Guideline 1-22-A Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC)/Ontario Health (Cancer Care Ontario) in Collaboration with the American Society of Clinical Oncology (ASCO)

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

Focused Update (2022)[1]: A. Eisen, M.R. Somerfield, M.K. Accordino, P.S. Blanchette, M.J. Clemons, S. Dhesy-Thind, M.S. Dillmon, S. D'Oronzo, G.G. Fletcher, E.S. Frank, S. Hallmeyer, I. Makhoul, B. Moy, A. Thawer, J.Y. Wu, and C.H. Van Poznak

Version 1 (2016): Sukhbinder Dhesy-Thind, Glenn G Fletcher, Phillip S Blanchette, Mark J Clemons, Sonal Gandhi, Rasna Gupta, Mihaela Mates, Ted Vandenberg, and the Adjuvant Bisphosphonates in Breast Cancer Guideline Development Group[2]

Report Date: Version 1 September 30, 2016, Version 2 (with revisions) July 14, 2022

This guideline should be used in conjunction with the ASCO-OH(CCO) Focused Update published in the Journal of Clinical Oncology in 2022, available at https://ascopubs.org/doi/full/10.1200/JCO.21.02647. The focused update was prompted by the full publications of the SWOG S0307, D-CARE, ABCSG-18, and Success A trials. On the basis of a review of this evidence, the Update Panel revisited recommendations concerning the choice and dose of bisphosphonates, the use of denosumab, and patient selection. This document consists of the original 2016 guideline recommendations and systematic review, with the recommendations annotated to indicate major changes from the 2022 update.

[1] Eisen A, Somerfield MR, Accordino MK, Blanchette PS, Clemons MJ, Dhesy-Thind S et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: ASCO-OH (CCO) guideline update. J Clin Oncol. 2022 Mar 1;40(7):787-800

[2] A full list of participants is given in Appendix 1.

An assessment conducted in November 2025 deferred the review of Guideline 1-22-A Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 1-22-A Version 2 contains 5 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/37761

Section 1:	Recommendations
Section 2:	Recommendations and Key Evidence
Section 3:	Guideline Methods Overview
Section 4:	Evidence Review
Section 5:	Internal and External Review

For information about this document, please contact Dr Andrea Eisen or Dr Sukhbinder Dhesy-Thind, the lead authors, through the PEBC via:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the OH(CCO) website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style)

Dhesy-Thind S, Fletcher GG, Blanchette P, Clemons M, Gandhi S, Gupta R, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer. Toronto (ON): Cancer Care Ontario 2016 Sep 30 with revisions 2022 July14 (Version 2). Program in Evidence-Based Care Guideline No.: 1-22.

Publications Related to this Report

Eisen A, Somerfield MR, Accordino MK, Blanchette PS, Clemons MJ, Dhesy-Thind S et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: ASCO-OH (CCO) guideline update. J Clin Oncol. 2022 Mar 1;40(7):787-800. DOI:10.1200/JCO.21.02647.

Dhesy-Thind S, Fletcher GG, Blanchette P, Clemons M, Dillmon MS, Frank ES, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 35, 2017. DOI:10.1200/JCO.2016.70.7257I

Copyright

Disclaimer

Disclaimer ASCO

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

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, the systematic review, and the guideline development process, see the Full Report.

GUIDELINE OBJECTIVE

To make recommendations regarding the use of bisphosphonates and other bone-modifying agents as adjuvant therapy in patients with breast cancer.

TARGET POPULATION

Patients with early or locally advanced (non-metastatic) breast cancer.

INTENDED USERS

Medical oncologists and other clinicians involved in post-surgical (adjuvant) treatment of patients with breast cancer.

