ASCO special articles

Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: ASCO-OH (CCO) Guideline Update

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abstract

PURPOSE To update recommendations of the American Society of Clinical Oncology (ASCO)-Ontario Health (Cancer Care Ontario [CCO]) adjuvant bone-modifying agents in breast cancer guideline.

METHODS An Expert Panel conducted a systematic review to identify new, potentially practice-changing data.

RESULTS Four articles met eligibility criteria and form the evidentiary basis for revision of the previous recommendations.

RECOMMENDATIONS Adjuvant bisphosphonate therapy should be discussed with all postmenopausal patients (natural or therapy-induced) with primary breast cancer, irrespective of hormone receptor status and human epidermal growth factor receptor 2 status, who are candidates to receive adjuvant systemic therapy. Adjuvant bisphosphonates, if used, are not substitutes for standard anticancer modalities. The benefit of adjuvant bisphosphonate therapy will vary depending on the underlying risk of recurrence and is associated with a modest improvement in overall survival. The NHS PREDICT tool provides estimates of the benefit of adjuvant bisphosphonate therapy and may aid in decision making. Factors influencing the decision to recommend adjuvant bisphosphonate use should include patients' risk of recurrence, risk of side effects, financial toxicity, drug availability, patient preferences, comorbidities, and life expectancy. When an adjuvant bisphosphonate is used to prevent breast cancer recurrence, the therapeutic options recommended by the Panel include oral clodronate, oral ibandronate, and intravenous zoledronic acid. The Panel supports starting bisphosphonate therapy early, consistent with the points outlined in the parent CCO-ASCO guideline; this is a consensus recommendation. The Panel does not recommend adjuvant denosumab to prevent breast cancer recurrence, because studies did not show a consistent reduction of breast cancer recurrence in any subset of those with early-stage breast cancer.

Additional information can be found at www.asco.org/breast-cancer-guideline.

J Clin Oncol 00. © 2022 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on November 24, 2021 and published at ascopubs.org/journal/jco on January 18, 2022: DOI https://doi.org/10.1200/JCO.21.02647

Evidence Based Medicine Committee approval:

November 5, 2021

Program in Evidence Based Care Report Approval Panel approval:

October 20, 2021

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INTRODUCTION

Cancer Care Ontario (CCO; now a division of Ontario Health [OH]) and ASCO published a joint guideline in 2017 on the use of adjuvant bisphosphonates and other bone-modifying agents (BMAs) in breast cancer.[1] ASCO updates its guidelines at intervals determined by the Panel leadership, on the basis of targeted literature searching and the expertise of ASCO guideline panel members to identify signals in the literature.[2] Signals are new, potentially practice-changing data that may translate into major revisions to current practice recommendations.

The 2017 Joint CCO-ASCO Guideline

The 2017 CCO-ASCO guideline[1] highlighted that, although the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis[3] found benefit for bisphosphonates in all subgroups of postmenopausal patients, the absolute benefit was small. For the subgroup of premenopausal patients, bisphosphonates had no significant effect on these outcomes. The EBCTCG meta-analysis found statistically significant benefit for bisphosphonates in all postmenopausal patients with breast cancer for bone recurrence (6.6% *v* 8.8%), fracture rates (9.1% *v* 10.3%), breast cancer mortality (14.7% *v* 18.0%), overall survival (any death 21.1% *v* 23.5%), and outcomes that included bone recurrence (ie, distant recurrence and any recurrence). These differences did not vary as a function of treatment features (bisphosphonate class, treatment schedule, and dose), tumor characteristics (hormone receptor

THE BOTTOM LINE

Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: ASCO-OH (CCO) Guideline Focused Update

Guideline Question

What is the role of bisphosphonates and other bone-modifying agents in adjuvant therapy among patients with breast cancer?

Target Population

Postmenopausal (natural or induced) patients, irrespective of hormone receptor status and human epidermal growth factor receptor 2 status, with nonmetastatic breast cancer for whom a bone-modifying agent is being considered as an adjuvant systemic therapy to reduce the risk of breast cancer recurrence (ASCO's breast cancer guideline for cisgender [or non-transgender] men recommends that men with early-stage breast cancer should not be treated with bone-modifying agents to prevent recurrence).

Target Audience

Oncology specialists, other health care providers (including primary care physicians, specialists, nurses, social workers, and any other relevant member of a comprehensive multidisciplinary cancer care team), caregivers, and patients.

Methods

An Expert Panel was convened to update clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Updated Recommendations

NOTE. The Panel acknowledges that access to adjuvant bone-modifying agents discussed herein is not universal because of limited reimbursement or availability.

Recommendation 1.1. Adjuvant bisphosphonate therapy should be discussed with all postmenopausal patients (natural or therapy-induced) with primary breast cancer, irrespective of hormone receptor status and human epidermal growth factor receptor 2 status, who are candidates to receive adjuvant systemic therapy. Adjuvant bisphosphonates, if used, are not substitutes for standard anticancer modalities.

The benefit of adjuvant bisphosphonate therapy will vary depending on the underlying risk of recurrence and is associated with a modest improvement in overall survival. The NHS PREDICT tool[8] provides estimates of benefit of adjuvant bisphosphonate therapy and may aid in shared decision making.

Factors influencing the decision to recommend adjuvant bisphosphonate use that should be weighed in the discussion with patients include the patient's risk of recurrence, the risk of side effects, financial toxicity, drug availability, patient preferences, comorbidities, and life expectancy (type: informal consensus; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation 2.1. The Panel supports starting bisphosphonate therapy early, consistent with the points outlined in the parent CCO-ASCO guideline. Many studies initiated bisphosphonate within 3 months of definitive surgery or within 2 months of completion of adjuvant chemotherapy; this is a consensus recommendation. The therapeutic options, listed alphabetically, with the strongest supporting data include:

- oral clodronate (1,600 mg daily for 2-3 years)
- oral ibandronate (50 mg daily for 3 years)
- zoledronic acid; dosing regimens as per the protocols of the clinical trials (including the option of dosing 4 mg once every 6 months for 3 years or dosing 4 mg once every 3 months for 2 years)

Patient preference should be factored into the choice of adjuvant bisphosphonate therapy. Access to adjuvant bisphosphonate therapy may currently limit choice of agent depending on jurisdiction (type: evidence-based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation 3.1. The Panel does not recommend the use of adjuvant denosumab (type: evidence-based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate).

Key evidence. Two Phase III studies of adjuvant denosumab did not show a consistent reduction of breast cancer recurrence in any subset of patients with early-stage breast cancer. The larger study, D-CARE, did not show improvement in cancer outcomes with use of denosumab.

Refer to Table 1 for the full list of recommendations.

