th>Skeletal Morbidity Rate</th>
<th>SRE Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 70604 every 4 weeks</td>
<td>212 of 427 (50)</td>
<td>No</td>
<td>26.2</td>
<td>15.7</td>
<td>0.4*</td>
<td>29.5</td>
</tr>
<tr>
<td>CALGB 70604 every 12 weeks</td>
<td>178 of 428 (42)</td>
<td>No</td>
<td>25.7</td>
<td>16.8</td>
<td>0.4</td>
<td>28.6</td>
</tr>
<tr>
<td>ZOOM every 4 weeks</td>
<td>142 of 216 (66)</td>
<td>Yes</td>
<td>57</td>
<td>NR‡</td>
<td>0.22†</td>
<td>15</td>
</tr>
<tr>
<td>ZOOM every 12 weeks</td>
<td>149 of 209 (71)</td>
<td>Yes</td>
<td>57</td>
<td>NR¶</td>
<td>0.26</td>
<td>15</td>
</tr>
<tr>
<td>OPTIMIZE-2 every 4 weeks</td>
<td>106 of 200 (53)</td>
<td>Yes</td>
<td>NR</td>
<td>NR§</td>
<td>0.46</td>
<td>22</td>
</tr>
<tr>
<td>OPTIMIZE-2 every 12 weeks</td>
<td>127 of 203 (63)</td>
<td>Yes</td>
<td>NR</td>
<td>NR§</td>
<td>0.50</td>
<td>23.2</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMA, bone-modifying agent; IV, intravenous; NR, not reported; SRE, skeletal-related event. *Skeletal morbidity rate defined as mean number of SREs per year. †Could not be calculated because of the low event rate. ‡Defined as SREs per patient per year. §Defined as events per year.

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**Fig 1.** Meta-analysis results from Ibrahim et al\(^8\) for on-study skeletal-related events. Reprinted with permission. Oxford University Press. Abbreviation: IV, intravenous.
produced a summary risk ratio of 0.90 (95% CI, 0.63 to 1.29) for standard 4-week dosing interval versus the 12-week dosing interval. The authors did not perform a meta-analysis on pain outcome data due to the variability in study measures and pain-reporting outcomes. However, on-study bone pain as an adverse event was not statistically different between the 4-week dosing interval and the 12-week dosing interval (95% CI, 0.46 to 1.62). ONJ summary risk ratio comparing the 4-week dosing interval to the 12-week dose interval was 0.83 (95% CI, 0.16 to 4.42). There was no statistically significant difference in on-study hypocalcemia as an adverse event, although more cases occurred in the 4-week dosing interval group. The biochemical markers of bone resorption, C-telopeptide and N-telopeptide were not statistically different between the 4-week and 12-week dosing schedules.

The literature review for this guideline update did not identify publications addressing BMA dosing intervals specific to hypercalcemia of malignancy. The Food and Drug Administration–approved packet inserts for denosumab, pamidronate, and zoledronic acid address the management of hypercalcemia of malignancy.

**Clinical Question 2**

What is the role of BMAs in control of pain secondary to bone metastases?

*Updated recommendation.* The analgesic effects of bone-modifying agents (denosumab, pamidronate, or zoledronic acid) are modest, and BMAs should not be used alone for bone pain. The Update Committee recommends that the current standard of care for supportive care and pain management be applied. This can include analgesia, adjunct therapies, radiotherapy, surgery, systemic anticancer therapy, and referral to supportive care and pain management. Evidence of a clinically meaningful benefit is insufficient to support the use of one BMA over another. Further research is needed on this clinical question (Type: evidence based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak).

**Literature review and analysis.** This recommendation remains unchanged from 2011. BMAs are an adjunctive therapy for pain control and are not recommended as primary therapy for analgesia. Clinicians should provide comprehensive pain management care for patients with metastatic breast cancer–related pain and can refer to the ASCO clinical practice guidelines on management of chronic pain in survivors of adult cancers11 and integration of palliative care into standard oncology care.12 When used concurrently with analgesics, BMAs may be of benefit for women with metastatic breast cancer with pain caused by bone metastases.