RECOMMENDATIONS AND KEY EVIDENCE

2022 Focused Update Modifications

The first version of this guideline was published on September 30, 2016. At that time, the SWOG S0307, D-CARE, and ABCSG-18 trials had only preliminary data and it was acknowledged that recommendations might need to be revised after completion of these trials. Based on full publication of these trials in 2019-2020, plus the Success A trial in 2021, a group was convened to provide a focused update of the recommendations. The update was published in 2022 in the Journal of Clinical Oncology (JCO) and is available at https://ascopubs.org/doi/full/10.1200/JCO.21.02647. Due to the focused or targeted nature of the update, the four new publications were not integrated with the full 2016 review and therefore the JCO publication should be read in conjunction with the original guideline and systematic review.

Modifications resulting from the focused update are indicated by blue italicized text in Sections 1 and 2. No changes have been made to the other parts of the document. Comments due to new data subsequent to the update are highlighted.

Preamble and Implementation Considerations

The focus of this guideline is on the relapse and survival benefit of bone-modifying agents in non-metastatic breast cancer. This guideline acknowledges there is clear evidence for use of bone-modifying agents such as bisphosphonates to reduce the risk of fragility fractures in at-risk populations (such as those with diagnosed low bone mass), and to treat

metastatic cancer to the bone. In addition, it is recognized that in many health care settings, bone-modifying agents such as bisphosphonates may currently be available, approved, and/or funded in specific doses and schedules only for the indications of improving bone mass and for the treatment of bone metastases. As such, the users of this guideline should consider available resources and access, and any other barriers within their local health care settings, to using these treatments as recommended in this guideline for adjuvant breast cancer.

Some of the trials in the included literature review (see Section 4) excluded patients with low bone mineral density (BMD), previous or current bisphosphonate administration, or history of fractures, and thus do not specifically address patients at high risk of fracture, other than due to other systemic treatment. Criteria for assessing patients for fracture risk were not evaluated in preparation of this guideline, and other guidelines such as those by Osteoporosis Canada [1], the National Osteoporosis Guideline Group (United Kingdom) [2] [3], and the National Osteoporosis Foundation (United States) [4], as well as the recent review of these by Black and Rosen [5], should be consulted. None of the recommendations in this guideline are meant to restrict such use of bone-modifying agents in these situations, although they may influence the specific bisphosphonate selected when administered for both bone health and adjuvant therapy. In patients prescribed these agents as adjuvant therapy there may be an additional benefit on BMD.

It should be noted that no attempt has been made to list all potential adverse effects of drugs mentioned in this guideline, or contraindications to their use. Drug monograms, formulary, or other prescribing information should be consulted. Osteonecrosis of the jaw (ONJ) is discussed in detail in the following recommendations and systematic review. Post-marketing surveillance has reported rare adverse effects such as inflammatory eye reactions, renal toxicity, and atypical femoral fractures. The risk of renal toxicity 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 but warrant prompt evaluation by an ophthalmologist [6-8]. Treatment is commonly with ophthalmic steroids [7,9,10]. Ongoing post-marketing surveillance of rare adverse effects associated with bisphosphonates is recommended.

Recommendation 1
It is recommended that administration of bisphosphonates as adjuvant therapy be considered for postmenopausal[1] patients with breast cancer deemed candidates for adjuvant systemic therapy. The final decision of whether or not to administer bisphosphonates should be made during consultation between the patient and oncologist, taking into account patient and disease characteristics including risk of recurrence, and weighing the potential benefits and risks (adverse effects). *2022 Update: "The NHS PREDICT tool provides estimates of the benefit of adjuvant bisphosphonate therapy and may aid in decision making."*
Qualifying Statements for Recommendation 1
• While the EBCTCG meta-analysis [11] found benefit for bisphosphonates in all subgroups of postmenopausal patients, the absolute benefit was small. For patients with cancers

[1] "Postmenopausal" includes patients premenopausal prior to treatment who have menopause induced by ovarian suppression as detailed in Recommendation 5.

assessed as having low risk of recurrence, the use of bisphosphonates may not result in clinically meaningful effect.