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Additional Resources: Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A2 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net

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.

status, nodal status, and tumor grade), or concurrent chemotherapy. There was no statistically significant improvement in distant recurrence outside bone.[3] The CCO-ASCO Expert Panel suggested that, for patients with cancers assessed as having low risk of recurrence, the use of bisphosphonates may not result in a clinically meaningful effect.[1]

In terms of adverse events, the CCO-ASCO guideline noted that postmarketing surveillance had reported uncommon to rare adverse effects such as renal toxicity, osteonecrosis of the jaw (ONJ), atypical femoral fractures, and inflammatory eye reactions. The risk of renal toxicity, ONJ, and atypical femoral fractures may be increased at higher dosing and prolonged use. Acute inflammatory eye reactions including conjunctivitis, uveitis, scleritis, episcleritis, and keratitis are rare. The Expert Panel recommended that risk factors for ONJ and renal impairment should be assessed.

When the CCO-ASCO guideline was published in 2017, there were three ongoing trials with potential to influence practice recommendations, SWOG/Alliance/Canadian Cancer Trials Group/ECOG-ACRIN/NRG Oncology study S0307 (SWOG S0307),[4] ABCSG-18,[5] and D-CARE.[6] The results of these three studies have since been published; these data, along with the findings from a fourth trial, SUCCESS A, published most recently,[7] form the basis for the current guideline update.

The 2021 ASCO-OH (CCO) Focused Update

As mentioned, the present update was prompted by the publication of three randomized clinical trials: ABCSG-18,[5] D-CARE,[6] and SWOG/Alliance/Canadian Cancer Trials Group/ECOG-ACRIN/NRG Oncology study S0307.[4] Subsequently, the results of the randomized clinical trial, Success A,[7] were published and incorporated into this update. On the basis of a review of this evidence, the Update Panel revisited recommendations from the original 2017 guideline concerning the choice and dose of bisphosphonates, and the use of denosumab. In addition, prompted by feedback on the 2017 guideline, the Panel refined and expanded the recommendations concerning patient selection—whom to treat with BMAs. The remaining recommendations from the 2017 guideline are unchanged because there were no new potentially practice-changing data to support substantive revisions (Table 1). The evidence supporting these unchanged recommendations is reviewed in the previous guideline publication.[1]

The focus of this guideline is on the relapse and survival benefit of BMAs in nonmetastatic breast cancer. The guideline does not address the use of BMAs to treat metastatic cancer to the bone metastases from breast cancer,[9] or general bone health in patients with breast cancer [10] (see ASCO guidelines addressing these topics). This guideline should be used in conjunction with the Multinational Association of Supportive Care in Cancer-International Society of Oral Oncology-ASCO guideline on medication-related ONJ.[11]

FOCUSED GUIDELINE QUESTIONS

Clinical Question 1: Which patients with primary breast cancer should be treated with bone-modifying agents?

Clinical Question 2: Which bisphosphonates are recommended for breast cancer adjuvant therapy and what doses, duration of administration, time to initiate treatment, and routes (intravenous, oral) are optimal?

Clinical Question 3: What is the role of the bone-modifying agent, denosumab, as an adjuvant therapy for primary breast cancer?

METHODS

Guideline Update Process

ASCO uses a signals approach to facilitate guideline updating.[2] 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, phase III randomized trials of bisphosphonates[4] and the bone-modifying agent (BMA), denosumab,[5,6] provided the signals.

This systematic review-based guideline product was developed by a joint ASCO-Ontario Health (OH; Cancer Care Ontario [CCO]) multidisciplinary Expert Panel, which included a patient representative and ASCO and OH (CCO) guidelines staff members with health research methodology expertise. The Program in Evidence-Based Care (PEBC) Practice Guidelines Development Cycle and the

TABLE 1. Complete List of Recommendations From 2017 CCO-ASCO Guideline and From the ASCO-OH (CCO) 2021 Focused Guideline Update

Recommendation	Evidence Rating
New Recommendations From 2021 ASCO-OH Focused Guideline Update	
Adjuvant bisphosphonate therapy should be discussed with all postmenopausal patients (natural or therapy-induced) with primary breast cancer, irrespective of hormone receptor status and HER2 status, who are candidates to receive adjuvant systemic therapy. Adjuvant bisphosphonates, if used, are not substitutes for standard anticancer modalities The benefit of adjuvant bisphosphonate therapy will vary depending on the underlying risk of recurrence and is associated with a modest improvement in OS. The NHS PREDICT tool[8] provides estimates of benefit of adjuvant bisphosphonate therapy and may aid in shared decision making Factors influencing the decision to recommend adjuvant bisphosphonate use that should be weighed in the discussion with patients include the patient's risk of recurrence, the risk of side effects, financial toxicity, drug availability, patient preferences, comorbidities, and life expectancy	Type: informal consensus Evidence quality: intermediate Strength of recommendation: moderate
The Panel supports starting bisphosphonate therapy early, consistent with the points outlined in the parent CCO-ASCO guideline. Many studies initiated bisphosphonate within 3 months of definitive surgery or within 2 months of completion of adjuvant chemotherapy; this is a consensus recommendation. The therapeutic options, listed alphabetically, with the strongest supporting data include: • oral clodronate (1,600 mg daily for 2-3 years) • oral ibandronate (50 mg daily for 3 years) • zoledronic acid; dosing regimens as per the protocols of the clinical trials (including the option of dosing 4 mg once every 6 months for 3 years or dosing 4 mg once every 3 months for 2 years) Patient preference should be factored into the choice of adjuvant bisphosphonate therapy. Access to adjuvant bisphosphonate therapy may currently limit choice of agent depending on jurisdiction	Type: evidence-based, benefits outweigh harms Evidence quality: intermediate Strength of recommendation: moderate
The Panel does not recommend the use of adjuvant denosumab Key evidence: two phase III studies of adjuvant denosumab did not show a consistent reduction of breast cancer recurrence in any subset of patients with early-stage breast cancer. The larger study, D-CARE, did not show improvement in cancer outcomes with use of denosumab	Type: evidence-based, benefits outweigh harms Evidence quality: intermediate Strength of recommendation: moderate
Recommendations Unchanged From 2017 CCO-ASCO Guideline	
For purposes of adjuvant bisphosphonate use, the definition of menopause should include both natural menopause (at least 12 months of amenorrhea before initiation of chemotherapy or endocrine therapy) and menopause induced by ovarian ablation or suppression (but not the cessation of menses because of chemotherapy alone). In people age ≤ 60 years with a previous hysterectomy and ovaries left in place, luteinizing hormone, follicle-stimulating hormone, and serum estradiol should be in the postmenopausal range and measured before initiation of any systemic therapy to receive adjuvant bisphosphonates	
A dental assessment is recommended, where feasible, before commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with before starting treatment, if possible. Patients should be informed of the risk of developing ONJ, especially with tooth extractions and other invasive dental procedures. Patients should inform their dental practitioner of their treatment. Patients with suspected ONJ should be referred to a dental practitioner with expertise in treating this condition. Recent guidelines or position papers by groups such as the International Task Force on Osteonecrosis of the Jaw, the American Association of Oral and Maxillofacial Surgeons, and the American Dental Association should be consulted.	
Patients should have serum calcium measured before starting treatment. Patients receiving intravenous bisphosphonates (zoledronic acid) should be monitored for renal function before starting this treatment, and for serum calcium and increase in serum creatinine throughout the treatment period.	
Calcium and vitamin D supplementation is recommended unless otherwise contraindicated. Oral bisphosphonates and calcium should not be taken concurrently; several monographs suggest an interval of at least 2 hours to allow for maximum absorption.	
Symptoms such as ocular pain or loss of vision may be because of serious inflammatory conditions such as uveitis or scleritis and should be promptly evaluated by an ophthalmologist	