BMAs have been associated with a modest pain control benefit in controlled trials (Table 3). The evidence is not sufficient to favor one BMA over another with regard to analgesic effect. Randomized studies of denosumab versus zoledronic acid evaluating effects on pain suggest a modest advantage of denosumab by Brief Pain Inventory–Short Form, FACT-G quality of life scores, and skeletal-related events.9,10 In the Martin et al trial,10 approximately 10% more patients had a clinically meaningful improvement in health-related quality of life with denosumab compared with zoledronic acid, regardless of their pain levels at baseline. Cleeland et al11 observed that fewer patients who received denosumab progressed from no or mild pain to moderate/severe pain, compared with patients who received zoledronic acid (relative difference, 15%; absolute difference, 5%); there was almost a 4-month delay in the median time to pain worsening to moderate or severe with denosumab versus zoledronic acid (9.7 months vs 5.8 months; P = .002). However, the studies are limited, and absolute differences between the two agents were small.

**COST CONSIDERATIONS IN THE USE OF BMAs IN PATIENTS WITH METASTATIC BREAST CANCER**

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance. Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.13,14 Table 4 shows estimated prices for BMAs. Of note, medication prices of BMAs vary markedly, depending on negotiated discounts and rebates. Discussion of cost can be an important part of shared decision making.15 Clinicians should exercise judgment and, whenever it is practical and feasible, discuss with patients the use of less expensive alternatives when considering two or more treatment options that are comparable in terms of benefits and harms.15

Depending on a patient’s particular insurance coverage, reimbursement for the BMA may originate in their medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. Patients should be asked about their financial concerns by their caregivers and be offered financial counseling to address this complex and heterogeneous landscape.15

As mentioned previously, the search for published cost-effectiveness analyses that might inform the clinical question of the relative value of available BMAs provided no definitive evidence to inform cost considerations. The Update Committee excluded articles from consideration identified from a first-level review of the literature search (Data Supplement) because the analyses in question lacked contemporary cost data for the agents studied, included agents that are not currently available in either the United States or Canada, and/or were industry sponsored.

**DISCUSSION AND DIRECTIONS FOR FUTURE RESEARCH**

The recent publications on the dosing interval of zoledronic acid are expected to change clinical practice. It is anticipated that there will soon be data on dosing intervals of denosumab in patients with metastatic bone disease from breast cancer. Until there are data to suggest otherwise, the Panel recommends that denosumab be prescribed as per packet insert labeling and clinical judgment.

The ongoing, open-label phase III study SAKK 96/12 (ClinicalTrials.gov identifier: NCT02051218; REDUSE) randomly assigns participants with metastatic breast cancer or prostate cancer to denosumab dosed every 4 weeks or every 12 weeks. The primary outcome is the time to first on-study symptomatic skeletal event. Secondary end points include additional measures of bone morbidity, as well as assessment of toxicity, quality of life, health economics, biochemical markers of bone turnover, and overall survival.