- Considerations in deeming patients at high enough recurrence risk to receive adjuvant systemic therapy may also apply in deciding on bisphosphonate use. The majority of patients (83%) in the meta-analysis had also received adjuvant chemotherapy. Standard clinical and pathologic risk factors and recognized clinical tools may be used where applicable to estimate risk of recurrence and mortality [12,13].
- Risk factors for ONJ and renal impairment should be assessed (see Recommendation 6).
- Patients should receive all other recommended breast cancer treatments including surgery, radiation, and/or systemic therapy (see, for example, the CCO guideline on systemic therapy in early breast cancer) [12].
- There is no information to guide the use of bone-modifying agents for patients receiving systemic adjuvant therapy for completely resected local recurrence.

Recommendation 2

Zoledronic acid and clodronate are the recommended bisphosphonates for adjuvant therapy in breast cancer.

There is need for more information comparing different agents and schedules, and it is recommended that such trials be conducted to establish the utility and optimal administration of other bisphosphonates for adjuvant therapy.

2022 Update: Options recommended are oral clodronate, oral ibandronate, and intravenous zoledronic acid (see update publication for rationale)

Caution: Subsequent to the 2022 update, longer-term follow-up results of TEAM IIb trial results were published and showed no adjuvant benefit for ibandronate, and significantly higher rates of osteonecrosis of the jaw.[2]

Qualifying Statements for Recommendation 2

- Preliminary data from the SWOG S0307 trial [14,15] suggested that clodronate, ibandronate, and zoledronic acid may provide similar DFS and OS benefit. ~~However, as this data has, to date, only been published in abstract form, no definitive recommendations regarding ibandronate can yet be made.~~ Full publication of the SWOG S0307 trial and results of the TEAM IIb (BOOG 2006-04) trial [16] may support adjuvant ibandronate use. *The focused update (based on SWOG S0307[3]) suggested ibandronate may be used;* however subsequent publication of TEAM IIb found no long-term benefit and increased adverse events[2]. There is a large difference in ibandronate dosage between these trials (50 mg/day) and that used in treating osteoporosis (150 mg/month orally or 3 mg every three months intravenously). This dosage difference should be considered in future comparisons.
- Clodronate has not been studied specifically in patients receiving aromatase inhibitors (AIs).

[2] Vliek SB, Noordhoek I, Kranenbarg EM-K, Rossum AGJv, Dezentje VO, Jager A, et al. Daily oral ibandronate with adjuvant endocrine therapy in postmenopausal women with estrogen receptor–positive breast cancer (BOOG 2006-04): Randomized phase III TEAM-IIB Trial. J Clin Oncol. 2022:JCO.21.00311.

[3] Gralow JR, Barlow WE, Paterson AHG, Miao JL, Lew DL, Stopeck AT, et al. Phase III randomized trial of bisphosphonates as adjuvant therapy in breast cancer: S0307. Journal of the National Cancer Institute. 2020;31

- While the direct evidence from adjuvant trials is considered sufficient only for zoledronic acid and clodronate, others have hypothesized that any agent proven to reduce the risk of fragility fractures in at risk populations (e.g., patients with postmenopausal or drug-induced osteoporosis) may be effective as adjuvant therapy for breast cancer. Administered orally for osteoporosis treatment, alendronate has been used daily or weekly, while risedronate and ibandronate have been used daily, weekly, or monthly [17]. Ibandronate has also been used intravenously. Less frequent administration compared with clodronate may make these preferable to patients if shown to be of adjuvant benefit. Further trials with adequate power and primary outcomes of DFS and OS are required to determine the optimal agent and dosing schedule.
- Different adverse effect profiles, frequency and route of administration, cost, and regulatory approval may influence selection.

Recommendation 3

While results for adjuvant denosumab look promising, data is insufficient at this time to make any recommendation regarding its use in the adjuvant setting.