Abbreviations: CCO, Cancer Care Ontario; HER2, human epidermal growth factor receptor 2; OH, Ontario Health; ONJ, osteonecrosis of the jaw; OS, overall survival.

ASCO guideline development methods include a systematic review, interpretation of the evidence, drafting of recommendations, and internal review by content and methodology experts. The PEBC is an initiative of the Ontario provincial cancer system, OH (CCO).

The Expert Panel searched the Medline, Embase, and PubMed databases to identify any additional randomized clinical trials (RCTs) and meta-analyses that addressed the focused update's three main clinical questions. A targeted systematic literature review was conducted to identify articles on the PREDICT online prognostication and treatment benefit tool. The electronic searches were supplemented by articles identified by Expert Panel members and by reviews of the bibliographies of relevant articles. The Methodology Manual available at www.asco.org/guideline-methodology provides additional information about the guideline update approach. Additional information about the results of the updated literature search and search strategy strings is reported in the Data Supplement (online only).

The Expert Panel met twice by teleconference to consider the evidence for each of the 2021 recommendations; the Panel cochairs held teleconferences that included

discussions with all Panel members to review the draft recommendations. The guideline was circulated in draft form to the Expert Panel. The entire Expert Panel (Appendix Table A1, online only) contributed to the development of the guideline, provided critical review, and finalized the guideline recommendations. The ASCO Evidence-Based Medicine Committee (EBMC) reviews and approves all ASCO guidelines before publication; the PEBC Report Approval Panel approves OH (CCO) guidelines. All funding for the administration of the project was provided by ASCO.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact 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 Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

The initial searches of Medline and Embase (from January 1, 2016, to April 13, 2020) conducted to identify publications that reported on studies addressing the clinical questions yielded a total of 812 abstracts; the search string was drawn from the review completed for the 2016 guideline (Data Supplement). An updated search (from April 1, 2020, to January 28, 2021) yielded an additional 136 abstracts. Articles were selected for inclusion in the systematic review of the evidence if they were phase III randomized controlled trials or meta-analyses of BMAs used in the adjuvant treatment of primary, nonmetastatic breast cancer. Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; or (3) published in a non-English language.

After review of the identified abstracts, three full-text articles were selected for review by the Expert Panel. Quality of Reporting of Meta-analyses (QUOROM) diagrams of the updated searches and the clinical questions are in the Data Supplement. A fourth RCT that met the inclusion criteria compared 2 versus 5 years of zoledronate acid therapy following adjuvant chemotherapy in patients with early breast cancer,[7] was identified by a Panel member after the electronic searches were performed, and was added to the systematic review. The results of the phase III RCTs included in the review are summarized in Table 2. Study quality was formally assessed for the four phase III RCTs identified (Data Supplement). Design aspects related to the individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, and funding sources generally indicating a low to intermediate potential risk of bias for most of the identified evidence. Refer to the Methodology Manual for definitions of ratings for overall potential risk of bias.

FOCUSED UPDATE RECOMMENDATIONS

Clinical Question 1

Which patients with primary breast cancer should be treated with bone-modifying agents?

TABLE 2. Results of the Phase III Randomized Clinical Trials Investigating the Role of Bisphosphonates in Adjuvant Therapy Among Patients With Breast Cancer

Trial Name and Reference	No. of Patients Patient Characteristics	Arms or Comparison	Survival	Recurrence and Other Outcomes	Outcomes Stated in Methods	Notes
ABCSG-18 Gnant et al[5]	N = 3,420 Postmenopausal, early, hormone receptor–positive, receiving nonsteroidal aromatase inhibitors Included proactive screening and monitoring for ONJ	Denosumab (60 mg sc once every 6 months) *v* placebo 500 mg elemental calcium plus at least 400 IU vitamin D recommended	At median 4-year follow-up: DFS HR = 0.816 (95% CI, 0.66 to 1.00), *P* = .051 3-year DFS 93.8% *v* 92.6%; 5-year DFS 88.9% *v* 86.8%; 7-year DFS 83.5% *v* 80.4% Exploratory subgroup analysis DFS: tumors > 2 cm HR = 0.66, *P* = .016; ductal histology HR = 0.79, *P* = .048; ER+/PR+ HR = 0.75, *P* = .013 At median 73 months follow-up: DFS 86% *v* 83.2%, HR = 0.82 (95% CI, 0.69 to 0.98), *P* = .0260 5-year DFS 89.2% *v* 87.3% 8-year DFS 80.6% *v* 77.5% Sensitivity analysis indicated DFS benefit was not changed after accounting for cross-over	Time to first clinical fracture delayed in denosumab group. Risk of fracture HR = 0.5, *P* < .0001; at 36 months: 5% *v* 9.6%; at 84 months: 11.1% *v* 26.2% Reduction similar in patients with normal BMD and with T-score < –1 at start of trial, *P* = .002 Improved BMD at 12 months, 24 months, and 36 months AEs: no difference, 80% *v* 79%; serious AEs 30% *v* 30%, mainly arthralgia and AI-related symptoms AEs because of study drug 80 patients *v* 49 patients 35 potential dental problems, of which 31 suspected ONJ, none met diagnosis after further investigation No cases of atypical femoral fracture were confirmed	Primary: time to clinical fracture Secondary: safety, AEs; BMD, DFS, BMFS, OS	Significant decrease in fractures overall and for subgroups (baseline BMD, age [< 60 years, ≥ 60 years] T stage, N+, N0, ductal, invasive) Note: DFS recommended by IDMC on the basis of only 370 DFS events and therefore needs confirmation Because of dramatic benefit in terms of fractures IDMC recommended patient choice of unblinding with optional start of denosumab (3 years, 7 doses of 60 mg) for patients on placebo; Significant decrease in fractures overall and for subgroups (baseline BMD, age (< 60 years, ≥ 60 years), T stage, N+, N0, ductal, invasive 275 patients in placebo group were then given denosumab DFS from oral presentation Listed by EBCTCG but no data Final analysis including BMFS and OS will take place after end of long-term follow-up in 2020
D-CARE Coleman et al[6]	N = 4,509 Early-stage (stage II-III), high risk of recurrence (N+, T3, or T4)	Denosumab (120 mg sc once per month for 6 months, then once every 3 months for total of 5 years) *v* placebo	At least 5 years of follow-up No significant difference in bone metastasis-free survival: HR = 0.97, (95% CI, 0.82 to 1.14), *P* = .70 DFS: 80% *v* 81%, HR = 1.04 (95% CI, 0.91 to 1.19) overall or in subgroups, no interaction with menopausal status No difference in distant recurrence-free survival: HR = 1.06, (95% CI, 0.92 to 1.21), *P* = .41 or OS: HR = 1.03, (95% CI, 0.85 to 1.25), *P* = .76	Grade ≥ 3 AEs: neutropenia 15% *v* 15%, febrile neutropenia 5% *v* 6%, leukopenia 3% *v* 3% Positively adjudicated ONJ in 122 *v* 4 patients (5% *v* < 1%), treatment-emergent hypocalcemia in 7% *v* 4%; two treatment-related deaths in placebo group (acute myeloid leukemia and depressed level of consciousness) Treatment discontinuation in 904 *v* 807 patients (withdrawn consent, AEs, disease progression, and death)	Primary: BMFS Secondary: DFS, OS, safety	Exclude patients with prior history or current evidence of osteomyelitis or ONJ; active dental or jaw condition which requires oral surgery; planned invasive dental procedure for the course of the study; or nonhealed dental or oral surgery