The REaCT-BTA Study (ClinicalTrials.gov identifier: NCT-02721433) will also add to our understanding of dosing intervals for denosumab. REaCT-BTA is an open-label, phase III,
<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Design</th>
<th>Patients</th>
<th>Agent(s)</th>
<th>Outcome Measures</th>
<th>Summary of Results</th>
</tr>
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<tbody>
<tr>
<td>Cleeland 2013</td>
<td>Randomized, double-blind, double-dummy, phase III trial.</td>
<td>2,046 patients with breast cancer: denosumab arm (n = 1,026), zoledronic acid arm (n = 1,020), with radiographic evidence of one or more bone metastases. Patients diagnosed with metastases a median of 2 months before random assignment; most (71%-72%) hormone receptor-positive.</td>
<td>Denosumab 120 mg monthly (subcutaneous injection) and IV placebo; or subcutaneous placebo and a monthly IV infusion of zoledronic acid 4 mg.</td>
<td>Pain severity and pain interference with daily functioning assessed with 11-item BPI-SF at baseline and at each monthly visit before study procedures or drug administration, and continued either until the patient came off study or at the end of the randomized component of the study. Analgesic use also was recorded using 8-point AQA at each assessment. Delay in the median time to an increase of $\geq 2$ points in pain severity: denosumab (8.5 months; n = 901); zoledronic acid (7.4 months; n = 892; HR, 0.90; 95% CI, 0.80 to 1.01; P = .08). Pain worsening among patients who had no or mild pain at baseline to moderate or severe pain on study: Fewer patients who received denosumab progressed from no or mild pain to moderate or severe pain compared with zoledronic acid (relative difference, 15%; absolute difference, 5%), with an almost 4-month delay in the median time to pain worsening to moderate or severe with denosumab compared with zoledronic acid (P = .002). Palliation of pain severity: Similar between treatment groups: 26% at 1 month to 16% at 18 months for denosumab (n = 979) and from 26% at 1 month to 18% at 18 months for zoledronic acid (n = 951). Median time to meaningful improvement in worst pain score: denosumab (n = 745), 2.8 months; zoledronic acid (n = 743); 1.9 months; zoledronic acid (n = 452), 1.9 months; HR, 0.97; 95% CI, 0.84 to 1.12; P = .68. Palliation of pain severity: Similar between treatment groups: 26% at 1 month to 16% at 18 months for denosumab (n = 979) and from 26% at 1 month to 18% at 18 months for zoledronic acid (n = 951). Pain interference with daily functioning: Time to an increase in aggregate pain interference of $\geq 2$ points from baseline: denosumab, 16.0 months; zoledronic acid, 14.9 months; HR, 0.89; 95% CI, 0.78 to 1.02; P = .09. Time to decreased pain interference (P = .92) was similar between the groups, denosumab: median, 2.9 months; zoledronic acid: 3.2 months; HR, 0.99; 95% CI, 0.86 to 1.15. Analgesic score: Fewer patients in the denosumab arm shifted from no or low analgesic use (AQA scores, 0-2) to strong opioid analgesic use (AQA scores, 3-7) compared with patients in the zoledronic acid arm (relative difference, 20%; absolute difference, 2%). FACT-G total score, median (Q1-Q3): zoledronic acid group, 74 (61-86); denosumab group, 74 (61-85). HRQoL improvement in overall study population: An average of 10% more patients in the denosumab group compared with the zoledronic acid group had a clinically meaningful improvement in HRQoL ($\geq 5$-point increase in FACT-G total score) over the course of the study (34% v 31%; P &lt; .09). In patients with no or mild pain at baseline (BPI-SF score, 0 to 4), the relative overall improvement in HRQoL was 14% greater with denosumab compared with zoledronic acid (P &lt; .05).</td>
<td></td>
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</table>

| Martin 2012 | Randomized, double-blind, double-dummy, parallel-group, phase III trial. | Patients with breast cancer, at least one bone metastasis, adequate organ function, and ECOG performance status ≤ 2. Patients randomly assigned over a 20-month period. | Denosumab 120 mg monthly (subcutaneous injection) and IV placebo; or subcutaneous placebo and a monthly IV infusion of zoledronic acid 4 mg. | Clinically meaningful change in HRQoL, defined as a 5-point change or more from baseline on the 27-item FACT-G questionnaire. FACT-G total score, median (Q1-Q3): zoledronic acid group, 74 (61-86); denosumab group, 74 (61-85). HRQoL improvement in overall study population: An average of 10% more patients in the denosumab group compared with the zoledronic acid group had a clinically meaningful improvement in HRQoL ($\geq 5$-point increase in FACT-G total score) over the course of the study (34% v 31%; P < .09). In patients with no or mild pain at baseline (BPI-SF score, 0 to 4), the relative overall improvement in HRQoL was 14% greater with denosumab compared with zoledronic acid (P < .05). |

Abbreviations: AQA, Analgesic Quantification Algorithm; BMAs, bone-modifying agents; BPI-SF, Brief Pain Inventory-Short Form; ECOG, Eastern Cooperative Oncology Group; FACT-G, functional assessment of cancer therapy-general; HR, hazard ratio; HRQoL, health-related quality of life; IV, intravenous; Q1, first quartile; Q3, third quartile.
randomized study in metastatic breast cancer or prostate cancer and assigns participants to one of two arms, either 4-week or 12-week dosing of denosumab, pamidronate, or zoledronic acid. This study investigates the “de-escalation” of therapy in those who may have had BMA exposure as well as those who are treatment naive. REaCT-BTA tests the hypothesis that 12-week dosing will be noninferior to 4-week dosing in terms of quality of life, pain, and symptomatic skeletal events, and will result in lower health care costs. The primary outcome is health-related quality of life. This study is currently recruiting.