It is recommended that studies directly comparing denosumab and bisphosphonates and evaluating administration schedules be conducted.

2022 Update: The panel does not recommend the use of adjuvant denosumab (see update publication for rationale)

Qualifying Statements for Recommendation 3

- While the ABCSG-18 trial studied denosumab use in postmenopausal women with hormone-receptor positive breast cancer receiving AIs and found clear fracture reduction benefit [18], DFS results have only been reported as a conference presentation/abstract [19,20]. ~~As survival data has, to date, only been published in abstract form, no definitive recommendations can yet be made. Results are promising but limited compared with the body of evidence for bisphosphonates.~~ Further results of the ABCSG-18 and D-CARE trials [21] may provide stronger evidence for adjuvant denosumab use. *As indicated in the targeted update, both ABSCG-18[4] and D-CARE[5] studies have now been published. D-CARE suggests high-dose denosumab should NOT be used due to lack of efficacy but high rates of ONJ. At lower dose (60 mg every six months), ABCSG-18 found small (2-3%) DFS benefit).*

[4] Gnant M, Pfeiler G, Steger GG, Egle D, Greil R, Fitzal F, et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(3):339-51.

[5] Coleman R, Finkelstein DM, Barrios C, Martin M, Iwata H, Hegg R, et al. Adjuvant denosumab in early breast cancer (D-CARE): an international, multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2020;21(1):60-72

Recommendation 4

For patients who will receive adjuvant bisphosphonates (see Recommendation 1), zoledronic acid at 4 mg intravenously over 15 min (or longer) every six months for three to five years or clodronate orally at 1600 mg/day for two to three years are recommended. Different durations may be considered.

More research is recommended comparing different bone-modifying agents, doses, dosing intervals and durations.

2022 update: zoledronic acid at 4 mg every 3 months for 2 years or ibandronate at 50 mg/day for 3 years may be additional options.

Caution: Subsequent to the 2022 update, longer-term follow-up results of TEAM IIb trial results were published and showed no adjuvant benefit for ibandronate, and significantly higher rates of osteonecrosis of the jaw.[6]

Qualifying Statements for Recommendation 4

- In jurisdictions where the recommendation cannot be followed due to availability, similar doses and schedules of zoledronic acid or clodronate are considered reasonable.
- The optimal dose and schedule of administration of zoledronic acid and clodronate have not been determined; however, the recommended doses and schedules have been found effective in many of the adjuvant breast cancer trials (see Section 4) and result in fewer or less severe adverse effects than regimens used in patients with metastatic disease (i.e., 4 mg zoledronic acid every three to four weeks).
- The optimal duration of adjuvant bone-targeted agents has not been determined; the recommendations reflect durations found effective in the EBCTCG meta-analysis and other trials included in the literature review (Section 4). It is unclear whether there is benefit to longer-term administration, although studies indicate that the benefit of bisphosphonates continues after administration is stopped due to persistence of the drug within the bone. There are concerns about adverse effects such as atypical bone fractures based on reports from the osteoporosis literature, and some osteoporosis recommendations allow a treatment holiday from bisphosphonates after three to five years for patients with a lower risk of fracture [5,22].
- Administration of clodronate for more than three years or zoledronic acid for more than five years has not been evaluated in adjuvant trials and therefore a recommendation of longer duration is not supported at this time. This limitation in the evidence may be especially relevant to patients receiving long-term endocrine therapy as the recent CCO guideline on systemic treatment [12] includes recommendations for endocrine therapy for up to 10 years based primarily on results from the ATLAS, aTTom, and MA.17 trials.
- The optimal timing to start bisphosphonates after diagnosis of breast cancer is unclear; however, most of the clinical trials started soon after surgery or chemotherapy.