(continued on following page)

TABLE 2. Results of the Phase III Randomized Clinical Trials Investigating the Role of Bisphosphonates in Adjuvant Therapy Among Patients With Breast Cancer (continued)

Trial Name and Reference	No. of Patients Patient Characteristics	Arms or Comparison	Survival	Recurrence and Other Outcomes	Outcomes Stated in Methods	Notes
SWOG S0307 Gralow et al[4]	N = 6,097; n = 2,262 ZOL, n = 2,268 clodronate, n = 1,567 ibandronate Ibandronate arm discontinued in last 6 months of trial because of discontinuation of pharmaceutical support Stage I-III, adjuvant systemic therapy (exclude patients at such low risk that adjuvant therapy not prescribed) Age > 18 years, median age 53 years with 58% postmenopausal or age ≥ 50 years Dental exam required within 6 months before initiation of treatment	ZOL (4 mg iv once every month × 6 then once every 3 months × 2.5 years) *v* clodronate (1,600 mg/day po for 3 years) *v* ibandronate (50 mg/day po for 3 years) Before random assignment, 73.2% of patients preferred oral formulations	No treatment differences on the basis of age or menopausal status 5-year DFS: 88.3% ZOL *v* 87.6% clodronate *v* 87.4% ibandronate, log-rank $P = .49$ 5-year OS: 92.6% *v* 92.4% *v* 92.9%, log-rank $P = .50$	Grade 3-4 events: 8.8% *v* 8.3% *v* 10.5%; predominantly pain (4.3% *v* 2.7% *v* 4.8%). Oral agents had more gastrointestinal toxicity No difference in bone as first site of recurrence, $P = .93$ ONJ: 1.26% *v* 0.36% *v* 0.77%, $P = .003$ Patients completing 3 years of therapy: 63.2% *v* 57.1% *v* 60.8% Those who completed 3 years' treatment had better DFS than those who did not: HR = 0.68 (95% CI, 0.56 to 0.81), $P < .001$ Fracture rates 7.1% *v* 9.3% *v* 7.4%, $P = .02$; differences mostly in spine Traumatic fractures 1.9% *v* 2.0% *v* 1.7%, $P = .83$	Primary: DFS Secondary: OS, sites of first recurrence, and AEs (ONJ, fractures)	No evidence of difference in efficacy overall or by age, menopausal status, tumor subtype, ER, PR, or HER2 status, nodal status, and systemic treatment Discontinuation because of AEs 10.0% *v* 17.0% *v* 17.2% Survival in all arms was higher than expected (87.8% actual *v* 80% DFS expected) and therefore power was lower than planned
SUCCESS A (treatment duration analysis) Friedl et al[7]	N = 2,987 5-year arm: n = 1,540; 2-year arm: n = 1,447 Primary invasive breast cancer; node-positive or high-risk node-negative Adjuvant therapy before second random assignment for zoledronic acid duration (3 × FEC, then three cycles of docetaxel ± gemcitabine; RT for all BCS and most mastectomy [multicentric, > 3 cm, 4+ positive nodes]), as well as endocrine therapy for 5 years if hormone receptor–positive Both premenopausal and postmenopausal patients included	5 years of zoledronate treatment (4 mg iv once every 3 months for 2 years, followed by 4 mg iv once every 6 months for 3 years) *v* 2 years of zoledronate treatment (4 mg iv once every 3 months for 2 years)	2-year landmark DFS (median follow-up, 35.4 months): HR = 0.97 (95% CI, 0.76 to 1.25), $P = .83$ 2-year landmark OS (median follow-up, 36.0 months): HR = 0.98 (95% CI, 0.67 to 1.42), $P = .90$ 2-year landmark DDFS: HR = 0.86, (95% CI, 0.65 to 1.18), $P = .38$	Bone recurrence-free survival: HR = 0.80, (95% CI, 0.47 to 1.38), $P = .43$ AEs, any grade, 5 years zoledronate: 46.2%; 2 years zoledronate: 27.2%, $P < .001$ AEs, grade 3-4, 5-year zoledronate: 7.6%; 2-year zoledronate: 5.1%, $P = .006$	Primary: DFS Secondary: OS, DDFS, skeletal-related AEs	No significant difference in survival outcomes between 5-year and 2-year arms, including DFS, OS, and DDFS AEs occurred more frequently in the 5 years arm

Abbreviations: AEs, adverse events; AI, aromatase inhibitor; BCS, breast-conserving surgery; BMD, bone mineral density; BMFS, bone metastasis-free survival; DDFS, distant disease-free survival; DFS, disease-free survival; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; ER, estrogen receptor; FEC, fluorouracil, epirubicin, and cyclophosphamide; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IDMC, independent data monitoring committee; iv, intravenously; LABC, locally advanced breast cancer; ONJ, osteonecrosis of the jaw; OS, overall survival; pCR, pathologic complete response; po, per os (orally); PR, progesterone receptor; RT, radiation therapy; sc, subcutaneously; ZOL, zoledronic acid.