No known RCTs are currently investigating the optimal duration of therapy with a BMA. Since 2000, the ASCO guidelines have recommended the use of BMAs indefinitely. There are no new data to alter the 2000 duration of therapy recommendation. The data reviewed for this update demonstrate that an extended duration of therapy recommendation. However, these studies did not address duration of bone-modifying therapy. Although initially designed with a placebo arm, OPTIMIZE-2 did not provide data on discontinuation of zoledronic acid after 1 year of therapy. There is a need to weigh the potential benefits and harms of therapy when considering long-term use of a BMA. In addition, the different mechanism of action between a bisphosphonate and denosumab should be also considered. There are no data outlining the risk-benefit ratio of stopping and potentially restarting BMA therapy during long-term care. Data on the long-term dosing and long-term effects of BMAs are needed.

Bone metastases and the risk of SREs continue throughout the trajectory of metastatic breast cancer. This has been shown in the early studies in which BMAs were compared with placebo, in the studies comparing the now US Food and Drug Administration–approved BMAs against one another, and in the dosing interval studies described in this ASCO guideline update. CALGB 70604, ZOOM, and OPTIMIZE-2 demonstrate that the risk of SREs is approximately 15% to 29% into the second year of dosing. The duration of bone-modifying therapy in these studies is of note given that the life expectancy of metastatic breast cancer involving the bone may approach or exceed the median length of follow-up of these studies. It is also of note that a minority (15% to 29%) of participants in these studies continued to have SREs on BMAs.

Role of Bone-Modifying Agents in Metastatic Breast Cancer

Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer

Integration of Palliative Care Into Standard Oncology Practice

Management of Chronic Pain in Survivors of Adult Cancers

ACS/ASCO Breast Cancer Survivorship Care

Table 4. Estimated Prices for BMAs in the United States

<table>
<thead>
<tr>
<th>Agent, Route</th>
<th>Dose</th>
<th>Schedule</th>
<th>Price Per Dose (USD)</th>
<th>Total Price Per 1-Year Treatment Cycle (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td></td>
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<tr>
<td>Pamidronate, intravenous</td>
<td>90 mg</td>
<td>Delivered over less than 2 hours every 3 or 4 weeks</td>
<td>$30.67*</td>
<td>Every 4 weeks price: $398.71 ($30.67 × 13)</td>
</tr>
<tr>
<td>Zoledronic acid, intravenous</td>
<td>4 mg</td>
<td>Delivered over less than 15 minutes every 12 weeks or every 34 weeks</td>
<td>$53.64†</td>
<td>Every 12 weeks price: $214.56 ($53.64 × 4)</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab, subcutaneous injection</td>
<td>120 mg</td>
<td>Every 4 weeks</td>
<td>$1,995.48†</td>
<td>Every 4 weeks price: $25,941.24 ($1,995.48 × 13)</td>
</tr>
</tbody>
</table>

NOTE. Prices per dose were for a single infusion or per single injection. Prices for drugs reimbursed through Medicare Part B only were identified from the 2nd Quarter 2017 Medicare Payment Allowable Part B Drugs Average Sales Price Data (https://www.cms.gov/apps/ama/license.asp?file=/Medicare/Medicare-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/Downloads/2017-April-ASP-Pricing.zip). Drug price may vary by plan and by pharmacy where a medication is filled (eg, preferred or nonpreferred pharmacies). Drug prices are dynamic; thus, the prices listed in the table may not reflect current prices.

Abbreviations: BMAs, bone-modifying agents; USD, US dollars.

* $10.223/30 mg × 3.
† $13.411/1 mg × 4.
‡ $16.629/1 mg × 120.
REFERENCES


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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology–Cancer Care Ontario Focused Guideline Update

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Appendix

<table>
<thead>
<tr>
<th>Table A1. Update Committee Membership</th>
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<tbody>
<tr>
<td>Beverly Moy, MD (co-chair)</td>
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<td>Catherine Van Poznak, MD (co-chair)</td>
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NOTE. American Society of Clinical Oncology staff: Mark R. Somerfield, PhD. Abbreviation: PGIN, Practice Guideline Implementation Network.