[6] Vliek SB, Noordhoek I, Kranenbarg EM-K, Rossum AGJv, Dezentje VO, Jager A, et al. Daily oral ibandronate with adjuvant endocrine therapy in postmenopausal women with estrogen receptor–positive breast cancer (BOOG 2006-04): Randomized phase III TEAM-IIB Trial. J Clin Oncol. 2022:JCO.21.00311.

Recommendation 5

For purposes of adjuvant bisphosphonate use, the definition of menopause should include both natural menopause (at least 12 months of amenorrhea prior to initiation of chemotherapy or endocrine therapy) and menopause induced by ovarian ablation or suppression (but not the cessation of menses due to chemotherapy alone). In women 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 prior to initiation of any systemic therapy in order to receive adjuvant bisphosphonates.

Qualifying Statements for Recommendation 5

- As indicated in the recent CCO guideline on systemic therapy in early breast cancer [12], assessing menopausal status is difficult in patients age ≤60 years experiencing amenorrhea secondary to chemotherapy or tamoxifen. Cessation of menses does not necessarily denote the absence of ovarian function, and premenopausal estradiol levels can be found in patients with transient chemotherapy-induced amenorrhea [23]. In addition, hormone levels and the absence of menses are unreliable indicators of menopause during treatment with tamoxifen [24].
- Some publications have suggested that patients experiencing chemotherapy-induced amenorrhea are at high risk for adverse bone effects and may be candidates for bone-modifying agents. Evidence is insufficient to address use of these agents as adjuvant treatment in this population.

Recommendation 6

A dental assessment is recommended, where feasible, prior to commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with prior to 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 [25], the American Association of Oral and Maxillofacial Surgeons [26], and the American Dental Association [27,28] should be consulted.

Patients should have serum calcium measured prior to starting treatment. Patients receiving intravenous bisphosphonates (zoledronic acid) should be monitored for renal function prior to 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 two hours to allow maximum absorption.

Symptoms such as ocular pain or loss of vision may be due to serious inflammatory conditions such as uveitis or scleritis and should be promptly evaluated by an ophthalmologist.

Qualifying Statements for Recommendation 6

- The risk of ONJ increases with frequency, dose, and duration of bisphosphonate administration. Risk can be reduced with appropriate screening prior to treatment and

modification of dental care. Risk of ONJ when bisphosphonates are administered as suggested in Recommendation 4 is lower than for patients receiving higher doses or more frequent administration as is used for cancers with bone metastasis.

- Some organizations advise dental assessment and care prior to any cancer treatment, preferably as soon as possible after diagnosis to allow time for dental procedures and adequate healing prior to treatment [29-33].
- The CCO formulary monograph for zoledronic acid recommends "comprehensive dental evaluation of both hard and soft tissues before starting bisphosphonate treatment; undergo invasive dental procedures, if needed, before starting bisphosphonate treatment" [34]. The United States Food and Drug Administration (US FDA) prescribing information for zoledronic acid indicates "cancer patients should maintain good oral hygiene and should have a dental examination with preventative dentistry prior to treatment with bisphosphonates" [35,36].
- It is unclear whether bone-modifying therapy should be withheld if invasive dental treatment is required. Some have hypothesized that withholding bone-modifying therapy may allow better bone healing, and suggested stopping treatment for two months prior to oral surgery and delaying restarting until osseous healing has occurred. The alternative view is that a short break in bisphosphonate administration will have no effect as bone effects of bisphosphonates are maintained for years after treatment stops.
- Hypocalcemia is a known adverse effect of bisphosphonate treatment, especially with the higher doses and more frequent administration given to patients with metastatic cancer. It is relatively rare (<1%) at lower doses (see Recommendation 4) in patients without pre-existing conditions such as renal insufficiency and who have adequate vitamin D status and calcium intake.
- There is conflicting evidence as to whether inflammatory eye conditions are directly caused by bisphosphonates or in conjunction with some underlying inflammatory disease process [37]; however, if not treated promptly these conditions may lead to blindness. Discontinuation of bisphosphonates may be necessary [38].