Recommendation 1.1. Adjuvant bisphosphonate therapy should be discussed with all postmenopausal patients (natural or therapy-induced) with primary breast cancer, irrespective of hormone receptor status and human epidermal growth factor receptor 2 (HER2) status, who are candidates to receive adjuvant systemic therapy. Adjuvant bisphosphonates, if used, are not substitutes for standard anticancer modalities.

The benefit of adjuvant bisphosphonate therapy will vary depending on the underlying risk of recurrence and is associated with a modest improvement in overall survival (OS). The NHS PREDICT tool[8] provides estimates of benefit of adjuvant bisphosphonate therapy and may aid in shared decision making.

Factors influencing the decision to recommend adjuvant bisphosphonate use that should be weighed in the discussion with patients should include the patient's risk of recurrence, the risk of side effects, financial toxicity, drug availability, patient preferences, comorbidities, and life expectancy (type: informal consensus; evidence quality: intermediate; strength of recommendation: moderate).

Literature review and analysis. The updated recommendations that address which patients with primary breast cancer should be treated with BMAs are largely unchanged from 2017. As noted in the 2017 joint guideline,[1] although the Oxford Overview (Early Breast Cancer Trialists' Collaborative Group [EBCTCG]) analysis of individual patient data[3] found statistically significant survival benefits—with reductions in recurrence, distant recurrence, and breast cancer mortality—for bisphosphonates in all subgroups of postmenopausal patients, the absolute benefit was small and depended on the underlying risk of recurrence. The joint Panel thus continues to recommend that adjuvant bisphosphonate therapy should be discussed with all postmenopausal patients with primary breast cancer who are candidates to receive adjuvant systemic therapy. This discussion should take into account the patient's risk of recurrence, risk of side effects, financial toxicity, drug availability, patient preferences, comorbidities, and life expectancy.

For this update, the Expert Panel's recommendation also highlights the potential value of the NHS PREDICT tool[8] as an aid to making a decision about bisphosphonate therapy among patients with nonmetastatic invasive breast cancer. PREDICT is a widely used online prognostication tool that can be used to estimate treatment benefit for patients with early-stage breast cancer.[12] The tool provides estimated 5-, 10-, and 15-year OS rates with and without the addition of various adjuvant treatment options, including bisphosphonate therapy. The benefit of these agents, although modest in magnitude, is in line with the benefit observed with other commonly used breast cancer therapies in the adjuvant setting.

This is a consensus recommendation. PREDICT is the only tool of which the Panel is aware that provides estimates of the benefit of adjuvant bisphosphonate therapy on the basis of disease (eg, tumor size and grade) and patient characteristics (age at diagnosis and menopausal status). The original PREDICT model has been validated and updated since 2010 to include additional elements.[13] The bisphosphonates treatment option, applicable only to those who are postmenopausal, was added in Version 2.1 of the tool, with the reduction in mortality rate after bisphosphonate therapy on the basis of the results of the EBCTCG meta-analysis.[3] The NHS PREDICT tool may help clinicians and their patients weigh the potential benefits of adjuvant bisphosphonate therapy, but the tool does not include a risk of toxicity.

Clinical interpretation. Many guidelines and expert consensus statements have advocated for the use of adjuvant bisphosphonate therapy in postmenopausal people with early-stage breast cancer.[1,14-16] However, it appears that the actual use of adjuvant bisphosphonates is lower than what might be expected following the 6+ years since the EBCTCG meta-analysis.[3] The 2019 St Gallen Panel voted 83.7% in favor of the use of adjuvant bisphosphonates in postmenopausal people. Yet, when asked if the panel was routinely using adjuvant bisphosphonates clinically, only 42.6% responded yes.[15] Similar findings have come from surveys. McGee et al[17] reported although only 13.2% of surveyed clinicians recommend the use of adjuvant bisphosphonate therapy in all patients with natural or treatment-induced menopause, 77.4% of clinicians recommended use for those with natural or treatment-induced menopause and high-risk disease. Although patient-reported preference for oral bisphosphonate therapy was noted in S0307, the McGee et al physician survey data indicate that 88.7% of clinicians prefer use of zoledronic acid.[17] In Ontario, zoledronic acid is publicly funded in the adjuvant setting. Despite guideline recommendations and survey data demonstrating support of adjuvant bisphosphonate use, in a separate publication, McGee et al[18] report that actual use of adjuvant bisphosphonate therapy is less than what appears to be recommended.

There are several hypotheses on why clinicians, including many on the ASCO Expert Panel, do not consistently use adjuvant bisphosphonates in their clinics as recommended by the ASCO 2017 guideline.[1] These range from questioning the validity of the data, questioning the mechanism of action by which bisphosphonates appear to have an impact on the basis of menopausal status, the lack of data on clinical or biologic features making a patient more or less likely to benefit, access to the agents where the data are strongest (clodronate, ibandronate, or zoledronic acid), uncertainty about the logistics of therapy (time to start, dosing intervals, and duration of therapy), and concern for toxicities.[17]

Some[19] have questioned if the small absolute reduction in risks of distant recurrence and cancer mortality is sufficient to warrant treating all postmenopausal people (see also

https://ascopost.com/issues/august-10-2017/one-size-may-not-fit-all-thoughts-on-the-new-adjuvant-bisphosphonate-guideline-for-early-stage-breast-cancer). Indeed, McGee et al[17] reported that 9% of survey responders indicated that they did not feel that the benefits to patients with breast cancer are clinically meaningful. However, it appears that many clinicians see the value of bisphosphonate for those with a high risk of breast cancer recurrence or death. Desnoyers et al[19] make an argument for using adjuvant bisphosphonates only in postmenopausal people with a very high risk of breast cancer recurrence and suggest that guidelines revisit the recommendations for adjuvant bisphosphonates. The clinician survey by McGee et al demonstrates that at a 10-year risk of > 10% for breast cancer recurrence or a > 5% for mortality, most clinicians would consider use of an adjuvant bisphosphonate.[17] In an editorial, Stopeck[20] stated that, for her own practice, she discusses adjuvant bisphosphonate therapy with all postmenopausal people in the adjuvant setting who have a risk of distant recurrence equal to or > 10% or osteopenia. Acknowledging that the strongest data are for zoledronic acid twice yearly, or the oral agents not available in the United States (clodronate 1,600 mg daily or ibandronate 50 mg daily), the editorialist acknowledged the potential to use a bisphosphonate at the same dosing schedule used when prescribing for treating osteoporosis when standard adjuvant regimens are not accessible. In the United States, zoledronic acid is not labeled for adjuvant breast cancer therapy, clodronate is not available, and ibandronate is only available in osteoporosis doses, which was not the dosing used in adjuvant breast cancer studies. This approach seems well worth formally investigating through clinical trials; the meta-analysis did not identify a preferred regimen.

Clinical Question 2

Which bisphosphonates are recommended for breast cancer adjuvant therapy and what doses, durations of administration, time to initiate treatment, and routes (intravenous or oral) are optimal? (This guideline does not address general bone health in patients with breast cancer; see the ASCO osteoporosis guideline.[10])

Recommendation 2.1. The Panel supports starting bisphosphonate therapy early, consistent with the points outlined in the parent CCO-ASCO guideline. Many studies initiated bisphosphonate within 3 months of definitive surgery or within 2 months of completion of adjuvant chemotherapy; this is a consensus recommendation. The therapeutic options, listed alphabetically, with the strongest supporting data include:

- oral clodronate (1,600 mg daily for 2-3 years)
- oral ibandronate (50 mg daily for 3 years)
- zoledronic acid; dosing regimens as per the protocols of the clinical trials (including the option of 4 mg once every 6 months for 3 years or dosing 4 mg once every 3 months for 2 years)

Patient preference should be factored into the choice of adjuvant bisphosphonate therapy. Access to adjuvant bisphosphonate therapy may currently limit choice of agent depending on jurisdiction (type: evidence-based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate).

Literature review and analysis. The systematic review identified one article that informs the question of which bisphosphonates are recommended for breast cancer adjuvant therapy and what doses, duration of administration, and routes (intravenous or oral) are optimal. The SWOG/Alliance/Canadian Cancer Trials Group/ECOG-ACRIN/NRG Oncology study S0307, an open-label phase III RCT,[4] compared the efficacy of three bisphosphonates in patients with stage I-III breast cancer. S0307 randomly assigned a total of 6,097 patients to 3 years of oral ibandronate (50 mg daily; n = 1,567), oral clodronate (1,600 mg daily; n = 2,268), or intravenous zoledronic acid (dosed once monthly for 6 months, then dosed once every 3 months; n = 2,261). There was no placebo or untreated control arm. Disease-free survival (DFS) was the primary end point of the trial; OS was a secondary end point.

The trial outcomes are summarized in Table 2. There were no differences among the three treatment arms in either 5-year DFS (log-rank P = .49) or 5-year OS (log-rank P = .50). The 5-year DFS was 88.3% among patients who received zoledronic acid (95% CI, 86.9 to 89.6); 87.6% among patients who received clodronate (95% CI, 86.1 to 88.9); and 87.4% among patients who received ibandronate (95% CI, 85.6 to 88.9). Among patients who received zoledronic acid, 5-year OS was 92.6% (95% CI, 91.4 to 93.6); it was 92.4% among those who received clodronate (95% CI, 91.2 to 93.5); and it was 92.9% among those who received ibandronate (95% CI, 91.5 to 94.1). No efficacy differences were observed across age- and tumor type–defined patient subgroups. There was also no difference seen among treatment arms in the outcome of bone as first site of recurrence (P = .93).

The incidence of grade 3-4 adverse events (AEs) was 10.5% in patients who received ibandronate; 8.8% in patients who received zoledronic acid; and 8.3% in patients who received clodronate. Pain was the principal toxicity. The incidence of grade 3 or 4 pain was higher with zoledronic acid (4.4%) and ibandronate (4.8%) versus clodronate (2.7%). More patients who received the oral agents of clodronate (2.3%) and ibandronate (2.2%) reported grade 3 or 4 gastrointestinal pain compared with patients who received zoledronic acid (0.47%). The rate of osteonecrosis of the jaw (ONJ) was higher in patients treated with zoledronic acid (1.26%) compared with ibandronate (0.77%) and clodronate (0.36%; exact Fisher P = .003). Across agents, just 60.3% of patients completed 3 years of therapy. The proportion of patients who stopped treatment because of toxicity was 10% in the zoledronic acid arm, 17% in the clodronate arm, and 17.2% in the ibandronate arm.

The systematic review identified one article that addressed the optimal duration and schedule of administration of zoledronic acid. Friedl et al[7] recently reported on an analysis of data from SUCCESS A, an open-label, prospective randomized phase III clinical trial, that compared 2 versus 5 years of treatment with zoledronic acid after adjuvant chemotherapy among patients with early-stage breast cancer at high risk of recurrence. SUCCESS A randomly assigned 2,987 premenopausal (n = 1,263) or postmenopausal (n = 1,724) people to receive zoledronic acid for either 5 years (dosed 4 mg intravenously once every 3 months for 2 years, then dosed once every 6 months for 3 years) or for 2 years (dosed 4 mg intravenously once every 3 months). The primary end point of the trial was DFS; secondary end points of the trial included OS, distant DFS, and incidence of skeletal-related AEs. At a median of 5 years after the start of zoledronic acid, there were no statistically significant differences observed between the 2- and 5-year treatment arms in DFS (hazard ratio [HR], 0.97; 95% CI, 0.75 to 1.25; $P = .81$), OS (HR, 0.98; 95% CI, 0.67 to 1.42; $P = .90$), or distant DFS (HR, 0.87; 95% CI, 0.65 to 1.18; $P = .38$). In terms of the incidence and severity of AEs, 5 years of treatment with zoledronic acid was associated with a higher frequency of AEs versus with 2 years of treatment. This was the case for all AEs (46.2% in the 5-year arm *v* 27.2% in the 2-year arm; $P = .001$); for grade 3 or 4 AEs only (7.6% *v* 5.1%; $P = .006$); and for the two most common AEs, in particular, musculoskeletal events, bone pain (8.3% *v* 3.7%), and arthralgia (5.1% *v* 3.1%). ONJ was more common in the longer treatment duration group (11 cases *v* 5 cases).

Clinical interpretation. These two trials help inform clinical decision making about the type and duration of adjuvant bisphosphonate therapy, but they do not address the overall benefit of adjuvant bisphosphonates because neither trial included a placebo control arm. The S0307 trial did not show any efficacy outcome differences among the three regimens. The ibandronate arm of the study was closed early, and the event rate was lower than initially estimated; thus, the trial may have been underpowered to identify differences among the agents.[21] The incidence of serious toxicity was low in all treatment arms. Although most patients indicated a preference for oral therapy before random assignment, fewer patients receiving zoledronic acid discontinued therapy because of side effects than those randomly assigned to oral agents. Finally, as pointed out by the investigators and in the accompanying editorial,[21] access to oral agents is limited in the United States.

The SUCCESS A trial[7] compared two schedules and durations of adjuvant zoledronic acid therapy, and demonstrated that a shorter duration (2 years) of therapy was as good as extended 5-year treatment, and was associated with less toxicity. The trial participants were patients with high-risk breast cancer, who were initially randomly assigned to different chemotherapy regimens (outcomes not yet reported). As noted,[19] the low event rate and dropout of patients before the random assignment to bisphosphonate, among other factors, may have made this study underpowered to detect a true difference between treatment arms.

These two studies considered together, along with the results of the EBCCTG overview analysis,[3] provide guidance to clinicians who have recommended adjuvant bisphosphonates to their patients. A 2- to 3-year schedule of intravenous zoledronic acid remains the most practical option in the United States; this shortened duration is a change from the original ASCO guideline[1] in light of the SUCCESS A trial findings. Where oral options are available, therapy with clodronate (2-3 years) or ibandronate (3 years) can be used, and access to these oral agents should be expanded as they are effective and preferred by patients.[4]

Clinical Question 3

What is the role of the bone-modifying agent, denosumab, as an adjuvant therapy for primary breast cancer?

Recommendation 3.1. The Panel does not recommend the use of adjuvant denosumab (type: evidence-based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate).

Key evidence. Two phase III studies of adjuvant denosumab did not show a consistent reduction of breast cancer recurrence in any subset of patients with early-stage breast cancer. The larger study, D-CARE, did not show improvement in cancer outcomes with use of denosumab.

Literature review and analysis. The systematic review identified two signals in the literature that relate to the question of the role of denosumab in adjuvant therapy for primary breast cancer (Table 2). Gnant et al[5] reported the results of the double-blind, placebo-controlled, phase III ABCSG-18 study that assessed the effect of denosumab on the secondary end point of DFS among postmenopausal people with hormone receptor–positive nonmetastatic breast cancer who had received an adjuvant aromatase inhibitor. Patients were randomly assigned to receive either subcutaneous denosumab (60 mg; n = 1,711) or placebo (n = 1,709) every 6 months during aromatase inhibitor therapy. Planned duration of treatment was 5 years; median follow-up duration was 73 months (range, 58-95 months). The analysis was descriptive. The results revealed a statistically significant DFS benefit of denosumab (HR, 0.82; 95% CI, 0.69 to 0.98). DFS at 5 years in the denosumab group was 89.2% (87.6 to 90.8) and 87.3% (85.7 to 89.0) in the placebo group; at 8 years of follow-up, DFS in the denosumab group was 80.6% (78.1 to 83.1) and 77.5% (74.8 to 80.2) in the placebo group. Thus, the absolute differences in DFS at 5 years and 8 years were, respectively, about two percentage points and three percentage points; and due to improvement in distant metastases or second primary cancer (not histologically verified) or to histologically verified second nonbreast cancer primary.

A similar number of treatment-emergent AEs was observed in the two groups: 1,367 (521 serious AEs) in the denosumab

group and 1,339 (515 serious AEs) in the placebo group. Among the serious AEs reported, the most common were osteoarthritis (3.6% of patients in the denosumab group *v* 3.4% of patients in the placebo group); meniscus injury (1.3% *v* 1.4%); and cataract (0.9% *v* 1.7%). No cases of ONJ that satisfied diagnostic criteria were recorded.

D-CARE, a double-blind, randomized, placebo-controlled, phase III trial, which defined its study participants as women, evaluated the effects of denosumab in combination with standard-of-care adjuvant or neoadjuvant chemotherapy with the primary outcome measurement of bone metastasis-free survival in participants with stage II or III breast cancer.[6] The trial randomly assigned patients to receive either denosumab (120 mg; n = 2,256) or placebo (n = 2,253) subcutaneously dosed once about every 4 weeks for approximately 6 months, and then dosed once every 12 weeks for a total duration of 5 years (median follow-up in the placebo group was 67.3 months and was 67.2 months in the denosumab group). The primary outcome of the trial was a composite end point of bone metastasis-free survival, defined as the time from random assignment to the first observation of bone metastasis, with or without disease recurrence, at other anatomical sites.

Intention-to-treat analysis revealed no difference in bone metastasis-free survival between the denosumab and placebo groups (median not reached in either group; HR, 0.97; 95% CI, 0.82 to 1.14; $P = .70$). In safety analyses, neutropenia, febrile neutropenia, and leukopenia were the most common grade 3 or worse treatment-emergent AEs observed. Among patients who received at least one dose of denosumab, 340 of 2,241 (15%) reported neutropenia versus 328 of 2,218 (15%) patients in the placebo group; 5% of patients who received denosumab reported febrile neutropenia versus 6% of patients in the placebo group; and 3% of patients who received denosumab reported leukopenia versus 3% of patients in the placebo group. Positively adjudicated ONJ occurred in 122 of 2,241 (5%) patients in the denosumab group and in four of 2,218 (< 1%) patients in the placebo group.

Clinical interpretation. The Panel carefully considered the evidence regarding the use of adjuvant denosumab, recognizing that it is widely used for maintenance of bone health in oncology patients, and that there is conflicting evidence from the two largest randomized trials of its impact on survival outcomes. The previous version of this guideline[1] did not endorse adjuvant denosumab as an adjuvant treatment because the evidence from the ABCSG-18 trial, although promising, was preliminary (in abstract form only) and appeared to confer a similar benefit as adjuvant bisphosphonates, for which there were greater supporting data. Since then, the ABCSG-18 trial results have been fully published and are summarized in the literature review and analysis section. In postmenopausal patients receiving adjuvant aromatase inhibitors, denosumab 60 mg dosed once every 6 months reduced bone fractures and improved DFS, the latter largely because of a reduction in distant recurrence events. Importantly, the treatment was well tolerated at this dose, with acceptable toxicity and no increase in ONJ. However, because of the dramatic reduction in fractures, ABCSG-18 underwent early unmasking and revisions to the analysis plan of the oncologic end points. The larger D-CARE study evaluated denosumab given at higher dose and greater frequency. As reported, there was no improvement in the primary outcome, bone metastasis-free survival, associated with denosumab therapy. There was also an unacceptably high risk of ONJ.

Given the inconsistent results from these two studies, the significant toxicity seen with denosumab when used at the higher dose, and the evidence supporting the safety and efficacy of adjuvant bisphosphonates, the Panel did not recommend the use of denosumab to reduce breast cancer recurrence. Additionally, data from trials directly comparing denosumab with bisphosphonates as adjuvant therapy are lacking.

GUIDELINE IMPLEMENTATION

Discussing the potential anticancer impact of adjuvant bisphosphonate therapy with postmenopausal people with early-stage breast cancer may be coordinated with the overall medical oncology discussion of adjuvant systemic therapy. As highlighted previously, ASCO's male breast cancer guideline[22] recommends that men with early-stage breast cancer should not be treated with BMAs to prevent recurrence but could still receive these agents to prevent or treat osteoporosis. Tools such as the NHS Predict[12] illustrate estimates associated with a wide range of adjuvant systemic therapy. If using such a tool is a clinician's practice, reviewing the estimated added benefit of adjuvant bisphosphonate therapy can be put into the context of other systemic therapies under consideration.

If an adjuvant bisphosphonate is to be used, the data best support the agents outlined in Recommendation 2.1. However, for various reasons, these agents are not uniformly accessible. In the United States, neither clodronate 1,600 mg daily nor ibandronate 50 mg daily is US Food and Drug Administration–approved or available. Zoledronic acid is available, but the 4 mg once every 6 months dosing regimen is not a US Food and Drug Administration–labeled dose or indication. Hence, not all insurance companies view zoledronic acid as covered by the patient's insurance policy. As outlined in the editorial by Stopeck,[20] some clinicians may use osteoporosis management dosing and scheduling of bisphosphonates. The benefits identified in the EBCTCG meta-analysis[3] were seen across the bisphosphonates; however, the volume of supporting data was greatest for clodronate and zoledronic acid.

GAPS IN THE LITERATURE AND FUTURE RESEARCH DIRECTIONS

Several important clinical questions remain unanswered that could further clarify the role of bone-modifying agents

in the adjuvant setting for patients with breast cancer. Additional research to identify the patient subgroups that might derive the most benefit is needed, including those examining biomarkers, for example, circulating tumor cells and *MAF* amplification.[23] One outstanding question concerns whether some premenopausal people may also benefit. It is not clear at all if some regimens (drug, dose, interval, and duration) are better suited for particular patients. Studies are needed as well to identify which patients may be at increased risk from toxicities (including financial). Further research may also wish to investigate the value of multigene profiling for predicting the benefit of adjuvant bisphosphonate therapy.

Given the clinical overlap between bone health and prevention of bone metastases, further guidance on whether an intensified bisphosphonate regimen is needed for anticancer outcomes, and if so, which patients will benefit from it. In the metastatic setting, the dosing and schedule of these agents have been successfully de-escalated, and this approach should be further explored in early-stage disease. Indeed, patient survey data indicate an interest in such trials.[18] Additionally, carefully designed studies further investigating the potential anticancer effects of denosumab, perhaps directly compared with bisphosphonates in early-stage breast cancer, would be of interest. Finally, research is needed to address what long-term effects may occur to skeletal health among younger people treated with ovarian suppression and a bisphosphonate, and what counseling they need to receive regarding future pregnancies and the potential risk of bisphosphonate recirculating and affecting fetal development.

OPEN COMMENT AND EXTERNAL REVIEW

The draft recommendations were released to the public for open comment from July 9, 2021, through July 23, 2021. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree, see comments" were captured for each of the three proposed recommendations with 11 written comments received across draft recommendations. A total of 82% of the respondents (9 of 11) either agreed or agreed with slight modifications with the recommendations and 18% (2 of 11) of the respondents disagreed with selected recommendations and offered comments, suggested revisions. The Expert Panel reviewed comments from all sources and determined whether to maintain the original draft recommendations; revise with minor language changes; or consider major recommendation revisions. All changes were incorporated before EBMC final review and approval.

ADDITIONAL RESOURCES

Additional information including a Data Supplement, evidence tables, and clinical tools and resources can be found at www.asco.org/breast-cancer-guidelines. Patient information is available there and at www.cancer.net.

RELATED ASCO GUIDELINES

- Patient-Clinician Communication[24] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Management of Osteoporosis in Survivors of Adult Cancers With Nonmetastatic Disease[10] (http://ascopubs.org/doi/10.1200/JCO.19.01696)
- Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline[11] (http://ascopubs.org/doi/10.1200/JCO.19.01186)

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[25] Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between gender and anatomy.[26-28] With the acknowledgment that ASCO guidelines may affect the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data on the basis of gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/breast-cancer-guidelines.

EQUAL CONTRIBUTION

A.E. and C.H.V.P. were Expert Panel cochairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02647.

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ACKNOWLEDGMENT

The Expert Panel wishes to thank the EBMC reviewers, Drs Shilpi Gupta and Pavan S. Reddy, and the Evidence-Based Medicine Committee for their thoughtful reviews and insightful comments on this guideline. The Expert Panel is grateful to Drs E. Claire Dees, Monica Fornier, Asha Karippot, Tara Kaufmann, Lisa Law, Mark Robson, Gregory Vidal, and Ms Jamie LaScala and Ms Dorinda (Dee) Sparacio for participating in external review of the draft practice recommendations. Finally, the Expert Panel wishes to thank Dr Ash Alpert and Ms Catherine Forrest for reviewing the draft manuscript for use of gender-inclusive language consistent with ASCO's policy for guidelines that was developed by Spence Adams, Ash Alpert, Charlie Manzano, Lexis Rivers, and Roman Ruddick.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: ASCO-OH (CCO) Guideline Update

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Patents, Royalties, Other Intellectual Property: UpToDate

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: ASCO-OH (CCO) Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
Andrea Eisen, MD (cochair)	Sunnybrook Odette Cancer Center; Ontario Health, Toronto, ON, Canada	Medical oncology
Catherine H. Van Poznak, MD (cochair)	University of Michigan, Ann Arbor, MI	Medical oncology
Melissa K. Accordino, MD	Columbia University HICCC, New York, NY	Medical oncology/health services research
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Melissa S. Dillmon, MD	Harbin Clinic LLC, Rome, GA	Medical oncology
Stella D'Oronzo, MD, PhD	University of Bari 'Aldo Moro', Bari, Italy	Medical oncology
Elizabeth S. Frank, EdM	Brookline, MA	Patient representative
Sigrun Hallmeyer, MD	Advocate Lutheran General Hospital, Prospect Heights, IL	Medical oncology
Issam Makhoul, MD	University of Arkansas for Medical Sciences, Little Rock, AR	Medical oncology
Beverly Moy, MD	Massachusetts General Hospital, Boston, MA	Medical oncology
Alia Thawer, MD	Sunnybrook Odette Cancer Center; Ontario Health, Toronto, ON, Canada	Pharmacy
Joy Y. Wu, MD, PhD	Stanford University, Palo Alto, CA	Endocrinology
Glenn G. Fletcher, MSc	McMaster University, Hamilton, ON, Canada	Staff/health research methodologist
Mark R. Somerfield, PhD	American Society of Clinical Oncology (ASCO), Alexandria, VA	Staff/health research methodologist

Abbreviations: CCO, Cancer Care Ontario; OH, Ontario Health.

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of Evidence	
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (eg, balance of benefits *v* harms) and further research is very unlikely to change either the magnitude or direction of this net effect
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or direction of this net effect
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available
Strength of recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a. strong evidence for a true net effect (eg, benefits exceed harms); b. consistent results, with no or minor exceptions; c. minor or no concerns about study quality; and/or d. the extent of panelists' agreement Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a. good evidence for a true net effect (eg, benefits exceed harms); b. consistent results with minor and/or few exceptions; c. minor and/or few concerns about study quality; and/or d. the extent of panelists' agreement Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a. limited evidence for a true net effect (eg, benefits exceed harms); b. consistent results, but with important exceptions; c. concerns about study quality; and/or d. the extent of panelists' agreement Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation