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
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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 July 14 (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

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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, see Section 2.

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 assessed as having low risk of recurrence, the use of bisphosphonates may not result in

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

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).
- While the direct evidence from adjuvant trials is considered sufficient only for

[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

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].

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

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVE

To make recommendations regarding the use of bisphosphonates and other bone-modifying agents as adjuvant therapy for 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.

BACKGROUND

Despite advances in adjuvant therapy, bone remains the most common site of breast cancer recurrence. The pivotal effects of the interaction between the tumour and its microenvironment have been recognized for over 100 years through the so-called, "seed and soil" hypothesis [39]. It is therefore not surprising that there has been extensive interest in the use of bone-modifying agents in the adjuvant treatment of breast cancer. The results of population studies, pre-clinical research and clinical studies in patients with metastatic disease provided a rationale for testing bone-targeted agents in the adjuvant setting [40]. Despite the initial optimism, results from prospectively designed, randomized controlled studies powered to assess the value of adjuvant bone-targeted therapy in early breast cancer are conflicting [41]. Data has shown that, where benefit exists, it tends to be in women with a "low estrogen environment", either through menopause or suppression of ovarian function. This hypothesis was formed largely based on results of the ABCSG-12 trial [42-44] conducted in premenopausal patients on ovarian suppression (see Recommendation 5), in which there was benefit of zoledronic acid, and preplanned subgroup analysis of the AZURE/BIG 1-04 trial [45,46], in which there was survival benefit in postmenopausal patients. In the AZURE trial, patients had been randomized using a minimization process taking into account menopausal status (as well as other factors), and the study was designed to analyze results according to these factors [46].

The results of the recently published Oxford Overview (Early Breast Cancer Trialists' Collaborative Group, EBCTCG) analysis of individual patient data has provoked particular interest in this area [11] and are a key portion of the evidence on this topic. For zoledronic acid, most patients and events in the meta-analysis come from the ABCSG-12 and AZURE trials, and therefore results for zoledronic acid use of at least three years reflect these trial results. The EBTCG conducted subgroup analysis with and without these two key trials and still found significant benefit of bisphosphonates in postmenopausal patients. The individual patient data

allows analysis according to menopausal status and other factors not reported in several of the original publications.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF 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.

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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, nor 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 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.

Key Evidence for Recommendation 1

- The EBCTCG meta-analysis [11] found statistically significant benefit for bisphosphonates in all postmenopausal patients with breast cancer for bone recurrence (6.6% vs. 8.8%), fracture rates (9.1% vs. 10.3%), breast cancer mortality (14.7% vs. 18.0%), overall survival (OS) (any death 21.1% vs. 23.5%), and outcomes that included bone recurrence (i.e., distant recurrence, any recurrence). These differences did not vary as a function of treatment features (bisphosphonate class, treatment schedule, dose), tumour characteristics (hormone receptor status, nodal status, tumour grade), or

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

concurrent chemotherapy. There was no statistically significant improvement in distant recurrence outside bone.

- Patients in all trials received chemotherapy and/or endocrine therapy. The exception is trials of clodronate, where this was not a condition of the trials or part of the protocol for three of the four main trials (see Table 4-1); ≥95% received systemic treatment in the two largest trials [47,48], and 81% in the smaller GABG Germany trial [49]. There is therefore no evidence from adjuvant trials in patients not receiving systemic treatment.
- Data for patients with induced menopause (see Recommendation 5) were included in the EBCTCG meta-analysis and come mainly from the ABCSG-12 trial [44]. Premenopausal patients received endocrine therapy (tamoxifen vs. anastrozole) along with goserelin for ovarian suppression. Zoledronic acid decreased risk of disease progression (hazard ratio [HR]=0.77, p=0.042) and improved disease-free survival (DFS) (88.4% vs. 85.0%, HR=0.77, 95% confidence interval [CI] 0.60 to 0.99, p=0.042). OS benefit was statistically significant up to 76 months of follow-up, but not at 94 months (OS 96.1% vs. 94.4%, HR=0.66, 95% CI 0.43 to 1.02, p=0.064). It should be noted that this follow-up is much longer than the three-year duration of zoledronic acid administration.

Interpretation of Evidence for Recommendation 1

- While the EBCTCG meta-analysis indicated a statistically significant survival benefit for all postmenopausal patients, the absolute benefit was small and will depend on risk of cancer recurrence. Some of the trials included in the meta-analysis were designed with non-cancer primary endpoints such as bone mineral density and were not powered for overall or disease-free survival. The authors considered use of bisphosphonates at the recommended levels (see Recommendation 4) to have a relatively low risk of ONJ or other serious adverse effects, and therefore benefits in reducing bone recurrence and improving survival generally outweigh the risks for most postmenopausal patients (see Recommendations 2 and 4, as well as Section 4, for further discussion of adverse effects). However, for patients with pre-existing conditions (see Recommendation 6) or with very low risk of recurrence, the risk of toxicity may indeed outweigh the benefits. Some of the co-authors expressed uncertainty about recommending adjuvant bisphosphonates for patients with a low risk of breast cancer recurrence. Evidence is insufficient to determine precise subgroups of patients who would or would not benefit, and therefore the recommendation to "consider" use for all patients deemed at high enough risk of relapse to warrant standard adjuvant systemic therapy was deemed most appropriate.
- Trials such as the SOFT-EST substudy [50] found incomplete estradiol suppression in some premenopausal patients. Some of the guideline authors suggested caution in assuming very young patients (≤40 years of age) on ovarian suppression have estrogen levels at a postmenopausal level, and therefore it is unclear whether they should be considered truly "postmenopausal" (see Recommendation 5).

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).
- 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.

Key Evidence for Recommendation 2

- The EBCTCG meta-analysis [11] found that, in postmenopausal patients, clodronate (1600 mg/day for two to three years) significantly reduced bone recurrence (4.6% vs. 7.0%, rate ratios [RR]=0.57, 95% CI 0.41 to 0.79, p=0.0007), breast cancer mortality (10.6% vs. 14.2%, RR=0.66, 95% CI 0.52 to 0.83, p=0.0004), any death (17.4% vs. 21.3%, RR=0.77, 95% CI 0.64 to 0.93, p=0.005), and fractures (8.4% vs. 10.7%, RR=0.77, 95% CI

[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

0.59 to 0.99, p=0.05). As indicated in Section 4, clodronate trials were completed several years ago and results are based on at least five to ten years' follow-up.

- The EBCTCG meta-analysis found that, in postmenopausal patients, zoledronic acid reduced bone recurrence (3.4% vs. 4.5%, RR=0.73, 99% CI 0.53 to 1.00); the difference in breast cancer mortality was not statistically significant (7.1% vs. 7.9%, RR=0.88, 99% CI 0.69 to 1.11). For trials with longer (three to five years) zoledronic acid treatment, bone recurrence was 3.4% with zoledronic acid versus 4.6% without (RR=0.72, 95% CI 0.57 to 0.92, p=0.008) and mortality was 8.8% versus 9.8% (RR=0.87, 95% CI 0.74 to 1.03, p=0.10).
- The GAIN trial [51] found no survival benefit for ibandronate compared with placebo.
- *The SWOG S0307 trial compared adjuvant zoledronic acid (4 mg iv q month × 6 then q3 months × 2.5 y) versus clodronate (1600 mg/day po for 3 y) versus ibandronate (50 mg/day po for 3 y) in 6097 patients with Stage I-III breast cancer and considered at high enough risk that adjuvant systemic therapy (other than bisphosphonates) was also used.* Preliminary results of the SWOG S0307 trial [14,15] which was conducted in women age >18 years, show no significant survival differences between clodronate, ibandronate, and zoledronic acid. *Subsequent publication (evaluated in the focused update) reported that 5-y DFS was 88.3% versus 87.6% vs 87.4% (p=0.49), and 5-y OS was 92.6% versus 92.4% vs 92.9% (p=0.50). There was no difference in efficacy based on age, menopausal status, tumour subtype, ER/PR/HER2 status, nodal status, or systemic treatment. Grade 3-4 adverse events occurred in 8.8%, 8.3%, and 10.5% of patients; ONJ occurred in 1.26%, 0.36%, and 0.77% (p=0.003); and fractures in 7.1%, 9.3%, and 7.4% (p=0.02). Prior to randomization, 73.2% of patients expressed preference for oral formulations; oral agents resulted in more gastrointestinal adverse effects. DFS was much higher than anticipated and therefore the trial was underpowered to find any differences; the lack of control (no treatment) arm complicates interpretation.* ~~Further details from a full publication of this trial are required.~~
- *The TEAM IIb (BOOG 2006-04) trial investigated use of adjuvant ibandronate in 1,116 postmenopausal patients with stage I-III ER+ and/or PR+ disease receiving adjuvant tamoxifen or exemestane. Patients were randomized to hormonal therapy with or without ibandronate (50 mg/day for 3 years). Preliminary results at a median 4.6 years follow-up were reported in an abstract[4]; 3 y DFS was 94.4% versus 90.8% (HR=0.84, 95% CI 0.60-1.17) and bone metastases 1.6% versus 4.6% (HR=0.76, 95% CI 0.43-1.32).*
    - New data since the 2022 update[5]: At median follow-up of 8.5 years there were no differences in survival or recurrence outcomes (8-y DFS 79% vs. 79%, OS 86% vs. 87%, any recurrence 12% vs. 14%, locoregional recurrence 4% vs. 5%, distant recurrence 11% vs 12%, bone recurrence 7% vs. 8%, visceral recurrence 8% vs. 8%), despite earlier (short-term) benefit for overall and bone recurrence. In the ibandronate arm there were significantly more patients with gastrointestinal issues (16% vs. 10%, p<0.003) and osteonecrosis of the jaw (12 vs 1 event, p=0.002). Study

[4] Vliek SB, Meershoek-Klein Kranenbarg E, Van Rossum AGJ, Tanis BC, Putter H, Van Der Velden AWG, et al. The efficacy and safety of the addition of ibandronate to adjuvant hormonal therapy in post-menopausal women with hormone-receptor positive early breast cancer. First results of the TEAM IIB trial (BOOG 2006-04). Cancer Res. 2017;77(4 Supplement 1):S6-02.

[5] 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.

authors concluded that daily ibandronate for three years should not be recommended.

- The EBCTCG concluded that no benefit was seen with pamidronate (based on the DBCG 89D trial [52,53]) and numbers were insufficient to assess the efficacy of oral risedronate or alendronate, which are standard treatments for osteoporosis.

Interpretation of Evidence for Recommendation 2

- The authors believe the evidence is insufficient to distinguish between clodronate and zoledronic acid. Other bisphosphonates such as ibandronate may be effective but evidence is more limited. A dissenting opinion among the co-authors was that ibandronate has sufficient evidence for use as adjuvant therapy.
- The authors consider it desirable to have multiple agents with different modes of administration, even if efficacy is similar. Patient preference, regulatory approval, cost, and availability may be factors. Some issues to consider are as follows:
  - Oral bisphosphonates, including daily clodronate, are more likely to cause gastrointestinal adverse effects than intravenous drugs and can be difficult to swallow for some patients; these issues maybe be especially important for elderly patients and those with gastroesophageal problems [10,54]. Some patients prefer oral medication because a hospital visit is not required.
  - Zoledronic acid is administered intravenously and therefore may have a higher compliance rate than for daily oral medications such as clodronate. Administration once every six months is considered more convenient to some patients. Acute-phase response resulting in mild to moderate flu-like symptoms may occur after intravenous administration.
  - Some publications indicate a lower risk of renal problems and ONJ with clodronate, compared with zoledronic acid; however, comparisons included patients administered zoledronic acid more frequently (monthly) as is used for metastatic disease. As more frequent or higher doses are known to increase the risk of ONJ, these trials may not be directly comparable. Considering trials of zoledronic acid at 4 mg every six months, the ABCSG-12 trial [44] found no cases of ONJ, while 0.8% of patients in the E-ZO-FAST trial [55] and 0.45% to 0.95% of patients in the ZO-FAST trial [56] developed ONJ.

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[6] and D-CARE[7] 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).*

Key Evidence for Recommendation 3

- *At high dosage as used in the D-CARE trial (120 mg monthly for 6 months then every 3 months for 5 years total) there was no significant difference in DFS (80% vs. 81%, HR=1.04) or BMFS (HR=0.97, p=0.70) but high rates of ONJ (5% vs. <1%) and increased treatment-emergent hypocalcaemia (7% vs. 4%).*
- In the ABCSG-18 trial [19], DFS at a median of four years' follow-up was 90.2% versus 88.1% (HR=0.816, p=0.051). In subgroup analysis, DFS benefit appeared greater for patients with tumours size >2 cm (28% of patients; HR=0.66, p=0.016) and those that were estrogen and progesterone receptor positive (83% of patients; HR=0.75, p=0.013) [18,19] . The magnitude of DFS benefit in the ABCSG-18 trial is comparable to that found in the EBCTCG meta-analysis for bisphosphonates [19]. ~~This data has only been published as an abstract; further DFS follow-up and OS results are pending.~~
- *In the subsequent publication of the ABCSG-18 trial (see focused update), DFS at a median 73 months of follow-up was 86% vs 83.2% (HR=0.82, 95% CI=0.69-0.98, p=0.0260); 5-y DFS was 89.2% versus 87.3% and 8-y DFS was 80.6% versus 77.5%. The authors also analyzed DFS data with sensitivity analysis and censoring to account for unblinding and partial cross-over, and the survival benefit was still significant. The improvement of 1.9% in 5-y DFS is comparable to the 2.4% effect size in the EBCTCG meta-analysis for bisphosphonates in postmenopausal patients. Univariate descriptive subgroup analysis of DFS results as displayed in a Forest plot suggested benefit in several subgroups, though degree varied, and all are not statistically significant. The trial authors indicated a full interaction model could not verify significant benefit for any subgroup. Survival outcomes were secondary outcomes, and BMFS and OS are still to be reported.*
- The patient incidence of adverse events in the ABCSG-18 trial [18] did not differ between the denosumab group (1366 events, 80%) and the placebo group (1334 events, 79%), nor did the numbers of serious adverse events (521 vs. 511 [30% in each group]). There was no increased risk of hypocalcemia (0.1% with denosumab vs. 0.2% placebo), renal or urinary disorders (2.5% vs. 3.1% overall; 0.8% vs. 0.6% serious) and no confirmed cases of ONJ. Increased rates of ONJ and hypocalcemia have been found in metastatic trials [57-59] which used higher dosages of denosumab (120 mg monthly metastatic vs. 60 mg every six months adjuvant).
- In the ABCSG-18 trial, time to occurrence of clinical fractures was significantly delayed by denosumab (HR=0.5, 95% CI 0.39 to 0.65, p<0.0001). Clinical fracture rates were 5.0% versus 9.6% at 36 months and 11.1% versus 26.2% at 84 months [18].

[6] 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.

[7] 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

Interpretation of Evidence for Recommendation 3

- The ABCSG-18 trial provides limited data on DFS benefit ~~(abstract only)~~, along with stronger evidence of benefit in reducing fracture risk.
- As the overall evidence is stronger for adjuvant bisphosphonates (see Recommendation 1) than denosumab and no adjuvant trials directly comparing denosumab to bisphosphonates have been completed, the authors considered it premature to recommend denosumab for general use in adjuvant therapy. There was considerable discussion as to whether to recommend use in selected patients.
    - Some of the authors suggested denosumab (60 mg subcutaneously every six months for three to five years) be considered as an alternative to bisphosphonates in patients for whom bisphosphonates would otherwise be recommended but are not suitable due to compliance, intolerance, administration difficulty, or availability.
    - As the various bisphosphonates and denosumab have different routes and frequency of administration, mechanism of action, and adverse effect profiles, the authors considered denosumab may be more appropriate for some patients. Ability to swallow oral medication, distance from hospital facilities for intravenous administration, differential costs to patients or hospitals, intolerance, compliance, and regulatory approval were considered by the authors as factors that may influence drug selection.
- Some of the co-authors strongly opposed any recommendation regarding denosumab due to the limited data and all eventually agreed that while data from the ABCSG-18 trial suggests use of adjuvant denosumab may be of benefit, the evidence is insufficient at this time to make a recommendation. ~~Further data from the ABCSG-18 trial and D-CARE trial are awaited. The D-CARE trial completed enrolment in late 2012 [21]; with five years' denosumab administration and 7.5 years' follow-up, the trial is not expected to be completed until 2022 (https://clinicaltrials.gov/show/NCT01077154~~). *Authors do not recommend denosumab due to the contradiction between ABCSG-18 and D-CARE results.*

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.[8]

[8] Vliek SB, Noordhoek I, Kranenbarg EM-K, Rossum AGJv, Dezentje VO, Jager A, et al. Daily oral

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.

Key Evidence for Recommendation 4

- In the EBCTCG meta-analysis [11], clodronate at 1600 mg/day for two to three years or zoledronic acid for three to five years decreased bone recurrence and improved survival (see Section 4 and Recommendation 2).
- The meta-analysis did not find a significant difference between low (osteoporosis) and high (cancer metastasis) dose/frequency, but did not subdivide results according to bisphosphonate used. For zoledronic acid, almost all data comes from trials of three to five years' administration. Zoledronic acid was used at 4 mg every six months in the ABCSG-12 trial [44] and Z-FAST/ZO-FAST/E-ZO-FAST trials [55,56,60] (these trials were conducted in patients receiving endocrine therapy, with primary outcome of the latter studies being preservation of bone mineral density) and at 4 mg every three to four weeks (with decreased frequency after six cycles) in the AZURE/BIG 1-04 trial [45,46,61,62]. Adverse events, including ONJ (see Recommendation 6) are greater with more frequent administration.
- In most trials, bisphosphonates were started soon after surgery or chemotherapy (within zero to twelve weeks; see Section 4). In the ZO-FAST trial [56,63] of immediate versus delayed administration of zoledronic acid (until decline in bone density or fracture), DFS and BMD were better with immediate administration, although there was still a DFS

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.

benefit (HR=0.46; p=0.0334) of starting later compared with none at all [56].

- 2022 update: The Success A trial[9] found no difference in DFS or OS between 4 mg zoledronic acid administered for 2 years every 3 months or the same regimen followed by 4 mg every 6 months for 3 years. There was no non-treatment control so it cannot be determined whether there was benefit of zoledronic acid in either arm. This study was not restricted to postmenopausal patients and therefore does not follow the hypothesis that effect is only in postmenopausal patients (although subgroup analysis suggests greater benefit with longer duration in postmenopausal patients). It is unknown whether increase in initial dose intensity (compared to previous recommendations) has benefits that outweigh potential risks of greater adverse events.

Interpretation of Evidence for Recommendation 4

- As indicated in the Qualifying Statements, optimal dose and timing are unclear, and therefore we consider those used in the adjuvant and osteoporosis trials to be appropriate. The lower frequency of zoledronic acid (4 mg every six months) results in fewer adverse effects than more intensive treatment (e.g., 4 mg monthly). While zoledronic acid at 4 mg/month was effective in the AZURE trial (stage II-III cancers), there has been no direct comparison with lower frequency; in the absence of comparative efficacy data but established adverse effects, we are unable to recommend more intensive treatment in the adjuvant setting. We consider it plausible that the risk/benefit balance of more frequent administration may depend on disease stage.
- The authors debated whether to make a recommendation regarding timing of bisphosphonate initiation. It was initially proposed bisphosphonates be started within six months of completion of chemotherapy as this would cover the various timings used in the randomized controlled trials (RCTs), as well as concerns some of the authors had about overlapping toxicities of chemotherapy and bisphosphonates (gastrointestinal effects in particular). While the ZO-FAST trial results suggest immediate initiation is preferable but delayed initiation of zoledronic acid is better than none, this trial was designed primarily as a BMD trial and not considered sufficient to make a recommendation. As the other included RCTs did not compare timing of initiation, the authors decided not to make any recommendation in this regard.

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

[9] Friedl TWP, Fehm T, Müller V, Lichtenegger W, Blohmer J, Lorenz R, et al. Prognosis of patients with early breast cancer receiving 5 years vs 2 years of adjuvant bisphosphonate treatment: A phase 3 randomized clinical trial. JAMA Oncol. 2021;7(8):1149-57.

- 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.

Key Evidence for Recommendation 5

- In the EBCTCG meta-analysis [11], subgroup investigations considered patients postmenopausal if they had undergone either natural or induced menopause, with the latter being either potentially reversible using luteinising hormone-releasing hormone analogues or permanent by oophorectomy. The meta-analysis did not attempt to look at these separately. Most postmenopausal patients were naturally postmenopausal, with the exception being the ABCSG-12 trial [44] conducted in patients with induced menopause. A small proportion of patients in the ZO-FAST [56,63] and E-ZO-FAST trials [55] (17% and 16% of patients, respectively), and approximately one-half of the patients in the HOBOE trial [64] also had induced menopause; these trials provided a relatively small contribution compared with the ABCSG-12 trial.
- The ABCSG-12 trial [44] studied use of zoledronic acid in premenopausal patients undergoing treatment with goserelin for ovarian suppression and randomized to either tamoxifen or anastrozole. Zoledronic acid improved risk of disease progression (HR=0.77, p=0.042) and DFS (88.4% vs. 85.0%, HR=0.77, 95% CI 0.60 to 0.99, p=0.042) up to the last follow-up (median 94 months), and OS up to 76 months; the trend for OS continued but was no longer statistically significant at 94 months (HR=0.66, p=0.064) (see Recommendation 1).

Interpretation of Evidence for Recommendation 5

- As the EBCTCG meta-analysis authors included both natural and induced menopausal patients to derive their conclusions, we have also used this definition. It is noted that evidence in induced menopausal patients is weaker as it is derived from only one trial.
- Trials such as the SOFT-EST substudy [50] have found incomplete estradiol suppression in some premenopausal patients. Some of the guideline authors suggested caution in assuming very young patients (age ≤40 years) on ovarian suppression have estrogen levels at a postmenopausal level, and therefore it is unclear whether they should be considered truly “postmenopausal”.

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].

Key Evidence for Recommendation 6

- Many recent trials [16,21,46,55,65-68] excluded patients with current active dental problems involving the jawbone or with recent or planned dental or jaw surgery including tooth extraction or implants (see Section 4). SWOG S0307 required a dental exam within six months prior to initiation of treatment [69]. ONJ incidence in patients receiving six monthly doses of zoledronic acid and then every three or six months thereafter was 1.5% to 2.1% in the AZURE / BIG 01/04 trial [62] and 1.2% in the SWOG S0307 trial [14]. With ibandronate (50 mg/day), ONJ occurred in 0.1% of patients in the GAIN trial [51] and 0.6% of patients in the SWOG S0307 trial [14].
- As development of ONJ is believed to be dependent on dose and duration of treatment, trials of adjuvant zoledronic acid administered every six months, as is more often used in osteoporosis treatment may be more relevant. ONJ rates were 0.8% in the immediate administration arm of the E-ZO-FAST trial [55], 0.45% to 0.95% in the ZO-FAST trial [56], and 2% (upfront arm) or 1% (delayed arm) in the NO3CC trial [67]. No cases were found in the ABCSG-12 trial [44].
- With clodronate, ONJ occurred in 0.06% of patients in the NSABP B-34 trial [47] and 0.3% in the SWOG S0307 trial [14]. Published reviews of lower-dose ibandronate in treatment of postmenopausal osteoporosis (150 mg/month orally, or 2 mg every two months or 3 mg every three months intravenously) reported benefit, and with greater effect than a daily oral dose of 2.5 mg [17,70]. ONJ was not detected in the major RCTs, although there have been occasional case reports. Adjuvant studies of ibandronate at these lower doses in early breast cancer were not found.
- Most trials gave (or recommended) supplemental vitamin D (400-800 IU) and calcium (500-1000 mg). While these were primarily to maintain BMD, it has been suggested they may also minimize mild anemia and serum electrolyte imbalances associated with intravenous bisphosphonates [71] and decrease the risk of osteoclast inhibition-induced hypocalcemia [72]. Trials in metastatic cancer found increased risk of hypocalcemia with denosumab and thus a need to monitor for this adverse effect [10,73]. Lower doses of denosumab were used in the ABCSG-18 trial [18] and the Freedom trial [74] and resulted in no increase in hypocalcemia.
- Ocular effects were not noted in the RCTs in the literature review, other than one case of scleritis [75]; trials were too small and not designed to detect rare events. A recent RCT of intravenous zoledronate for osteopenia found acute anterior uveitis in 8/1001 patients (6 had mild/moderate uveitis and 2 had severe uveitis [7]). Other evidence is mainly from case series [76,77], retrospective cohort studies [8], and adverse effect reporting [38].

Interpretation of Evidence for Recommendation 6

- The evidence suggests risks of adverse effects are low when bone-modifying agents are administered at doses in Recommendation 4 and the precautions suggested above are followed.
- The authors agreed that optimizing dental health is always ideal, but there was dissention on whether dental assessment prior to treatment should be required in all patients. As noted in the key evidence, several trials excluded patients with current dental problems and therefore do not provide evidence for or against dental assessment and treatment. Some co-authors believed it a wise precaution without attendant risk. Others stated there was no evidence it would make a difference in outcomes; that some patients may not have or be able to afford dental care; or that there could be other

resource implications. The recommendation therefore contains a proviso "where feasible".

RESEARCH NEEDS

There is an urgent need for trials directly comparing different bone-modifying agents and different doses schedules and durations of therapy. Some of the ongoing trials listed in Table 2-1 (see also Section 4) as well as those suggested in Table 2-2 may be important.

Table 2-1. Ongoing or not fully reported trials (see Tables 4-2 and 4-3 for further details).

Trial name(s) NCT or other trial ID	Number of patients and characteristics	Arms or comparison	Outcomes reported, notes
SWOG S0307, NCT00127205	N=6097 Age >18 y	Clodronate (1600 mg/day po for 3 y) vs. ibandronate (50 mg/day po for 3 y) vs. ZOL (4 mg iv q month × 6 then q3 months × 2.5 y)	DFS (primary) in abstract only ONJ, fracture, adverse events (secondary) in abstract only Early reporting at 4th interim analysis; no realistic chance of statistically significant difference
TEAM IIb, ISRCTN17633610	N=1116 Postmenopausal, HR+, endocrine therapy	Ibandronate (50 mg/d for 3 y)	Ongoing, results not reported DFS (primary) metastasis, recurrence, OS, 5-y DFS, safety (secondary)
HOBOE, version 2 NCT00412022	N=1050 Original version (first 500 pts): age ≥18 (triptorelin if premenopausal); letrozole in both arms Version 2 (after March 2010): premenopausal only; triptorelin + letrozole in both arms	ZOL, 4 mg q6m for 5 y	Enrolment complete, results not reported for version 2 or combined DFS (primary, version 2) BMD, OS, toxicity; DFS (original version) (secondary)
Success A NCT02181101	N=3754 High-risk; adjuvant chemotherapy	ZOL, 2 y vs. 5 y ZOL at 4 mg iv q3m for 24 m vs. q3m for 24 followed by q6m for 36 m	Ongoing, results not reported DFS (primary) OS, distant metastasis (secondary)
JONIE-1 UMIN000003261	N=188 Age 20-70	ZOL (4 mg iv over 15 min, q3-4w for 6 m)	pCR (primary) DFS (secondary) in abstract only; follow-up to 2017 planned
Z-FAST Study-Japan UMIN000001104	N=204 Postmenopausal, HR+, adjuvant letrozole	ZOL upfront or delayed start; 4 mg iv q6 m for 5 y	BMD (primary) reported at 12 m Fracture, adverse events, BMD (secondary) at 36 months in abstract only
CHO-BC-039 NCT02595138	N=430 (planned) Triple-negative	ZOL	Started 2015, ongoing DFS (primary) OS, adverse effects (secondary)
ABCSG-18 NCT00556374	N=3420 Postmenopausal, HR+, receiving non-steroidal aromatase inhibitors	Denosumab (60 mg sc q6m) vs. placebo	Time to clinical fracture (primary) DFS (secondary) in abstract only Patients on placebo may switch to denosumab in 2016, follow-up will be ongoing
D-CARE, 2010-2012 NCT01077154	N=4500 High risk	Denosumab (120 mg sc monthly for 6 months then every 3 months for total of 5 y) vs. placebo	Enrolment completed 2012, ongoing administration of denosumab (5 years) and planned 7.5 years' follow-up, no results reported Primary: bone metastasis free survival Secondary: DFS, OS, safety
GeparX, 2016- NCT02682693	N=778 (planned) cT1c-cT4a-d BC; HR-; assessed HER2, Ki-67, TIL and RANK status	Neoadjuvant chemotherapy +/- denosumab (120 mg sc q4w×6)	Primary: pCR (ypT0 ypN0) Secondary: breast conservation rates, toxicity, compliance, survival

Abbreviations: BMD, bone mineral density; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HR+, hormone-receptor positive; iv, intravenously; OS, overall survival; pCR, pathologically complete response; po, per os (orally) sc, subcutaneously; ZOL, zoledronic acid

Table 2-2. Suggested clinical trials to be conducted*.

Trial type	Endpoint recommended	Other endpoints
Comparison of single zoledronate infusion [78] vs. seven infusions of zoledronate every six months	• Disease-free survival • Bone-specific disease-free survival • Quality of life • Compliance	• Survival • Breast cancer specific survival • Adverse events (acute phase reactions, renal, osteonecrosis of the jaw) • Patient-reported outcomes (consider using PRO-CTCAE) • Health care costs (patient and system)
Denosumab vs. zoledronate every six months for seven infusions		
Denosumab vs. clodronate		
Zoledronic acid vs. denosumab: once vs. every six months vs. yearly for 2 years or 5 years		
Risedronate or alendronate (standard osteoporosis treatment) vs. denosumab vs. zoledronic acid		

* Trials should appropriately test the post-menopausal hypothesis by stratifying patients by menopausal status at enrolment.

OTHER IMPLEMENTATION CONSIDERATIONS

- It is desirable to have multiple agents with different modes of administration (see Recommendation 2)
- As with any novel therapy or new indication for existing medications, cost, access, funding, and drug approval need to be considered in the implementation of treatment recommendations. As mentioned in the preamble of this document, several health care settings currently may only have access to bone-modifying agents to improve bone-density or for the treatment of metastatic cancer. As such, drug formularies and governing bodies may need to revise approved dose and scheduling parameters for these relevant medications before clinicians may be able to utilize them. As examples in North America:
  - Zoledronic acid has recently been added to the CCO Drug Formulary (April 2016) [34] for the adjuvant treatment of breast cancer in postmenopausal women. Clodronate thus far only has Health Canada Approval for the management of hypercalcemia of malignancy and for treatment of bone metastases; is included in the CCO Formulary [6] and British Columbia Cancer Agency Cancer Drug Manual [79] for these purposes.
  - Zoledronic acid is approved in the United States for treatment of low bone mass and metastatic disease and clodronate is not available.
  - Ibandronate is not currently approved for use in Canada. It is approved by the US FDA for the prevention or treatment of postmenopausal osteoporosis.
  - Direct patient cost and health system resource impact should be considered in implementing such recommendations.

RELATED GUIDELINES

- Alibhai S, Zukotynski K, Walker-Dilks C, Emmenegger U, Finelli A, Morgan S, Hotte S, WInquist E, and the Genitourinary Cancer Disease Site Group. Bone Health and Bone-

Targeted Therapies for Prostate Cancer. Toronto (ON): Cancer Care Ontario; 2016 September 23. Program in Evidence-Based Care Guideline No.: 3-14 v2. https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31716

- Van Poznak CH, Moy B, Barlow WE, Biermann JS, Bosserman L, Clemons MJ, Dhesy-Thind S, Dillmon MS, Eisen A, Frank ES, Jagsi R, Jimenez R, Theriault RL, Vandenberg T, Yee G. ASCO-CCO Clinical Practice Guideline Focused Update on the Role of Bone Modifying Agents in Metastatic Breast Cancer. https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/43266

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

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

BACKGROUND FOR GUIDELINE

Bisphosphonates and other bone-modifying agents have been used in prevention or treatment of osteoporosis and in patients with bone metastases. Results of RCTs evaluating use as adjuvant (and/or neoadjuvant) treatment in early (non-metastatic) breast cancer in reducing relapse and metastasis and improving survival have been conflicting. During preparation of the PEBC/CCO guideline "Optimal Systemic Therapy for Early Female Breast Cancer" [12], it was noted that results of several trials of adjuvant bisphosphonate use were not yet available and that the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was conducting an individual patient data meta-analysis of adjuvant bisphosphonate use. Preliminary results of the EBCTCG meta-analysis were presented at the 2013 San Antonio Breast Cancer Symposium [80]. The systemic therapy Working Group decided to defer any recommendations on bisphosphonate use to a subsequent and separate guideline; the Breast DSG agreed that the bisphosphonate guideline should be commenced once the EBCTCG meta-analysis was fully published.

The EBCTCG meta-analysis was released online in July 2015 and appeared in a subsequent issue of *The Lancet* [11]. Primary outcomes in the meta-analysis were time to recurrence, time to first distant recurrence, and breast cancer mortality. Significant reductions in breast cancer mortality, breast cancer recurrence, and bone recurrence were found in postmenopausal women, but not in premenopausal women

GUIDELINE DEVELOPERS

This guideline was developed by the Adjuvant Bisphosphonates in Breast Cancer GDG (Appendix 1), which was convened at the request of the Breast Cancer DSG.

The project was led by a small Working Group of the Adjuvant Bisphosphonates in Breast Cancer GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology and health research methodology. Other members of the Adjuvant Bisphosphonates in Breast Cancer GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 2, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

Traditionally, guideline topics have been determined with CCO and then search for existing guidelines conducted in order to determine whether there are other guidelines that could be endorsed or adapted instead of creating a totally new guideline. The adaptation process can be quite long and costly. In discussion with the American Society for Clinical Oncology (ASCO), it was determined there would be benefit in co-developing several guidelines, with either PEBC or ASCO taking the lead and the other organization being involved at various stages. In this manner, input of both groups would be given at an earlier stage in development such that later adaptation would not be required. For this guideline PEBC took the lead, including planning the project and its scope and constituting the Working Group. ASCO nominated four additional members to the Expert Panel as well as suggested some of the external reviewers. Approval was sought from both the PEBC and ASCO guideline approval panels (see below). Additional details regarding the Expert Panel and the review process are given in Section 5.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [81,82]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [83] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation, using the ADAPTE framework [84], or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.

- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.

To be considered, guidelines must have had a systematic search for RCTs (optionally supplemented with other data) and be issued within the past five years (past three years to consider endorsing). In addition, the guideline needed to consider the results of the EBCTCG meta-analysis [11,80]. A search for existing guidelines for adaptation or endorsement did not yield an appropriate source document. A search of the primary literature was required (see Section 4 Evidence Review).

In January 2016, when our literature review was almost complete, we became aware of a European consensus guideline [85] on this topic released as a prepublication version in December 2015. Evaluation of the systematic review using AMSTAR [86] and the guideline using AGREE II [83] led to the conclusion that the guideline did not meet our criteria for endorsement. In particular, the systematic review did not state the research questions, search strategy, or inclusion/exclusion criteria, and selectively reported results for only nine trials which the authors considered major. There was no indication of how many other trials were considered on topic or were excluded. There was no mention of any external review process. The guideline's strengths are that it considered results of the EBCTCG meta-analysis [11] and authors included experts in relevant fields who had been involved in several of the major trials.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must have cast a vote indicating they approved the document or abstained from voting for a specified reason; of those that voted, 75% must have approved the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, was required to unanimously approve the document. The Expert Panel and RAP members could specify that approval was conditional, and that changes to the document were required. If substantial changes were subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel. As part of the collaboration with ASCO, the ASCO Clinical Practice Guidelines Committee (CPGC) was also required to approve the document before it could be released as a joint PEBC-ASCO guideline. Due to differences in structure of PEBC/CCO and ASCO guidelines, the ASCO CPGC approved a document with the same content and recommendations but rearranged according to usual ASCO and *Journal of Clinical Oncology* requirements.

External Review

Feedback on the approved draft guideline was obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise were identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline were contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation was intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

ACKNOWLEDGEMENTS

The Adjuvant Bisphosphonates in Breast Cancer GDG would like to thank the following individuals for their assistance in developing this report:

- Eitan Amir, Melissa Brouwers, Craig Earle, William Grandisher, Donna Maziak, Sheila McNair, Hans Messersmith, Sandy Paterson, Kathy Pritchard, Lesley Souter, and Emily Vella for providing feedback on draft versions.
- The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee, and in particular Eric D Mininberg, the ASCO reviewer for this committee.
- Mark Somerfield and Tom Oliver for co-coordinating the collaboration with ASCO.
- Umangjot Bharaj for conducting a data audit.
- Sara Miller for copy editing.

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

Section 4: Evidence Review

INTRODUCTION

In women, breast cancer is the most common cancer, accounting for approximately 25% of all cancers [87,88]. It is estimated there will be 25,000 new cases and 5100 deaths in Canada in 2015. In Ontario there will be an estimated 9800 new cases and 1900 deaths. Despite improvements in long-term outcomes for early breast cancer, recurrence and death rates are still significant. As bisphosphonates and other bone-modifying agents are effective in prevention or treatment of osteoporosis and in patients with bone metastases, it has been hypothesized that they may have benefit as adjuvant treatment in early breast cancer as well. Results of RCTs evaluating use as adjuvant (and/or neoadjuvant) treatment in early (non-metastatic) breast cancer in reducing relapse and metastasis and improving survival have been conflicting. Several papers [51,89,90] had indicated that an individual patient data meta-analysis was required to confirm survival benefit in the subgroup of postmenopausal women that had been suggested in individual RCTs [44,46,47]. The Working Group of the Adjuvant Bisphosphonates in Breast Cancer Guideline Development Group (GDG) developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1. Does administration of bisphosphonates or other bone-modifying agents as adjuvant treatment in patients with breast cancer reduce metastasis and/or recurrence and improve survival?
2. Does effectiveness depend on patient or disease characteristics, especially age or menopausal status (natural or induced menopause)?
3. Do effectiveness and adverse effects differ according to which bisphosphonate or bone-modifying agent is used?
4. What doses, duration of administration, and route (intravenous, oral) are optimal?

METHODS

During project planning it was anticipated that the primary evidence base would be the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) individual patient data meta-analysis [11]. Due to the extensive worldwide collaboration by the EBCTCG it was considered unlikely that any major completed trial within its scope (except in the past few years) would have been missed. As the EBCTCG only included trials starting before 2008, a literature search for recent data would be required.

Initial review of the EBCTCG publication revealed that the meta-analysis included data from 26 trials; 24 additional trials without data met their inclusion criteria and were listed. These additional trials were noted as starting after 2006, ongoing, or data requested but not received. For most of the RCTs without data it was impossible to determine from the EBCTCG publication whether useful data would eventually be available. The meta-analysis did not report data on adverse effects and did not provide references to publications for the included trials. It focused on bisphosphonates and, therefore, did not include other bone-modifying agents such as

denosumab. It was therefore considered necessary to conduct a full literature search to identify the included studies, determine the reason for missing data and whether it had been subsequently published, to look for more recent data of included trials, to identify ongoing or recently completed trials starting around 2008 or later (and therefore excluded by the EBCTCG), and to include trials of non-bisphosphonate bone-modifying agents.

Search for Systematic Reviews and Primary Literature

MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched for the period 2005 to September 15, 2015. An update of the literature search was conducted on June 6, 2016. It was assumed that any trials published entirely before 2005 would be identified from the EBCTCG meta-analysis or other reviews. The search included terms for breast cancer, bisphosphonates or bone-modifying agents, and publication type (see Appendix 3). Abstracts from the American Society of Clinical Oncology (ASCO) conferences (2009-2015), San Antonio Breast Cancer Symposia (SABCS; 2011-2015), and the European Society of Molecular Oncology conferences (2011-2015) were searched separately from the conference or journal websites for years not indexed in the above databases. The SABCS 2015 and ASCO 2016 conferences were searched when available (November 2015 and June 2016, respectively), while the others were searched around the same time as the initial MEDLINE/Embase searches. Several recent systematic reviews were identified on bisphosphonates [12,91-93], zoledronic acid [94-98] or clodronate [99]. Review of these suggested none were more recent or more complete than the EBCTCG meta-analysis and therefore the located reviews were not considered to replace the EBCTCG meta-analysis plus RCTs from the current search as the evidence base for the current guideline. The included trials and associated publications were reviewed to ensure no trials had been missed.

Study Selection Criteria and Process

In the current literature review, studies were included that were RCTs evaluating adjuvant or neoadjuvant use of bisphosphonates or other bone-modifying agents (primarily denosumab) compared with some control (none, placebo, other bisphosphonates, or different administration of the same bisphosphonate). Studies designed to measure cancer recurrence, survival, or distant metastasis (bone or visceral metastases) provided the strongest evidence. Studies primarily designed to evaluate bone-modifying effects such as bone mineral density (BMD) were excluded unless recurrence or survival outcomes were also part of the design (primary or secondary outcomes) and were reported in detail. To be included, studies had to evaluate at least 30 randomized patients. RCTs were excluded that were designed to evaluate agents that primarily modify hormonal levels such aromatase inhibitors (AIs), tamoxifen, or raloxifene, but which may have secondary bone effects. A review of the titles and abstracts that resulted from the search was conducted by one reviewer (GGF). The same reviewer looked at items that warranted full text review.

The inclusion criteria of the EBCTCG meta-analysis [11] were broader, and included any trial in which women were randomized to bisphosphonate versus a control group without bisphosphonate. The EBCTCG therefore included several additional trials designed primarily with BMD or similar outcomes, and for which there was no published data on survival or recurrence outcomes. While some of these trials included large numbers of patients, there were few events of interest (recurrence or survival outcomes) and these additional trials contributed very little to the overall meta-analysis.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data from the EBCTCG meta-analysis and RCTs was extracted by one member of the Working Group (GGF). Ratios, including hazard ratios, were expressed with a ratio <1.0 indicating

benefit of the experimental treatment (bisphosphonate). All extracted data and information were audited by an independent auditor.

Trial name(s) or location, trial identification/registration number, enrolment period, number of patients, patient characteristics, treatment arms or comparison, and outcomes stated in the trial design were summarized for all studies. As the EBCTCG meta-analysis results comprised the main evidence, detailed outcome data from most of the individual trials included in this meta-analysis were not extracted. Some exceptions were made when results in the meta-analysis appeared inconsistent or unclear, or an individual study appeared to contribute all the data for a subgroup analysis. During interpretation of the data, it became apparent that outcomes not included in the EBCTCG meta-analysis such as osteonecrosis of the jaw (ONJ) and other adverse effects were required, and these were added to the data extraction tables.

For studies not already included in the EBCTCG meta-analysis, recurrence, survival, and other outcome results were also extracted. Formal assessment of study quality was conducted only for trials that needed to be looked at in detail (i.e., in addition to the EBCTG meta-analysis data). This also applied to major trials not included in the EBCTCG meta-analysis. To aid in assessing the quality of studies, the following details were looked for in the trial methods or publications (see Appendix 5): randomization method, allocation concealment and blinding, balanced baseline characteristics, industry funding, statistical power and target sample size, intention-to-treat analysis, description of patients who withdrew or were lost to follow-up, and whether the trial was terminated early.

Synthesizing the Evidence

Due to the existing EBCTG meta-analysis on bisphosphonates [11], as well as ones on narrower topics of clodronate [99], zoledronic acid [97], and neoadjuvant zoledronic acid [100], no further meta-analysis was contemplated. However, a few of the subgroup results were recalculated after excluding one or more trials.

RESULTS

Literature Search Results

A flow diagram of the literature search results is given as Figure 4-1. The initial literature search, after removal of duplicates, resulted in 3850 citations from MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. The literature update in June 2016 found 486 citations, of which 207 were new non-duplicate publications. The conference abstract searches resulted in 14 additional citations. Searches for guidelines and reviews from other sources resulted in an additional 26 publications, and searches for additional information for specific trials or as cited in other publications found 25 articles. Two additional ongoing trials without publications were found in clinicaltrials.gov.

Of the systematic reviews and meta-analyses found, the EBCTCG individual patient data meta-analysis [11] was the most comprehensive. One recent systematic review on clodronate [99], and five on zoledronic acid [94-98] were located, as well as meta-analyses (abstracts only) on zoledronic acid in postmenopausal women [101] and on neoadjuvant therapy [100]. Three systematic reviews on adjuvant bisphosphonates [91-93], plus the recent PEBC/CCO review on systemic therapy in early breast cancer [12] were found. An additional individual patient meta-analysis on neoadjuvant chemotherapy with or without zoledronic acid, with the outcome of pathological response, was found during the literature update [102]. Examination of studies included in these reviews suggested one additional study not in the literature search [103]; however, it was subsequently excluded as having no outcomes of interest. The EBCTCG meta-

analysis was determined to be the main evidence source for the accompanying guideline, to be supplemented by additional RCTs and updated data found in the primary literature search.

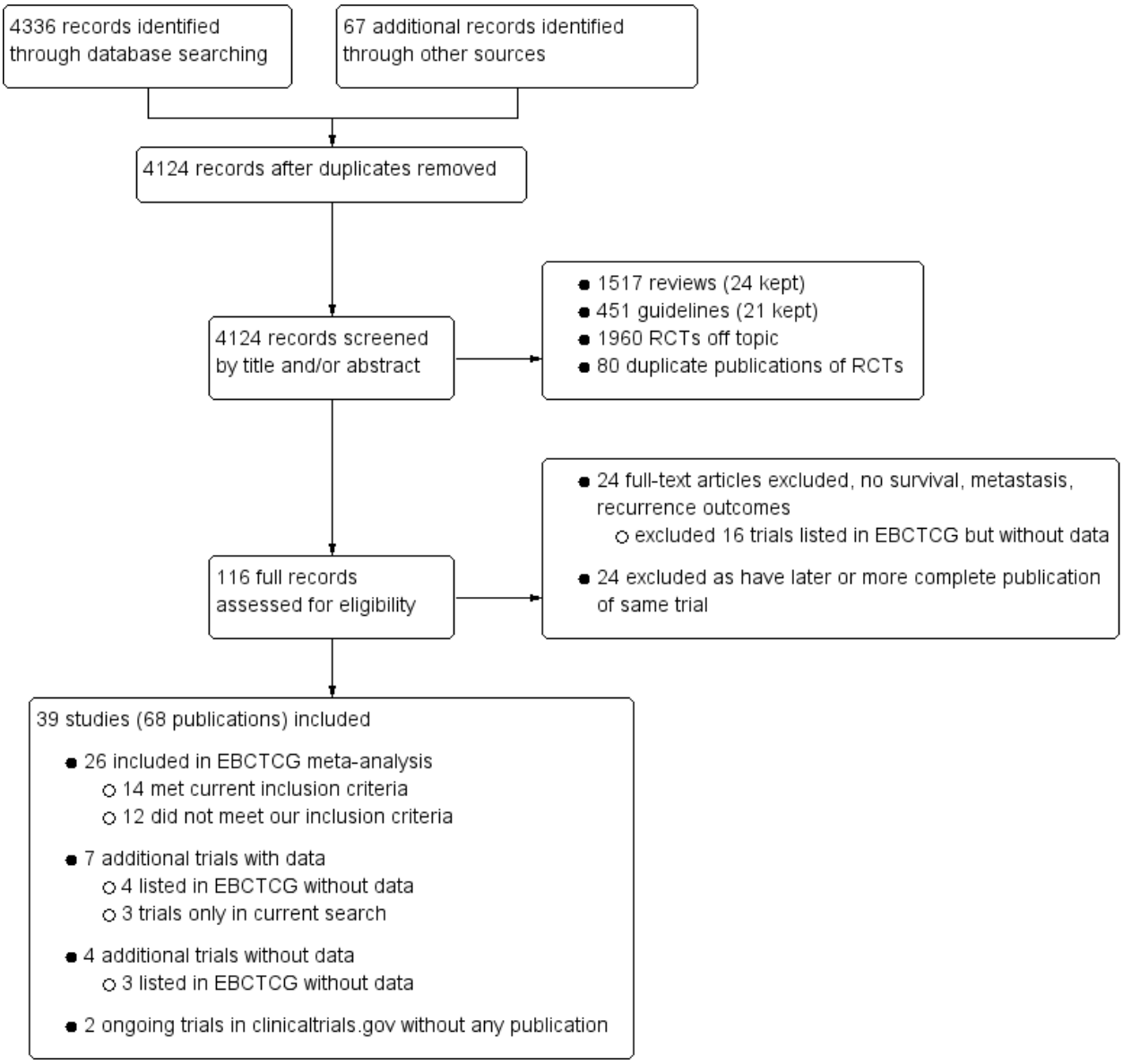

Figure 4-1. Flow diagram of literature search results.

EBCTCG meta-analysis

The EBCTCG meta-analysis included data from 26 trials (see Table 4-1 and Figure 4-1) [42-49,51-53,55,56,60-65,67,68,75,104-129], of which 14 met our inclusion criteria based on data in the corresponding publications. The meta-analysis also listed an additional 23 trials for which data was not available (see Appendix 4). Sixteen of these additional 23 trials did not meet our inclusion criteria. Of the additional twenty-three trials, three were classified by EBCTCG as not within scope (two prevention trials and one with no recurrence data). The meta-analysis obtained individual patient data directly from the trial investigators and did not cross-reference data to authors or publications. Trials were identified by name or location, and reported the comparison

made and size (number of patients). These names did not always match those found in publications of the same trials. Trial registry numbers were given for only a few studies.

Current Literature Search

As indicated in Figure 4-1, the literature search plus EBCTCG meta-analysis combined found 39 trials. Basic data had to be extracted for each trial in order to match trials from the literature search and EBCTCG meta-analysis and ensure all publications for a given trial were grouped together. At least one publication was found in the MEDLINE/Embase literature search for each of the trials included by the EBCTCG, with the exception of the British Columbia trial. Contact with the authors indicated it was an in-house trial with endpoints of BMD and bone markers; it was published only as an abstract [120]. As the meta-analysis included individual patient data for all trials, outcome results have not been extracted for these publications. Fourteen of the RCTs included in EGCTCG meta-analysis did not meet the current inclusion criteria, primarily because they are BMD studies and did not report recurrence or survival outcomes. These trials are listed in the second portion of Table 4-1, with an indication that they do not meet the criteria for the current systematic review. These studies account for a small proportion of patients and events in the meta-analysis; for recurrence, they account for 3% of events and 8% of patients.

In addition to trials with data included in the EBCTCG meta-analysis, the literature search also found results for the SWOG S0307 (abstract only [14,15]) and ABCSG-18 trials [18-20], as well as a few small studies (see Table 4-2 [130-138]). While these publications mentioned at least some outcomes, complete publication or longer follow-up is still required for several of them. Other ongoing trials without results yet are listed in Table 4-3 [16,21,66,139,140]. SWOG S0307 [14,15] compared clodronate versus ibandronate versus zoledronic acid, and as such gives data not in the EBCTCG meta-analysis. ABCSG-18 [18,19] (along with the ongoing D-CARE trial [21]) provides data on denosumab, which is also not in the meta-analysis. These trials will therefore be discussed separately.

Several trials that evaluated bisphosphonates in early breast cancer were excluded; most of these were primarily studies of bone effects (bone loss, BMD) or clinical/molecular response to neoadjuvant treatment. This set of studies is summarized in Appendix 4 [103,141-166] and includes most of the trials without data listed in the EBCTCG publication (other than the ongoing trials noted in Tables 4-2 and 4-3).

Table 4-1. Trials with data included in EBCTCG meta-analysis.

Trial name(s) or location, enrolment period; NCT or other trial ID; publication	Number of patients (N) Patient characteristics and treatment	Arms or comparison	Outcome stated in trial methods	Notes
Clodronate				
Royal Marsden, 1989-1995 ISRCT83688026 Powles, 2002, 2006 [48,104]; Atula, 2003 [105]; McCloskey, 2010 [106]	N=1069 Primary operable breast cancer, stage I-III. Standard treatment (surgery, radiotherapy, adjuvant chemotherapy and/or tamoxifen); 95% received systemic treatment 50% postmenopausal, median age 53 y, 37% N+, 81% T1-T2, 64% ER+, 59% PR+	Clodronate (1600 mg/d) for 2 y vs. placebo	Primary: bone relapse (metastasis) Secondary: other relapse, mortality, toxicity Median 5.6 y follow-up	Reduction in bone metastasis and mortality GI disorders more common with clodronate; no ONJ
GABG Germany University Hospital Heidelberg, 1990-1995 Diel, 1998, 2008 [49,107]	N=302 Primary breast cancer with tumour cells in the bone marrow, T1-4, N0-2 (47% N0), no distant metastasis. Standard surgical treatment and customary hormonal therapy or chemotherapy; 81% received systemic treatment 62% postmenopausal, 73% ER+, 62% PR+	Clodronate (1600 mg/d) for 2 y vs. standard follow-up	Primary: bone metastasis, visceral metastases, OS Median 103 months follow-up	Reduction in distant metastasis (osseous and visceral) at 36 m and 55 m but not 103 m; improved OS
Helsinki Finland, 1990-1993 Saarto, 2001, 2004, 2008 [108-110]; Leppa, 2005 [111]	N=282 (299 randomized) N+ operable breast cancer, T1-3, N1-2, age <75 y. All received adjuvant therapy: Premenopausal CMF; postmenopausal antiestrogens (tamoxifen vs. toremifene for 3 y) 48% postmenopausal (52% clodronate, 43% control), 64% ER+, 55% PR+ Received chemotherapy: 50% vs. 58%	Clodronate (1600 mg/d for 3 y) vs. control	Primary: bone metastasis, metastasis-free survival, OS 10-year follow-up data	Decreased DFS, more non-skeletal recurrence, no difference in bone metastasis, improved osteoporosis-free survival
NSABP B-34 USA, 2001-2005 NCT00009945 Paterson, 2012 [47]	N=3323 Operable, stage 1-3 Pts stratified by age (<50, ≥50), number of positive nodes (75% N0, 18% N1, 7% N2+), ER status; 35% age <50 78% HR+ Local and systemic treatment at investigator's discretion: ≥95% received chemotherapy and/or hormonal therapy	Clodronate (1600 mg/d) for 3 y vs. placebo	Primary: DFS Secondary: OS, RFS interval, bone metastasis-free interval Median 90.7 months follow-up	No difference in DFS or OS. Age >50: benefit in recurrence, bone metastasis, non-bone metastasis, but not OS 1 possible case of ONJ (0.06%) No increase in hypocalcemia (Grade 3: 1 case clodronate, 2 cases placebo: no cases grade4/5 in either group)

Trial name(s) or location, enrolment period; NCT or other trial ID; publication	Number of patients (N) Patient characteristics and treatment	Arms or comparison	Outcome stated in trial methods	Notes
Risedronate, ibandronate, pamidronate				
DBCG 89D Denmark, Sweden, Iceland, 1990-1996 Ejlertsen, 2008 [52]; Kristensen, 2008 [53]	N=953 A. Premenopausal, N-, grade 2-3, ≤5 cm (24% of pts) B. Premenopausal, HR- or HR unknown, either N+ or >5 cm (43%) C. Postmenopausal, HR-, N+ or >5 cm (34%). Surgery + (CMF or CEF) in all pts; RT according to guidelines at participating centres 15% ER+, 56% ER-, 28% unknown; 11% PR+, 28% PR-, 60% unknown	RT + (CEF vs. CMF) ± pamidronate (150 mg po q12h for 4 y) vs. none	OS, DFS, bone metastasis, adverse events, fractures; BMD in subgroup	No difference in OS, bone, or distant metastasis
GAIN Germany, 2004-2008 NCT00196872 Von Minckwitz, 2013 [51]	N=3023 (2015 ibandronate, 1008 observation) High-risk, pN+, suitable for intensive dose-dense chemotherapy, complete resection including ≥10 axillary nodes, pT1 to operable pT4a-c 50% age <50 y; 52% postmenopausal, 77% HR+	(EPC vs. EC-PX) ± ibandronate (50 mg/d po for 2 y) vs. observation	Primary: DFS Secondary: OS, safety, EFS in subgroups HR+ or HR-, number of nodes involved	No difference in DFS (HR=0.945, p=0.589) or OS (HR=1.040, p=0.803) ONJ in 2 ibandronate pts (0.1%)
Zoledronic Acid				
ABCSG-12 1999-2006 NCT00295646 Gnant, 2009, 2011, 2015 [42-44]	N=1083 Premenopausal, stage I/II, HR+, <10 positive nodes, standard goserelin therapy Preoperative chemotherapy allowed, RT according to institutional guidelines (none received adjuvant chemotherapy)	Goserelin (3.6 mg q28d) + (anastrozole 1 mg/d vs. tamoxifen 20 mg/d for 3 y) ± ZOL (4 mg q6m for 3 y) [ZOL given at 8 mg iv q4 w until protocol amendment in October 2000, 254 pts were enrolled at that time]	Primary: DFS Secondary: RFS, OS, BMD Exploratory: bone metastasis-free survival	Improved DFS at 5 y (ns at 8 y), lower risk of disease progression. No cases of ONJ; thorough monitoring of adverse effects Serious adverse events (life-threatening, permanent damage, hospitalization, required medical/surgical intervention): no difference ± ZOL Any adverse events: increased with ZOL: arthralgia (24% vs. 18%), tachycardia, bone pain (35% vs. 25%), cognitive disorder (1.4% vs. 0.3%), nausea/vomiting (8.6% vs. 6.1%), fever (8.9% vs. 2.2%), hypocalcemia (0.4% vs. 0%), skin disease (6.5% vs. 4.3%), tachycardia (2.1% vs. 0.8%), peripheral nerve disease (5.7% vs. 3.4%)

Trial name(s) or location, enrolment period; NCT or other trial ID; publication	Number of patients (N) Patient characteristics and treatment	Arms or comparison	Outcome stated in trial methods	Notes
Washington University, St Louis, MO, USA, 2003-2006 NCT00242203 Aft, 2010, 2012 [116,117]	N=119 Stage II/III (≥T2 and/or ≥N1; LABC) Neoadjuvant (4 cycles)+ adjuvant (2 cycles) chemotherapy; RT, endocrine, trastuzumab when indicated Menopausal status was defined as 1 year with no menstrual activity, previous bilateral oophorectomy, or age >56 years. Median age 48 y, 46% postmenopausal, 56% ER+, 46% PR+	ZOL (4 mg iv q3w for 1 y) or none (control) for 1 y, starting at time of neoadjuvant chemotherapy and continuing after surgery	Primary: DTC in bone marrow Secondary: DFS Tertiary: OS	DFS and OS similar overall; recurrence and death lower in ER- pts with ZOL ONJ in 1 ZOL pt (1.7%)
AZURE, BIG 01/04 2003-2006 NCT00072020, ISRCTN79831382 Coleman, 2011, 2014 [45,46,61]; Rathbone, 2013 [62]	N=3360 Stage II-III, either pN+ or T3-T4; previous complete resection occurred (or planned for neoadjuvant therapy); scheduled to receive (neo)adjuvant chemotherapy and/or endocrine therapy Stratified by nodal status, T stage, ER status (78% ER+), systemic therapy, statins, menopausal status, participating centre 45% premenopausal; 79% received endocrine treatment, 78% ER+ The protocol was amended in July 2005 to exclude patients with significant active dental problems or recent jaw surgery	(Neo)adjuvant therapy ± ZOL (5 y). 4 mg iv q3-4w × 6 then q3m × 8 then q6m × 5 Ca + vitamin D recommended for first 6 m, then at physician discretion	Primary: DFS Secondary: invasive DFS, OS, time to bone metastases, distant recurrence, subgroup analysis, adverse events	Reduced bone metastasis at median 84 m: HR=0.81, 95% CI 0.68–0.97, p=0.022; fractures 6.2% vs. 8.3%, HR=0.69, 95% CI 0.53-0.90, p=0.005 Survival improvement at median 59 m: 5-y OS 84.6% vs. 78.8%, HR=0.74, 95% CI 0.55-0.98, p=0.04 [45]), and but not at a median follow-up of 84 months (HR=0.81, 95% CI 0.63-1.04 [46]) Improved disease outcomes for postmenopausal pts: DFS HR=0.78 (95% CI 0.62-0.97); invasive DFS HR=0.77 (95% CI 0.63-0.96), distant DFS HR=0.75 (95% CI 0.58-0.97). Suspected ONJ in 33 ZOL pts, of which 26 cases confirmed (1.5-2.1%; different percentages quoted in text, appendix, and different publications). In 22 cases a dental extraction took place before onset of ONJ. No other difference in adverse effects.

Trial name(s) or location, enrolment period; NCT or other trial ID; publication	Number of patients (N) Patient characteristics and treatment	Arms or comparison	Outcome stated in trial methods	Notes
University of Saarland, Germany, 2002-2004 NCT00172068 Banys, 2013 [114]; Solomayer, 2012 [115]	N=96 Disseminated tumour cells (DTC) in bone marrow at time of surgery, were to receive adjuvant therapy (hormonal and/or cytotoxic) Age ≥18 y, median 54 y, 61% postmenopausal, 81% ER+, 66% PR+ Excluded if active dental problems or ONJ	Adjuvant therapy ± ZOL (3-4 mg q4w iv, 24 m)	Primary: DTC counts Secondary: safety, bone-metastasis-free survival, DFS	Longer survival and less recurrence with ZOL, though differences ns due to small sample size ONJ in 1 ZOL pt (2.3%)
NATAN GBG 36, ABCSG XX Germany, 2005-2009 NCT00512993 Von Minckwitz, 2013 [112] [abstract]; Goodman, 2014 [113] [meeting report]	N=693 ypT1-4 or ypN+ after neoadjuvant chemotherapy (anthracycline-taxane), within 3 y of surgery HR+ pts received letrozole for 5 y if postmenopausal or tamoxifen if premenopausal; adjuvant trastuzumab if HER2+ since 2007 amendment Median age 51 y; 72% postmenopausal, 82% HR+, 19% HER2+	Neoadjuvant endocrine (if ER+) ± ZOL (4 mg iv q4w for 6 m then q3m for 2 y then q6 m for 2.5 y) + Ca + vitamin D	Primary: EFS Secondary: OS, EFS depending on delay after surgery, bone-metastasis-free survival, toxicity, predictive value of neoadjuvant response	No OS or DFS difference; nonsignificant trend favouring ZOL in women age >55 y (analysis at 48-m interim analysis due to futility)
Z-FAST CZOL446EUS32 USA, 2002-2003 NCT00050011 Brufsky, 2007, 2009, 2012 [60,118,119]	N=602 Postmenopausal, HR+, early (stage I-IIIa). Adjuvant letrozole (2.5 mg/d for 5 y) ± ZOL	ZOL upfront (4 mg iv q6m for 5 y) vs. ZOL delayed (if lumbar spine or total hip T score decreased to < -2.0, or non-traumatic fracture or asymptomatic vertebral fracture at 36 m) Ca + vitamin D encouraged	Primary: LS BMD Secondary: TH BMD, bone-turnover markers, clinical fracture, AE, time to disease recurrence	Recurrence and death better with upfront ZOL up to 48 m, no difference at 61 m ONJ reported in 2 pts (0.67%) on upfront ZOL; 1 was ruled inconsistent with ONJ and the other indeterminate
ZO-FAST CFEM345D2405 International (not Canada/USA), 2003-2004 NCT00171340 Eidtmann, 2010 [63]; Coleman, 2013 [56]	N=1065 (n=525 received immediate ZOL; n=144 received delayed ZOL) Postmenopausal, HR+, stage I-IIIa, lumbar spine and total hip T-scores ≥-2, surgical resection completed, chemotherapy and/or RT completed in previous 12 wk. Letrozole (2.5 mg/d for 5 y) ± ZOL	ZOL upfront (4 mg q6m for 5 y) vs. ZOL delayed (if T-score fell below -2, or non-traumatic clinical fracture, or asymptomatic fracture at 36-m assessment Ca + vitamin D in all pts	Primary: LS BMD Secondary: TH BMD, fractures, recurrence, DFS, OS, safety	Immediate ZOL improved DFS; improved DFS and OS in pts age 60+ 9 potential cases of ONJ in 7 pts; of these it was confirmed in 3 cases, possible in 2 cases (insufficient data) and excluded in the others; (0.45-0.95%).

Trial name(s) or location, enrolment period; NCT or other trial ID; publication	Number of patients (N) Patient characteristics and treatment	Arms or comparison	Outcome stated in trial methods	Notes
E-ZO-FAST CFEM345D2406 International (mostly Europe; not North America), 2004-2007 NCT00171314 Llombarto, 2012 [55]	N=527 Postmenopausal or recently postmenopausal from ovarian-ablative treatment, receiving letrozole (2.5 mg/d for 5 y or until disease progression) Resected, stage I-IIIa, HR+, lumbar spine and total hip BMD T-score ≥-2.0 After the initiation of the trial (2006 or later), baseline dental health screening for risk assessment of ONJ and preventative oral health practices were implemented.	ZOL upfront (4 mg by 15 min iv q6m for 5 y) vs. ZOL delayed (if T-score fell below -2, or clinical fracture, or asymptomatic at 36-m assessment Ca + vitamin D in all pts	Primary: LS BMD Secondary: TH BMD, fractures, recurrence, safety	12-m report, further follow-up needed (ongoing) ONJ in 2 pts (0.4%) on upfront ZOL; one pt after 3 doses and 1 after 6 doses [note may be more with longer follow-up]
Exclude by 1-22 criteria				
British Columbia Cancer Agency About 2000-2001 Bryce, 2002 [120]	N=72 Operable pT1-3, pN0-1, cM0, menses in previous 12 months (premenopausal), standard chemotherapy (AC, AC/Taxol, CEF)	Standard chemotherapy + Ca + vitamin D ± clodronate [300 mg iv q3-4w]×4 plus at 6 months	Endpoint: spinal and TF BMD and bone markers	Exclude Only BMD data
ARIBON UK, 2003-2005 N0276137347 (UK) Lester, 2008, 2012 [121,122]	N=50 in RCT portion (131 total) Postmenopausal, ER+, surgically treated, to receive anastrozole Only the 50 patients with osteopenia (T score -1.0 to -2.5) at the hip or lumbar spine were randomized. Patients who developed osteoporosis while taking Ibandronate/ placebo were unblinded and offered open-label ibandronate treatment.	Anastrozole (1 mg/d) + Ca + vitamin D ± ibandronate (150 mg q28d for 2 y) vs. placebo	Primary: LS and TH BMD Secondary: bone resorption and formation markers, adverse events (including fracture)	Exclude by 1-22 criteria, primarily BMD study ONJ did not occur
N02C1 North Central Cancer Treatment Group and Mayo Clinic, USA, 2003-2006 NCT00054418 Hines, 2009 [123]	N=216 Premenopausal, stage I-IIIB, >age 18 y Adjuvant or neoadjuvant chemotherapy Excluded if undergone dental extraction, root canal, or dental implants ≤3 months before registration	Risedronate (35 mg/wk for 1 y) vs. placebo Ca + vitamin D + in all pts	Primary: LS BMD Secondary: FN and TH BMD, toxicity, osteoporosis	Exclude by 1-22 criteria, primarily BMD study
ARBI Hellenic Society of Breast Surgeons, Greece, 2005-2007 NCT00809484 Markopoulos, 2010 [124]	N=70 (213 total) Postmenopausal, HR+, completed surgery (and chemotherapy if indicated), mild osteopenia (T-score ≤1.0 for spine or hip but > -2.0 at both sites, mild to moderate risk of AIBL osteoporosis). Scheduled to receive anastrozole	Anastrozole (1 mg/d) + Ca + vitamin D ± risedronate (35 mg/wk) Assessment at 12 m and 24 m	Primary: LS and hip BMD	Exclude by 1-22 criteria, primarily BMD study No ONJ cases

Trial name(s) or location, enrolment period; NCT or other trial ID; publication	Number of patients (N) Patient characteristics and treatment	Arms or comparison	Outcome stated in trial methods	Notes
SABRE 2004-2007 NCT00082277 Van Poznak, 2010 [125]	N=154 (234 total) Postmenopausal, HR+, scheduled to receive anastrozole; moderate risk of fracture	Anastrozole (1 mg/d) plus either risedronate (35 mg/wk for 2 y) or placebo Ca + vitamin D recommended	Primary: LS BMD Secondary: TH BMD	Exclude by 1-22 criteria, primarily BMD study
ANZAC EUDRACT 2007-001526-27 Sheffield, UK, 2007-2009 NCT00525759 Winter, 2013 [65]	N=40 Age 18+, scheduled for neoadjuvant anthracycline-based chemotherapy (18 wk) then surgery; concurrent tamoxifen or AI not allowed; excluded those with active dental problems or ONJ 45% postmenopausal, 15% ER+	Neoadjuvant chemo ± ZOL (single 4 mg infusion 24 h after first cycle of fluorouracil + epirubicin + cyclophosphamide)	Primary: short term biologic effects by measuring biomarkers	Exclude by 1-22 criteria, biomarkers only, pilot study
HOBOE Napoli, Italy, 2004-2009 NCT00412022 Nuzzo, 2012 [64]	N=303 in RCT of ZOL (483 total study) HR+, age 18+ y, Postmenopausal received letrozole; premenopausal (53%) received triptorelin + letrozole Excluded pts treated by or requiring invasive therapeutic procedures for dental disease	Letrozole ± ZOL (3 mg-4 mg, depending on creatinine clearance, q6m for 5 y)	Primary: LS T-score (BMD)	Exclude by 1-22 criteria, primarily BMD study No cases of ONJ
KCSG BR06-01 Korea, 2007-2008 Kim, 2011 [68]	N=116 Premenopausal, age >40 y, scheduled for 4 cycles adjuvant chemotherapy (adriamycin + cyclophosphamide →paclitaxel or docetaxel). Tamoxifen after 8th cycle chemotherapy if HR+ 83% ER+, 83% PR+ Excluded pts that had undergone dental extraction or dental implants ≤2 months before registration	ZOL (4 mg iv over 15 min q6m for 12 m; d1 of 1st and 8th chemotherapy cycle) vs. delayed ZOL (non-traumatic fracture or 6-m follow-up BMD T-score ≤-2.5 at LS or total hip Ca and vitamin D for all pts for 1 y	Primary: LS BMD, Secondary: FN BMD, bone turnover markers, AEs	Exclude by 1-22 criteria, primarily BMD study No cases of ONJ
N03CC North Central Cancer Treatment Group (now part of the Alliance for Clinical Trials in Oncology), USA, 2005-2006 NCT00107263 Hines, 2009 [126]; Wagner-Johnston, 2015 [67]	N=551 Postmenopausal, stage I-IIIa, HR+, completed ≤6 y tamoxifen and undergoing letrozole treatment, T-score ≥-2.0 at study entry	Letrozole (2.5 mg/d) + Ca + vitamin D plus ZOL upfront (3-4 mg iv over 15 min q6m for 5 y) vs. delayed (BMD T-score <-2.0 or non-traumatic fracture)	Primary: LS BMD at 12 months Secondary: LS BMD up to 5 y, hip BMD, osteoporosis, fractures, toxicity	Exclude by 1-22 criteria, primarily BMD study ONJ in 4/274 pts (2%) upfront and in 2/277 pts (1%) delayed (after cross-over)

Trial name(s) or location, enrolment period; NCT or other trial ID; publication	Number of patients (N) Patient characteristics and treatment	Arms or comparison	Outcome stated in trial methods	Notes
ProBONE I, CZOL446GDE13 Germany, 2005-2008 NCT00333229 Hadji, 2012 [127]	N=11 (70 planned) HR-; (neo)adjuvant chemotherapy Premenopausal	(neo)adjuvant chemo ± ZOL (2 y)	Primary: LS BMD Secondary: TH BMD, femur bone metabolism markers, endocrine hormones, fractures, safety, tolerability	Exclude, small number; study terminated early
ProBONE II CZOL446GDE21 Germany, 2005-2009 NCT00375505 Hadji, 2014 [128,129]	N=70 Premenopausal, age 18+ y, HR+; T1-T4, ≤4 positive nodes (adjuvant) or N0 (neoadjuvant), bone density T-score of ≥−2.5. Endocrine therapy (goserelin or tamoxifen) for 24 m alone or with (neo)adjuvant chemotherapy + Ca + vitamin D Excluded pts with current active dental problems, current/prior ONJ, recent(within 6 weeks) or planned dental or jaw surgery	ZOL (4 mg iv over 15 min q3m for 2 y) or placebo	Primary: LS BMD Secondary: FN and TH BMD, markers of bone turnover, hormone levels, safety, fractures, recurrence. Study underpowered to detect difference in recurrence	Results reported at 2 y, disease progression to be assessed at 60 m, study might be ongoing. Does not currently meet 1-22 inclusion criteria. One case of ONJ in pt receiving ZOL (3%) in a pt who had a dental extraction during therapy
Tel Aviv, Israel, 2005-2011 NCT00376740 Safra, 2011 [75] https://clinicaltrials.gov/ct2/show/study/NCT00376740	N=90 Postmenopausal, stage I-III, HR+, previous tamoxifen for 2.5-3 y. Phase II trial. Excluded pts with dental disease and the need for dental surgery	Letrozole (2.5 mg/d for 5 y) + Ca + vitamin D ± ZOL (4 mg iv q6m for 2 y)	Primary: LS BMD Secondary: fractures, AEs, OS, recurrence	Median 41 m follow-up. No recurrence or survival data reported. Does not meet 1-22 criteria No cases of ONJ; 1 case of scleritis

Abbreviations: AEs, adverse effects; AI, aromatase inhibitor; BMD, bone mineral density; CEF, cyclophosphamide + epirubicin + fluorouracil; CMF, cyclophosphamide + methotrexate + fluorouracil; DFS, disease-free survival; DTC, disseminated tumour cells; ER-, estrogen receptor negative; ER+, estrogen receptor positive; FN, femoral neck; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; HR-, hormone-receptor negative; HR+, hormone-receptor positive; iv, intravenously; LS, lumbar spine; N+, node-positive; N0, node negative; ONJ, osteonecrosis of the jaw; OS, overall survival; pts, patients; progesterone-receptor negative; PR+, progesterone-receptor positive; RFS, recurrence-free survival; RT, radiation therapy; TH, total hip; ZOL, zoledronic acid

Table 4-2. RCTs from literature search (data not in EBCTCG meta-analysis) with full or partial reporting of results[1].

Trial name(s) or location, enrolment; NCT or other trial ID; Source	Number of pts Patient characteristics	Arms or comparison	Survival	Recurrence and other outcomes	Outcomes stated in methods	Notes
SWOG S0307, 2005-2010 NCT00127205 Gralow, 2014, 2015 [14,15] [abstracts] [69] [protocol]	N=6097 Stage I-III, adjuvant systemic therapy (exclude pts at such low risk that adjuvant therapy not prescribed) Age >18 y, median age 53 y with 58% postmenopausal or age ≥50 y Dental exam required within 6 months prior to initiation of treatment	Clodronate (1600 mg/day po for 3 y) vs. ibandronate (50 mg/day po for 3 y) vs. ZOL (4 mg iv q month × 6 then q3 months × 2.5 y) Prior to randomization, 76% preferred oral medication	5-y DFS: 88% vs. 87% vs. 88%, p=0.71 OS: 93% in all arms No treatment differences based on age or menopausal status	ONJ: 0.3% clodronate vs. 0.6% ibandronate vs. 1.2% ZOL, p=0.003 Fractures: equal in all arms (4.8% vs. 4.1% vs. 4.5%, ns) Grade 3-4 events: 8.3% vs. 10.5% vs. 8.8%	Primary: DFS Secondary: OS, sites of first recurrence, and adverse events (ONJ, fractures)	Early reporting at 4th interim analysis; no realistic chance of statistically significant difference (abstract only) No evidence of difference in efficacy overall or by age or menopausal status. Listed by EBCTCG but no data
Slovak Clodronate Collaborative Group (SCCG) 1990-1993 Mardiak, 2000 [130]	N=66 LABC; n=7 visceral metastasis without skeletal or CNS involvement Stage III without osseal metastases Median age 55 y (29-79)	Clodronate 1600 mg po (800 mg twice a day) vs. placebo for 2 y	At median observation of 84 m: Death 50% vs. 61%, p=0.40 Median OS 59.4 m vs. 54.7 m, p=0.35 5-y survival 41% vs. 39%	At median observation of 84 m: Bone metastases 30% vs. 21%, p=0.42 Visceral metastases 53% vs. 48%, p=0.70 Median time to bone metastases 13.4 m vs. 28.4 m, p=0.43; Median time to visceral metastases 20.2 m vs. 16.3 m, p=0.95	Bone metastases, other metastases, survival	Completed, median 84 m follow-up Listed by EBCTCG but no data
JONIE-1 Japan, 2010-2012 UMIN000003261 Hasegawa, 2015 [131] Miura, 2013 [132]; Hasegawa, 2012 [133];	N=188 Resectable stage IIA-IIIB, HER2-, age 20-70 Excluded pts with dental or jaw infection or traumatic condition of the teeth	ZOL (4 mg iv over 15 min, q3-4w for 6 m) or placebo plus neoadjuvant chemotherapy (FEC100 q3w×4 then paclitaxel q1w×12 or vice versa) ± ZOL	3-y DFS 88.4% vs. 81.1% 2-y DFS 88.4% vs. 84.8% 1-y DFS 97.7% vs. 100%	<u>pCR:</u> Overall 14.8% vs. 7.7%, p=0.066 postmenopausal 18.4% vs. 5.1%, p=0.071 triple negative 35.3% vs. 11.8%, p=0.112	Primary: pCR Secondary: DFS, BCS ratio, tumour response rate. Not powered for subgroup results.	Follow-up to 2017 planned Listed by EBCTCG but no data

[1] As indicated in the trial identification and notes columns, several of these trials have only been published as abstracts and/or require further follow-up.

Trial name(s) or location, enrolment; NCT or other trial ID; Source	Number of pts Patient characteristics	Arms or comparison	Survival	Recurrence and other outcomes	Outcomes stated in methods	Notes
Horiguchi, 2013 [134] [abstracts] UMIN website				postmenopausal triple negative subgroup 50% vs. 0%, p=0.029 No difference in severe toxicity		
Egypt/Saudi Arabia 2005-2012 El-Ibrashi, 2016 [135] [abstract]	N=300 Premenopausal, stage I-II, HR+, <10 positive lymph nodes Scheduled for tamoxifen plus goserelin for 5 y	TAM (20 mg/d for 5 y) + goserelin (3.6 mg q28d) ± ZOL (4 mg q6m for 3 y)	Median 98.4 m follow-up: DFS 90% vs. 85%	Recurrence 12% vs. 16% Loco-regional recurrence 3% vs. 5% Distant metastasis 6% vs. 7% Bone metastasis 3% vs. 5% ZOL generally well tolerated, no renal failure or ONJ	Primary: toxicity, DFS Secondary: OS	Fewer recurrence and metastasis with ZOL (significance not reported)
Z-FAST Study-Japan 2008-2009 UMIN000001104 Takahashi, 2012 [136]; Takahashi, 2013 [137] [abstract]	N=204 Postmenopausal, HR+, early, adjuvant letrozole Excluded pts with current active dental problems including infection of the teeth or jaw, and recent (≤6 weeks) or planned dental or jaw surgery (e.g., extraction, implants)	Letrozole ± ZOL (upfront or delayed start; 4 mg iv q6 m for 5 y The delayed group received ZOL when lumbar spine (L2-L4) BMD decreased to less than young adult mean – 2.0 S.D or when a non-traumatic fractured occurred.		Recurrence 3.1% upfront vs. 1.0% delayed Fracture 1% upfront vs. 4.1% delayed, ns No significant difference in adverse events except fever Change in L1-L4 BMD: 10.7% higher upfront than in delayed group, p<0.001 No cases of ONJ	Primary: L1-L4 BMD; secondary: BMD, clinical fracture, AE, time to disease progression.	12-m data, 36-m in abstract, powered only for BMD endpoint
Egypt Abu-Taleb, 2014 [138] [abstract]	N=120 Postmenopausal, HR+, completed initial therapy	Letrozole ± ZOL for 2 y	No difference in DFS at 37 m follow-up, p=0.714	No difference in toxicity	Primary: BMD, bone turnover marker, DFS, toxicity	
ABCSG-18 2006-2013 NCT00556374 Gnant, 2015 [18]; Gnant, 2016 [19] [abstract] and [20] [presentation]; [167-169] [news]	N=3420 Postmenopausal, early, HR+, receiving non-steroidal aromatase inhibitors Included proactive screening and monitoring for ONJ	Denosumab (60 mg sc q6m) vs. placebo 500 mg Ca plus at least 400 IU vitamin D recommended	At median 4-y follow-up: DFS HR=0.816 (0.66-1.00), p=0.051. 3-y DFS 93.8% vs. 92.6%; 5-y DFS 88.9% vs. 86.8%; 7-y DFS 83.5% vs. 80.4%	Time to first clinical fracture delayed in denosumab group. Risk of fracture HR=0.5, p<0.0001; at 36 m: 5% vs. 9.6%; at 84 m: 11.1% vs. 26.2% Reduction similar in pts with normal BMD and with T-score < -1 at start of trial, p=0.002 Improved BMD at 12 m, 24 m, 36 m	Primary: time to clinical fracture Secondary: safety/AEs; BMD, DFS, BMFS, OS	Significant decrease in fractures overall and for subgroups (baseline BMD, age (<60 y, >60 y), T stage, N+/N0, ductal/ invasive Note: DFS recommended by independent data monitoring committee (IDMC) based on

Trial name(s) or location, enrolment; NCT or other trial ID; Source	Number of pts Patient characteristics	Arms or comparison	Survival	Recurrence and other outcomes	Outcomes stated in methods	Notes
			Exploratory subgroup analysis DFS: tumours >2 cm HR=0.66, p=0.016; ductal histology HR=0.79, p=0.048; ER+/PR+ HR=0.75, p=0.013	Adverse events: no difference, 80% vs. 79%; serious AEs 30% vs. 30%, mainly arthralgia and AI-related symptoms; AEs due to study drug 80 pts vs. 49 pts; 35 potential dental problems, of which 31 suspected ONJ, none met diagnosis after further investigation No cases of atypical fracture		only 370 DFS events and therefore needs confirmation Due to dramatic benefit in terms of fractures IDMC recommended pt choice of unblinding with optional start of denosumab (3 years, 7 doses of 60 mg) for pts on placebo; this will occur in 2016 DFS from oral presentation Listed by EBCTCG but no data

Abbreviations: AEs, adverse effects; BMD, bone mineral density; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HR+, hormone-receptor positive, HR, hazard ratio; iv, intravenously; LABC, locally advanced breast cancer; ns, not significant; ONJ, osteonecrosis of the jaw; OS, overall survival; po, per os (orally); ZOL, zoledronic acid

Table 4-3. Ongoing trials without publication of results[2].

Trial name(s) or location, enrolment; NCT or other number	Number of patients	Patient characteristics	Arms or comparison	Outcome	Notes
Success A 2005-2007 EUDRA-CT No. 2005-000490-21 NCT02181101 Andergassen, 2013 [139]; Rack, 2015 [66] [abstract]	3754	High-risk breast cancer (N+ or T2-T4 or grade 3 or age ≤35 y or HR-). Adjuvant chemotherapy randomized: 3 cycles epirubicin-fluorouracil-cyclophosphamide followed by 3 cycles of either docetaxel or gemcitabine-docetaxel	2×2 design. 2 vs. 5 y ZOL in 2nd randomization; ZOL at 4 mg iv q3m for 24 m vs. q3m for 24 followed by q6m for 36 m	Primary: DFS Secondary: OS, distant metastasis, survival, QoL, skeletal morbidity, secondary cancers	Ongoing, survival and metastasis results not reported; listed in EBCTCG but no data Exclude pts with current active dental problems including infection of the teeth or jawbone (maxilla or mandibular); dental or fixture trauma, or a current or prior diagnosis of ONJ, of exposed bone in the mouth, or of slow healing after dental procedures. Exclude if recent (within 6 weeks) or planned dental or jaw surgery (e.g., extraction, implants)
TEAM IIb, BOOG 2006-04 Leiden University, Netherlands, 2006-2010 ISRCTN17633610 Netherlands Cancer Institute, 2014 [16] ISRCTN registry	1116	Stage I-III; ER+ and/or PR+, will receive adjuvant hormonal therapy (tamoxifen and/or exemestane) Postmenopausal women: age more than or equal to 50 y and amenorrhoea for more than one year; or bilateral surgical oophorectomy and no HRT (any age is acceptable); or age less than 50 with natural amenorrhoea more than one year at breast cancer diagnosis (and uterus in situ). Postmenopausal due to chemotherapy excluded	Adjuvant systemic therapy including hormonal therapy ± ibandronate (50 mg/d for 3 y)	Primary: 3-y DFS Secondary: metastasis, recurrence, OS, 5-y DFS, safety	Ongoing, completed enrolment, study results not reported; listed in EBCTCG but no data Exclude pts with current active dental problems including dental abscess or infection of the jawbone (maxilla or mandible), or a current or prior diagnosis of ONJ requiring maxillo-facial surgery Exclude if recent (within four weeks of study entry) or planned dental or jaw surgery (e.g., extraction, implants).
D-CARE, 2010-2012 NCT01077154 Goss, 2013 [21] [abstract]	4500	Early stage (stage II-III), high risk of recurrence (N+, T3, or T4)	Denosumab (120 mg sc monthly for 6 months then every 3 months for total of 5 y) vs. placebo	Primary: bone metastasis free survival Secondary: DFS, OS, safety	Enrolment complete, no results yet, follow-up ongoing; listed in EBCTCG but no data Exclude pts with prior history or current evidence of osteomyelitis/ONJ; active dental or jaw condition which requires oral surgery; planned invasive dental procedure for the course of the study; or non-healed dental or oral surgery

[2] See also studies in Table 4-2 as final data for many of those trials is still pending

GeparX, 2016- NCT02682693 Kummel, 2016 [abstract] [140]	778 (planned)	Primary cT1c-cT4a-d BC; centrally confirmed HR-; and centrally assessed HER2, Ki-67, TIL and RANK status on core biopsy	Neoadjuvant chemotherapy (+/- denosumab (120 mg sc q4w×6)	Primary: pCR (ypT0 ypN0) Secondary: pCR in subgroups, breast conservation rates, toxicity, compliance, survival	Recruitment to start mid 2016 in 60 sites in Germany, planned to take 18 months
CHO-BC-039 NCT02595138	430 (planned)	Triple-negative, early (stage II-III)	Zoledronic acid	Primary: DFS Secondary: OS, adverse effects	Chinese Academy of Medical Sciences Started October 2015, estimated primary completion October 2018
HOBOE, version 2 NCT00412022	1050	Original: age ≥18 (triptorelin if premenopausal); letrozole in both arms Version 2: premenopausal only (triptorelin + letrozole in both arms)	Zoledronic acid, 4 mg q6m for 5 y	Primary: DFS (version 2) Secondary: BMD, OS, toxicity; DFS (original version)	Study amended so that after enrolling 500 pts (March 2010) it enrolled premenopausal pts only and changed the primary outcome to be DFS in premenopausal pts receiving triptorelin + letrozole See Table 4-1 for early data from the original protocol Enrolment 2004-2015; estimated primary completion March 2016; estimated study completion March 2017

Abbreviations: BMD, bone mineral density; DFS, disease-free survival; ER+, estrogen-receptor positive; HER2, human epidermal growth factor receptor 2; HR-, hormone-receptor negative; HRT, hormone-replacement therapy; iv, intravenously; N+, node-positive; ONJ, osteonecrosis of the jaw; OS, overall survival; pCR, pathologically complete response; pts, patients; PR+, progesterone-receptor positive; QoL, quality of life; sc, subcutaneously; ZOL, zoledronic acid

Study Design and Quality

The EBCTCG (see https://www.ctsu.ox.ac.uk/research/ebctcg) is an international collaboration formed in 1985 to evaluate studies on early (operable) breast cancer. They obtain individual patient data from all relevant RCTs throughout the world. Individual patient meta-analysis is considered the strongest evidence [170] and provides the most reliable and least biased means of addressing questions that are not answered in individual RCTs [171]. The EBCTCG had strict inclusion criteria and protocols and included individual patient data for all studies; it was considered unnecessary to extract data from or evaluate the quality of all of the individual trials included by the EBCTCG. Additionally, the individual patient data and several of the reported outcomes are not available except in the meta-analysis. However, as mentioned earlier and discussed below, there were also concerns about and limitations in the meta-analysis, and certain key trials addressing questions not covered in the meta-analysis were looked at in more detail. In order to conduct meta-analysis combining different drugs, there must be reason to believe results are homogeneous. There was controversy about whether it was appropriate to include all bisphosphonates as a group, and the EBCTCG report did not address their rationale for doing so. Results for bisphosphonates other than clodronate and zoledronic acid are extremely limited (or non-existent for several agents) and inconsistent. Inclusion of many extremely small trials not designed to measure the outcomes of interest, and without any publications including these outcomes, was also considered controversial.

The EBCTCG meta-analysis included data from trials starting before 2008 in which there was random assignment between bisphosphonate (any type, does, or schedule) versus a control group with no bisphosphonate. All other treatments had to be similar for both groups. During 2012 to 2014 the EBCTCG authors requested individual patient information directly from the study investigators on date of randomization, allocated treatment, menopausal status, age, tumour grade, diameter, locoregional lymph node involvement, human epidermal growth factor receptor 2 status, and estrogen receptor (ER) and progesterone receptor status, dates and sites of any breast cancer recurrence, other second primary cancer, bone fracture, and the date and cause of death.

Primary outcomes in the analysis were breast cancer recurrence (distant, locoregional, or new primary in the contralateral breast); distant recurrence, ignoring any previous locoregional or contralateral recurrence; and breast cancer mortality. Secondary outcomes were all-cause mortality, death without recurrence, bone recurrence as the first distant recurrence (with or without concurrent other recurrence), other first (extra-skeletal) distant recurrence, locoregional recurrence as first event (ipsilateral breast, chest wall, or locoregional lymph nodes), contralateral new primary breast cancer as first event, and any bone fractures.

Bisphosphonate and control groups were compared on an intent-to-treat basis, regardless of compliance. Time-to-event analysis was conducted using log-rank statistics, with groups stratified by age, ER status, nodal status, and trial. Subgroups were pre-specified and included sites of first distant recurrence (bone, other), menopausal status, class of bisphosphonate, and specific bisphosphonate used. Menopausal status was categorized as premenopausal, perimenopausal, or postmenopausal, with postmenopausal being natural or induced (luteinising hormone-releasing hormone analogues or oophorectomy). Age groupings (<45, 45–54, and ≥55 years) were also used as menopausal status was not always available. For patients of unknown menopausal status, those less than age 45 years were classified as premenopausal, those age 45-54 years classified as perimenopausal, and those age ≥55 years as postmenopausal (presentation on EBCTCG website). Exploratory investigation looked at the role of ER status, nodal status, histological grade, use or not of adjuvant chemotherapy, and follow-up period. Bone recurrence was used as the primary endpoint for subgroup comparisons since it was the only recurrence significantly reduced by bisphosphonate use.

Data on a per-trial basis was presented in Forest plots, with separate plots for each outcome; these were presented for all patients and separately for the subgroup of postmenopausal patients. In these plots, trials were grouped and results calculated for categories of clodronate less than two years or for two years or more; and for aminobisphosphonate less than one year, approximately one year, two years, and greater than two years (of which all trials were for three to five years). As data was listed by trial, it was possible to determine which bisphosphonate contributed to the results for each of these categories. All this information is presented as supplementary data and a thorough analysis of it was not presented in the text. This is considered a severe shortcoming of the meta-analysis.

A few individual studies in the EBCTCG meta-analysis addressed specific issues and therefore the original publications were looked at in more detail. For these trials, as well as key trials not included in the EBCTCG overview, additional details of trial design were looked at to aid in assessing quality (see Appendix 5). As indicated in the inclusion criteria, all trials were prospective randomized trials. Most were open label, though the ABSCG-18 and D-CARE trials of denosumab were double-blind. Outcomes assessment was not blinded; blinding is not expected to have a large influence for measures of survival and recurrence. Baseline characteristics were generally balanced among the treatment and control groups. Of potential concern is that the Z-FAST, ZO-FAST, and E-ZO-FAST were industry sponsored and with several of the investigators/co-authors from the sponsoring company. Trials by the ABCSG received industry funding (drugs only in the ABCSG-12 trial, other support in the ABCSG-18 trial); however, the role was clearly indicated and was not assessed as being of concern. THE AZURE trial also received partial funding from Novartis; however, the role was clearly defined and did not include data interpretation, analysis, or publication decisions. The SWOG S-0307, TEAM IIb, and D-CARE trials are ongoing with no full publications and many details are not yet available. In the SWOG S-307 trial, interim results were released in abstract form due to an assessment that there was no realistic chance of statistically significant difference. The GAIN trial results were released early based on a futility assessment and therefore is considered underpowered. Completeness of follow-up was also relatively low (77%) in this trial. In the ABCSG-18 trial, large differences in fracture rate led the data monitoring committee to recommend patients in the control arm be allowed to receive denosumab if they so choose; this is expected to complicate longer-term follow-up analysis.

The overall assessment is that study results are of high quality, with the limitation that some outcomes have not yet been completely reported. This limitation will be noted in the following results and discussion.

Outcomes

EBCTCG Meta-analysis

The EBCTCG meta-analysis [11] included data from 18,766 women in 26 trials. Of women with known nodal status, 66% were node positive, and 83% of all study participants had received systemic chemotherapy. Most (97%) of women were in trials investigating use of bisphosphonate for two to five years' duration. There were 3453 first recurrences and 2106 deaths. Based on the Kaplan-Meier curves and 10-year risk of recurrence data (see Table 4-4), use of bisphosphonates gave the greatest improvement in bone recurrence (RR=0.83, p=0.004) and bone fractures (RR=0.85, p=0.02). Other outcomes that included bone recurrence were also improved, although to a lesser extent (distant recurrence RR=0.92, p=0.03; breast cancer mortality RR=0.91, p=0.04; any death RR=0.92, p=0.06; recurrence RR=0.94, p=0.08). There appeared to be no effect on distant recurrence outside bone (RR=0.98, p=0.69). For the subgroup of premenopausal patients, bisphosphonate had no significant effect on these outcomes. In contrast, in postmenopausal patients bisphosphonates had greater benefit in all

the outcomes (i.e., lower risk ratios and more highly significant differences) than for the full patient population. Only bisphosphonate effect on distant recurrence outside the bone was not statistically significant (p=0.10). Again, effect was greatest for bone recurrence (RR=0.72, p=0.0002).

Table 4-4. 10-year risk of recurrence, mortality or fractures and associated rate ratios from Kaplan-Meier curves in the EBCTCG meta-analysis [11].

Outcome	Recurrence rate, rate ratio, 95% confidence interval, and significance		
	All patients (n=18,766)	Premenopausal (n=6,171)	Postmenopausal (n=11,767)
Recurrence	24.9% vs. 25.9% at 10 y RR=0.94 (0.87–1.01), p=0.08	29.4% vs. 28.7% RR=1.02 (0.91-1.15), p=0.69	22.8% vs. 25.8% RR=0.86 (0.78–0.94), p=0.002
Distant recurrence	20.4% vs. 21.8% at 10 y RR=0.92 (0.85–0.99), p=0.03	25.6% vs. 24.6% RR=1.02 (0.90-1.15), p=0.81	17.9% vs. 21.2% RR=0.82 (0.74–0.92), p=0.0003
Bone recurrence	7.8% vs. 9.0% at 10 y RR=0.83 (0.73–0.94), p=0.004	10.3% vs. 10.3% RR=0.92 (0.75-1.12), p=0.42	6.6% vs. 8.8% RR=0.72 (0.60–0.86), p=0.0002
Distant recurrence outside bone	13.6% vs. 14.1% RR=0.98 (0.89-1.08), p=0.69	17.0% vs. 15.9% RR=1.08 (0.92-1.26), p=0.35	12.1% vs. 13.6% RR=0.90 (0.79-1.02), p=0.10
Breast cancer mortality	16.6% vs. 18.4% at 10 y RR=0.91 (0.83–0.99), p=0.04	20.6% vs. 20.7% RR=1.00 (0.86-1.15), p=0.96	14.7% vs. 18.0% RR=0.82 (0.73–0.93), p=0.002
Any death	20.8% vs. 22.3% RR=0.92 (0.85-1.00), p=0.06	22.3% vs. 22.3% RR=1.01 (0.89-1.16), p=0.84	21.1% vs. 23.5% RR=0.86 (0.77-0.96), p=0.005
Bone fractures	9.1% vs. 10.4% RR=0.85 (0.75–0.97), p=0.02	8.9% vs. 9.7% RR=0.98 (0.76-1.26), p=0.85	9.1% vs. 10.3% RR=0.83 (0.71-0.98), p=0.03

Subgroup analysis was conducted for several factors, with an emphasis on the outcome of bone recurrence (see Table 4-5). The EBCTCG presented this data in forest plots, and while the trends are the same as for the Kaplan-Meier curves, the confidence intervals are not identical, likely due to use of 95% confidence intervals in the curves and 99% confidence intervals in the forest plots for subgroups and 95% intervals in totals.

Forest plots reporting individual trials grouped by class of bisphosphonate (clodronate or aminobisphosphonate [zoledronic acid, ibandronate, alendronate, risedronate, pamidronate]) and duration of administration were presented for several outcomes. Data was extremely limited for clodronate less than two years and for aminobisphosphonates less than one year or approximately one year. For two years of aminobisphosphonate compared with none or placebo there was a non-significant improvement in bone recurrence (3.5% vs. 4.2%, RR=0.74, 95% CI 0.51-1.07, p>0.1) offset by an increase in distant recurrence outside bone (6.3% vs. 5.0%, RR=1.17, 95% CI 0.87-1.50, p>0.1), and no difference in mortality (5.7% vs. 5.4%, RR=0.95, 95% CI 0.70-1.28, p>0.1. The GAIN/GBG 33 trial was the only large trial (n=3023) administering aminobisphosphonate (ibandronate) for two years, and results for this category are almost entirely due to this study. The ARIBON trial was the only other using ibandronate, and there were no recurrence events reported. Due to the limited and conflicting data with

very wide confidence intervals due to small studies with few events, no other conclusions are apparent for trials administering bisphosphonates for two years or less.

Table 4-5. Subgroup analysis from forest plots for bone recurrence in the EBCTCG meta-analysis [11].

Factor	Subgroup	Number of patients, n	Events (%) and rate ratio with confidence interval
Overall	All patients	18,766	5.0% vs. 6.1%, RR=0.829 (95% CI 0.730-0.941), p=0.004
	Pre-menopausal	6,171	6.6% vs. 7.4%, RR=0.92 (99% CI 0.71-1.20)
	Postmenopausal	11,767	4.1% vs. 5.5%, RR=0.72 (99% CI 0.57-0.90)
Age	<45 y	4,616	6.6% vs. 7.1%, RR=1.00 (99% CI 0.79-1.26)
	45-54 y	6,765	4.3% vs. 5.4%, RR=0.83 (99% CI 0.61-1.11)
	Pre-menopausal	2,627	5.4% vs. 6.3%, RR=0.88 (99% CI 0.63-1.23)
	Postmenopausal	3,345	3.2% vs. 4.8%, RR=0.64 (99% CI 0.40-1.04)
	55-69 y	6,336	5.1% vs. 6.5%, RR=0.74 (99% CI 0.56-0.98)
	≥70 y	1,052	2.4% vs. 4.2%, RR=0.49 (99% CI 0.19-1.29)
	≥55 y	7,388	4.7% vs. 6.2%, RR=0.72 (99% CI 0.59-0.88)
Duration	<1 y	560	1.4% vs. 1.4% (limited data)
	2 y	5,172	5.5% vs. 7.4%, RR=0.76 (99% CI 0.56-1.04)
	Postmenopausal	2,672	5.3% vs. 8.0%, RR=0.60 (99% CI 0.39-0.92)
	>2 y	13,034	5.0% vs. 5.9%, RR=0.85 (99% CI 0.70-1.04)
	Postmenopausal	9,020	3.7% vs. 4.9%, RR=0.77 (99% CI 0.59-1.01)
Bisphosphonate type and duration	Clodronate, 2-3 y	4,981	5.6% vs. 6.5%, RR=0.79 (95% CI 0.62-1.00), p=0.05
	Postmenopausal	2,762	4.6% vs. 7.0%, RR=0.57 (95% CI 0.41-0.79), p=0.0007
	Aminobisphosphonate	13,713	4.9% vs. 5.9%, RR=0.85 (99% CI 0.70-1.03)
	2 y	3,514	3.5% vs. 4.2%, RR=0.74 (95% CI 0.51-1.07), p>0.1
	Postmenopausal	1,743	3.8% vs. 4.9%, RR=0.63 (95% CI 0.39-1.03), p=0.06
	>2 y	9,711	5.7% vs. 6.6%, RR=0.86 (95% CI 0.73-1.02), p=0.08
	Postmenopausal	7,187	4.1% vs. 5.1%, RR=0.83 (95% CI 0.66-1.03), p=0.09
	Postmenopausal	9,003	4.0% vs. 5.0%, RR=0.79 (99% CI 0.60-1.03)
	Zoledronic Acid	9,290	4.3% vs. 5.4%, RR=0.80 (99% CI 0.63-1.03)
	Postmenopausal	7,090	3.4% vs. 4.5%, RR=0.73 (99% CI (0.53-1.00)
	Ibandronate	3,072	3.8% vs. 4.7%, RR=0.75 (99% CI 0.46-1.22)
	Postmenopausal	1,412	4.2% vs. 5.9%, RR=0.62 (99% CI 0.32-1.21)
	Risedronate	398	0% vs. 1% (limited data, RR not reported)
	Pamidronate	953	17.4% vs. 15.4%, RR=1.17 (99% CI 0.83-1.64)*
	Postmenopausal	319	19.1% vs. 15.6% (limited data, RR>1)*
	Alendronate	None	No data

*Both pamidronate and control data very high compared with data in other trials

Four trials (4981 patients) administered clodronate for two to three years and, compared with the placebo or control group, found improvement in bone recurrence (5.6% vs. 6.5%; RR=0.79, 95% CI 0.62 to 1.00, p=0.05) and mortality (15.7% vs. 18.1%, RR=0.82, 95% CI 0.71 to 0.95, p=0.007). In postmenopausal patients, clodronate significantly reduced bone

recurrence (4.6% vs. 7.0%, RR=0.57, 95% CI 0.41 to 0.79, p=0.0007), breast cancer mortality (10.6% vs. 14.2%, RR=0.66, 95% CI 0.52 to 0.83, p=0.0004), any death (17.4% vs. 21.3%, RR=0.77, 95% CI 0.64 to 0.93, p=0.005), and fractures (8.4% vs. 10.7%, RR=0.77, 95% CI 0.59 to 0.99, p=0.05).

Nine trials (9711 patients) administered aminobisphosphonate for three to five years (categorized by the EBCTCG as more than two years). Seven of these reported bone recurrence data and suggested improvement with bisphosphonate (5.7% vs. 6.6%, RR=0.86, p=0.08), although not statistically significant. However, if the DBCG 89D trial is removed from the analysis then RR=0.79 and p=0.01. Analysis elsewhere indicates this trial is the only one using pamidronate (all the rest in the comparison used zoledronic acid), and both bisphosphonate and control group bone recurrence rates are much higher than for other analysis, except for patients with N4+ nodal status. It appears that patients in this trial have differences compared with other trials. Review of the trial publications [52,53] indicates patients in this study may have more advanced cancer, as well as more extensive follow-up to detect bone metastases (x-ray of the spine and pelvis every six months and bone scintigraphy every year) than some of the other trials.

The EBCTCG meta-analysis found that, in postmenopausal patients, zoledronic acid reduced bone recurrence (3.4% vs. 4.5%, RR=0.73, 99% CI 0.53 to 1.00); the difference in breast cancer mortality was not statistically significant (7.1% vs. 7.9%, RR=0.88, 99% CI 0.69 to 1.11). For the current review, results were recalculated to include only trials using three to five years of zoledronic acid (i.e., all aminobisphosphonate trials of this duration as reported by the EBCTCG meta-analysis with the DBCG 89D pamidronate trial excluded). Bone recurrence was then 3.4% versus 4.6% (RR=0.72, 95% CI 0.57 to 0.92, p=0.008) and mortality was 8.8% versus 9.8% (RR=0.87, 95% CI 0.74 to 1.03], p=0.10).

Further subgroup analysis was also conducted in the EBCTCG meta-analysis. There were no significant differences based on nodal status, grade, ER status, or concomitant chemotherapy. As shown in Table 4-5, bisphosphonates resulted in less bone recurrence in patients >55 years old, 45-54 years old and postmenopausal, and in postmenopausal patients overall. When subdivided according to bisphosphonate type there was insufficient data for alendronate and risedronate; the study for pamidronate showed no benefit.

The meta-analysis found a significant reduction in bone fractures (6.3% vs. 7.3%; RR=0.85, p=0.02) and five-year fracture risk (5.1% vs. 6.3%) in studies with two to three years clodronate or more than two years aminobisphosphonate (no data for shorter trials). When sub-grouped according to menopausal status, the benefit was greater in postmenopausal patients (5.3% vs. 6.6% at five years and 9.1% vs. 10.3% at ten years, RR=0.83, p=0.03) and not statistically significant in premenopausal patients (4.6% vs. 5.1% at five years, 8.9% vs. 9.7% at ten years, RR=0.98, p=0.85).

Some Key Trials in the EBCTCG Meta-analysis

The two largest trials of zoledronic acid, the ABCSG-12 (n=1083) and AZURE (BIG 01/04, n=3360) trials, had helped generate the hypothesis of the relevance of menopausal status to treatment effect. The meta-analysis therefore reported a sensitivity analysis without these trials and found this only marginally weakened the evidence of an interaction with menopausal status, and benefit was still significant in the remaining postmenopausal women. The ABCSG-12 trial was conducted in premenopausal patients with induced menopause [44], while the AZURE trial [45,46] included all patients age ≥18 years [46]. Adverse events were not included in the EBCTCG meta-analysis and so are described in more detail in the next sections. The meta-analysis did not give a separate analysis for ibandronate; as data on ibandronate is almost entirely from the GAIN trial, some details based on this trial are also given.

ABCSG-12

The ABCSG-12 trial [44] studied administration of zoledronic acid (4 mg every six months for three years) in premenopausal patients receiving endocrine therapy (tamoxifen vs. anastrozole) along with goserelin for ovarian suppression. This trial included thorough monitoring and reporting of adverse events [42]. Data interpretation is complicated due to the anastrozole versus tamoxifen comparison as well, and a large portion of adverse events appeared due to the endocrine treatment. There was no increase in serious adverse events (life-threatening, permanent damage, hospitalization, required medical/surgical intervention) in patients who received zoledronic acid compared with those without zoledronic acid. There were three suspected cases of ONJ; however, ONJ was ruled out after a detailed review of dental records. No serious renal events were reported. A cohort of 48 patients at one of the centres, who were treated with zoledronic acid without preventive dental measures, was examined 37 to 74 months after cessation of bisphosphonate therapy [172]. Five patients (10%) were classified as having stage 0 ONJ; no advanced stages were detected. It was concluded there is a need for cooperation between dentists and medical specialists, as well as pretreatment and follow-up dental examinations. Patients administered zoledronic acid had increased rates of minor adverse events: arthralgia (24% vs. 18%), bone pain (35% vs. 25%), nausea/vomiting (8.6% vs. 6.1%), fever (8.9% vs. 2.2%), skin disease (6.5% vs. 4.3%),cognitive disorder (1.4% vs. 0.3%), tachycardia (2.1% vs. 0.8%), peripheral nerve disease (5.7% vs. 3.4%), and hypocalcemia (0.4% vs. 0%).

AZURE (BIG 01/04)

The AZURE trial administered zoledronic acid at 4 mg every three to four weeks for six cycles, then at reduced frequency (eight cycles every three months, five cycles every six months). It included patients with more advanced disease than in the ABCSG-12 trial. To reduce imbalances in tumour and treatment characteristics, the AZURE trial used a minimization process during randomization; one factor was menopausal status (premenopausal, within five years of last menstruation, more than five years since last menstruation, unknown). Secondary subgroup analysis by variables included in the randomization was planned as part of the trial design. There were no differences in adverse effects except for ONJ, which was found only in patients administered zoledronic acid. ONJ was suspected in 33 patients and confirmed in 26 patients (1.5% to 2.1%; there were inconsistencies within and between publications for the percentage).

GAIN

Of 2040 patients administered ibandronate and 1032 controls in the EBCTCG meta-analysis, almost all came from the GAIN trial (2015 ibandronate and 1008 observation). The GAIN publication [51] excluded 29 patients who did not start chemotherapy from the intent-to-treat analysis. The trial included patients with cancers of stage pT1 to operable pT4a-c with at least one pathologically involved axillary or internal mammary lymph node based on resection of ≥10 axillary nodes. Patients were randomized to one of two chemotherapy regimens and to ibandronate versus observation, with ibandronate administered orally at 50 mg/day for two years or until disease progression, unacceptability toxicity, or withdrawal from the study. Of those assigned ibandronate, 78.2% completed treatment as planned. Patients received radiotherapy, endocrine therapy and trastuzumab (after 2005) according to Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) guidelines. Patients with hormone-receptor positive (HR+) tumours received AI or tamoxifen followed by AI if postmenopausal or tamoxifen alone or with luteinizing hormone-releasing hormone analogue if premenopausal. Approximately 77% of patients were HR+ and 52% were postmenopausal (1023 patients on

ibandronate and 526 without). When subdivided according to age, 15% were <40 years, 36% 40 to 49 years, 32% 50 to 59 years, and 18% ≥60 years of age. Overall, 161 patients (85 <40 years of age) had ovarian suppression and therefore would be classified as postmenopausal by the EBCTCG definition.

There was a target of 728 events to detect an increase in DFS at five years by 4.5% (from 75% to 79.5%); however, results were reported early at interim analysis after 405 events including 186 deaths, with 76.8% follow-up for a median of 38.7 months. This was allowed by the independent data monitoring committee after a futility analysis was conducted. The trial found no difference in DFS (hazard ratio [HR]=0.94, 95% CI 0.77 to 1.16, p=0.953) or OS (HR=0.96, 95% CI 0.71 to 1.31, p=0.801). While the conclusion regarding DFS or OS is unlikely to change with further follow-up, there are several subgroup analyses and other outcomes that may reach statistical significance once more events are included in the analysis. When DFS was analyzed according to subgroups, data suggest there may to be more benefit for postmenopausal patients (HR=0.90, 95% CI 0.67 to 1.20) than for pre- or perimenopausal patients, and for those <40 years of age (of which approximately 20% were on ovarian suppression) or ≥60 years of age compared with those 40-59 years of age.

The EBCTCG meta-analysis reported on several other outcomes for the GAIN trial (and for ibandronate based primarily on the GAIN trial) that have not been otherwise published. The EBCTCG did not report DFS; it found no benefit of ibandronate either in the full population or postmenopausal patients for outcomes of OS, recurrence, distant recurrence, or distant recurrence outside bone. The only outcome for which ibandronate appeared to have benefit was bone recurrence, although the difference was not statistically significant (overall 3.9% vs. 4.9%, HR=0.75, 99% CI 0.46 to 1.22, p=0.13; postmenopausal 4.4% vs. 5.1%, HR=0.62, 99% CI 0.32 to 1.21, p=0.07).

Trials Not in the EBCTCG Meta-analysis

SWOG S0307

The SWOG S0307 trial (Table 4-2) [14,15] compared three years of clodronate versus ibandronate versus zoledronic acid. It did not include a non-bisphosphonate control/placebo am. Patients received adjuvant chemotherapy and 58% were postmenopausal or age ≥50 years. It is the only major RCT to give direct comparison of various bisphosphonates. It should be noted that zoledronic acid, clodronate, and ibandronate were dosed as used in metastatic cancer, and are thus much higher than used in osteoporosis treatment. At the fourth formal interim analysis the data monitoring committee recommended early reporting as there was no realistic chance of a statistically significant difference. Results have been published only as an abstract but indicate no differences in five-year DFS (87% to 88%), OS (93%), or fractures. There were no treatment differences based on age or menopausal status. There were small differences in grade 3-4 events (10.5% ibandronate, 8.3% clodronate, 8.8% zoledronic acid) and ONJ (0.6% ibandronate, 0.3% clodronate, 1.2% zoledronic acid).

ABCSG-18

The ABCSG-18 trial [18-20] compared denosumab versus placebo in postmenopausal patients with early HR+ breast cancer being administered AIs. A significant reduction in fractures was reported overall (11.1% vs. 26.2% at 84 months, HR=0.5, p<0.0001) and for various subgroups (see Table 4-2). The recent presentation at the SABCS 2015 conference [20] reported the secondary outcome of DFS; three-year DFS was 93.8% versus 92.6%, five-year DFS was 88.9% versus 86.8%, and seven-year DFS was 83.5% versus 80.4% (HR=0.816, 95% CI 0.66 to 1.00, p=0.051). While follow-up is ongoing, due to the large decrease in fractures a patients'

choice unblinding option will be implemented in 2016, allowing those on placebo to switch to denosumab.

Other trials

Other RCTs with reported data are summarized in Table 4-2. The Slovak Clodronate Collaborative Group (SCCG) trial [130] included 66 patients with locally advanced breast cancer and 7 with metastatic cancer and found non-significant differences with clodronate administration. JONIE-1 [132-134], Z-FAST Japan [136,137], and studies by Abu-Taleb et al [138] and El-Ibrashi et al [135] also investigated zoledronic acid use. Survival or recurrence results were reported in abstracts and differences were non-significant (or significance not stated). Full publications with longer follow-up may provide more information. At this time, however, these results do not modify the conclusions of the EBCTCG meta-analysis and will not be discussed further.

Ongoing Trials

Most of the trials in Table 4-2 do not have fully published final results and follow-up is likely ongoing. In addition, three large ongoing trials without outcome data are listed in Table 4-3. TEAM IIb is studying ibandronate and completed enrolment in 2010 [16]. Success A is comparing two years versus five years of zoledronic acid; enrolment was completed in 2007 but survival and metastasis results have not been published [66,139]. The D-CARE study is comparing denosumab versus placebo in patients with high risk of recurrence. Results should therefore complement those of the ABCSG-18 trial. Enrolment was complete in 2012 [21]. As enrolment for all these trials was complete a few years ago, they may soon provide additional information on the use of bisphosphonates and denosumab.

Differences in Administration

Clodronate was administered orally at 1600 mg/day in most studies although it is sometimes administered intravenously, as in the British Columbia trial [120]. Zoledronic acid was administered at 4 mg intravenously either monthly (as used for bone metastasis), every six months (as used in osteoporosis trials), or some intermediate frequency (e.g., every three months, or monthly for the initial period and then every six months). Ibandronate was administered orally at 50 mg/day as is used in bone metastasis treatment, except in the ARIBON trial where it was administered at 150 mg every 28 days as is used in postmenopausal osteoporosis. The EBCTCG meta-analysis authors suggested effects on bone recurrence were similar (6.2% vs. 7.5% more intensive compared with 2.2% vs. 3.0% low intensity). The differences in the control data suggest trials may have been conducted in different patient populations or with different additional treatments. Different doses or modes were not directly compared within the same trial.

Osteonecrosis of the Jaw

One of the more serious adverse effects of bisphosphonate treatment is ONJ. To lower the risk, many of the more recent trials excluded patients with recent or planned dental or jaw surgery (extraction, implants) (see Tables 4-1 to 4-3). ONJ incidence in patients receiving monthly doses of zoledronic acid for six months and then every three or six months thereafter was 1.5% to 2.1% in the AZURE / BIG 01/04 trial [62] and 1.2% in the SWOG S0307 trial [14]. Several smaller trials administering zoledronic acid at 3 mg to 4 mg every three to four weeks for one to two years also reported ONJ (Washington University, 1.7% [117]; University of Saarland, 2.3% [115], ProBONE II, 3% [128]). With ibandronate (50 mg/day), ONJ occurred in 0.1% of patients in the GAIN trial [51] and 0.6% of patients in the SWOG S0307 trial [14]. A

systematic review by Varun et al [173] calculated ONJ occurred in 2.8% of patients with breast cancer with bone metastasis treated with zoledronate (typically 4 mg/month) or pamidronate.

As development of ONJ is believed to be dependent on both dose and duration of treatment, trials of adjuvant zoledronic acid administered every six months, as is more often used in osteoporosis treatment, are also important. ONJ rates were 0.8% in the immediate administration arm of the E-ZO-FAST trial [55] (1.2% reported in clinicaltrials.gov), 0.45% to 0.95% in the ZO-FAST trial [56], and 2% (upfront arm) or 1% (delayed arm) in the NO3CC trial [67]. The Z-FAST trial included two suspected cases (0.67%); however, one case was ruled inconsistent with ONJ and the other had insufficient evidence for final evaluation [60]. No cases were found in the ABCSG-12 trial [44]. With clodronate, ONJ occurred in 0.06% of patients in the NSABP B-34 trial [47] and 0.3% in the SWOG S0307 trial. Published reviews of lower dose ibandronate in treatment of postmenopausal osteoporosis (150 mg/month orally, or 2 mg every two months or 3 mg every three months intravenously) reported benefit, and with greater effect than a daily oral dose of 2.5 mg [17,70]. ONJ was not detected in the major RCTs, although there have been occasional case reports. Adjuvant studies of ibandronate at these lower doses in early breast cancer were not found.

The ABCSG-18 trial, which administered denosumab at 60 mg every six months, found 31 cases of suspected ONJ, but none met the diagnosis after further investigation.

Other Adverse Effects

The EGCTCG meta-analysis indicates impaired renal function is a known adverse effect but gives no incidence data. Dose modifications based on renal function were part of the protocol in several trials. For example, in the AZURE trial [61] dose reductions and interruptions for renal impairment (calculated creatinine clearance <60 mL/min) were as specified by the current prescribing information. According to a review on safety and compliance [71], renal effects are mainly found with bisphosphonates administered intravenously at high doses, and depend on concentration and infusion rates. Clinically 15 min. Other transient acute-phase reactions for intravenous administration occur in approximately one-third of patients and include low-grade fever, fatigue, arthralgia or myalgia, nausea, and increased bone pain. These effects were reported in the ABCSG-12 trial [42]. The E-ZO-FAST trial [55] also reported mild transient adverse events with zoledronic acid including bone pain, pyrexia, and acute-phase reaction.

Serious ocular or ophthalmic adverse effects such as uveitis, scleritis, and episcleritis are extremely rare but may lead to blindness if untreated. The Tel Aviv trial [75] reported scleritis in one patient treated with zoledronic acid; serious ocular adverse events were not reported in the other trials in the current literature review. However, a recent RCT of intravenous zoledronate for osteopenia found acute anterior uveitis in 8 of 1001 patients (6 had mild/moderate uveitis and 2 had severe uveitis [7]). Other evidence is mainly from case series [76,77], retrospective cohort studies [8], and adverse effect reporting [38]. Symptoms such as ocular pain or loss of vision should be evaluated by an ophthalmologist [6-8]; immediate treatment with steroid eye drops may be required to prevent permanent blindness [7,9,10].

Oral administration has low absorption (<5%) and therefore high doses, which can cause esophagitis and other gastrointestinal events (mucositis, nausea, vomiting, diarrhea), are required. Clodronate is administered in large capsules taken daily which may be difficult to swallow. Clodronate and ibandronate are to be taken on an empty stomach and require the patient to remain upright for at least 30 minutes.

DISCUSSION AND CONCLUSIONS

Given that bisphosphonates and denosumab are bone-modifying agents, it is consistent that the benefit as adjuvant treatment in breast cancer is primarily in preventing recurrence in the bone. The EBCTCG meta-analysis has shown that adjuvant bisphosphonates reduce the rate of bone metastasis and correspondingly improve survival in patients with early breast cancer. As suggested in a few individual studies, the meta-analysis demonstrates that the benefit is restricted to patients that are postmenopausal or >55 years of age. The magnitude of the benefit, however, is small (bone recurrence 6.6% vs. 8.8%, breast cancer mortality 14.7% vs. 18.0%). As these studies cover all non-metastatic cancers, it is expected that the absolute benefit would be less in patients with low-risk cancers, and this may be a factor in deciding whether to use bisphosphonates. While several trials were conducted in HR+ patients receiving AIs, as well as specific subgroups in some of the other trials, the EBCTCG meta-analysis did not report results based on AI use.

The EBCTCG meta-analysis did not distinguish between natural and induced (luteinising hormone-releasing hormone analogues or oophorectomy) menopause. The ABCSG-12 trial [42-44] was conducted in premenopausal patients administered goserelin, plus either tamoxifen or anastrozole, and is therefore most relevant to patients with induced menopause. In these patients zoledronic acid improved risk of disease progression (HR=0.77, p=0.042) and DFS (88.4% vs. 85.0%, HR=0.77, 95% CI 0.60 to 0.99, p=0.042) at a median of 94 months follow-up, as well at earlier analyses. OS benefit was statistically significant up to 76 months follow-up, and the same trend applied at 94 months (OS 96.1% vs. 94.4%, HR=0.66, 95% CI 0.43 to 1.02, p=0.064), although no longer statistically significant. Patients receiving zoledronic acid had fewer distant and locoregional recurrences, though differences were not statistically significant.

Bone-Modifying Effects

While trials on BMD and other similar outcomes were not within the scope of this systematic review, it should be noted that bisphosphonates and denosumab have been found to be effective at treating osteoporosis, improving bone density, and reducing fractures. Guidelines from Alberta [174,175], 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] may be consulted.

As reported in the results section, one of the major potential adverse effects of bone-modifying agents is ONJ. It is especially important considering its debilitating and sometimes irreversible nature. Data in the current review suggests ONJ rates of 1% to 3% with higher intensity treatments in the adjuvant setting, and 0% to 1% with lower intensity treatments. The ONJ rate in metastatic breast cancer treatment was reported to be 2.8% [173], while rates up to 15% are sometimes reported for a broader range of cancers. Recent data from three identically designed trials (with later combined analysis) of denosumab versus zoledronic acid in advanced breast, prostate, and other cancers reported ONJ in 1.8% of patients on denosumab and 1.3% of patients on zoledronic acid (difference not significant) [58]. Dental extraction preceded ONJ events in 63% of cases, while 82% had jaw pain, and 48% had coincident oral infection. The National Cancer Institute of Milan [176] reported incidence of ONJ in patients with metastasis of solid tumours (73% with breast cancer) receiving bisphosphonates decreased from 3.2% to 1.3% following implementation of preventive measures including baseline mouth assessment and dental care, if required. Data in Tables 4-1 to 4-3 include information on inclusion criteria related to dental health and indicate that many of the adjuvant breast cancer trials, especially the more recent ones, performed a dental assessment and excluded patients with recent dental extraction, root canal, or dental implants, or in need of such treatment. While it is unknown what rates of ONJ would be without any dental screening (and associated treatment if required), the body of evidence suggests it may be higher than reported in some of the major trials in which patients with recent dental extractions or other major invasive

work were excluded. While the absolute risk of ONJ is low, it would appear unwise to generalize the finding of overall adjuvant benefit in patients with good oral health to those with major dental problems or recent invasive treatment. This may be especially relevant as a wide range of doses, administration schedules, and treatment durations are being considered for adjuvant therapy.

Selection of Bone-Modifying Agents

Despite the lack of direct evidence from adjuvant trials, it has been suggested that any bisphosphonate shown to have beneficial effects on bone mineral density or fractures may have benefit when used as adjuvant treatment, and may be an unstated premise in the EBCTCG meta-analysis. A brief discussion of osteoporosis guidelines (see Table 4-6) and evidence is therefore considered relevant.

A network meta-analysis of RCTs by Murad et al [177] found denosumab, zoledronate, risedronate, ibandronate, and alendronate all reduced risk of fragility fractures (hip, vertebral, non-vertebral) and the differences between these was not statistically significant. Confidence intervals were wider for ibandronate versus placebo then for the other agents, and the benefit of ibandronate was only statistically significant for vertebral fractures. Some guidelines summarized in Table 4-6 note that evidence for ibandronate is only sufficient with regard to vertebral fractures and the Canadian guidelines do not include ibandronate in their recommendations [1,178]. Ibandronate is not currently approved for use in Canada.

In selecting a bone-modifying agent, factors such as ease of administration, compliance, cost, and availability may be important. Higher compliance is expected to also lead to greater benefit, as a drug is much more effective if used as directed. While several bisphosphonates have been used in patients with osteoporosis (see Table 4-6) and in metastatic disease, most trials of adjuvant use in early breast cancer were limited to clodronate or zoledronic acid and, therefore, the strongest evidence exists for their use. Preliminary results of the SWOG S0307 trial (see subsection on ibandronate above) suggest ibandronate at relatively high doses as used in metastatic trials may be equivalent to clodronate or zoledronic acid and some believe that this is sufficient evidence to use ibandronate in adjuvant treatment. Further follow-up and full publication of this trial is awaited.

Clodronate

Four trials in the EBCTCG meta-analysis evaluated clodronate administered at 1600 mg/day for two to three years' duration. Clodronate significantly improved bone recurrence, mortality, and bone fracture incidence in postmenopausal patients. Of the four trials, many of the results of the Helsinki trial [108-111] were inconsistent with the other trials. It was the smallest trial and the only trial where clodronate resulted in higher distant recurrence outside bone and worse mortality. However, it was also the only study conducted exclusively in node-positive patients and there was imbalance in menopausal status between the arms (48% vs. 57% premenopausal) and therefore in the proportion who received chemotherapy

Table 4-6. Selected drugs recommended in guidelines for osteoporosis prevention or treatment[1].

Group/ Location	Drug						
	Zoledronic Acid	Alendronate	Risedronate	Ibandronate[2]	Etidronate	Clodronate	Denosumab
Osteoporosis Canada [1,179]	• 5 mg, q1y	•10 mg/day or 70 mg/wk	•5 mg/d or 150 mg/month		•400 mg/d for 2 wk then calcium for 10 wk		• 60 mg q6m sc
Alberta [178] (adapted from [1])	•5 mg iv q1y for 3 y (up to 6 y)	•70 mg po q1w for 3-5 y (up to 10 y if high risk)	•35 mg po q1w for 3-5 y (up to 10 y if high risk)				• 60 mg q6m sc
US Food and Drug Administration [5]	•5 mg iv q1y (prevention or treatment)	•35-70 mg/wk po (prevention or treatment)	•35 mg/wk po •150 mg/ month[3] (prevention or treatment)	• 150 mg/month po • 3 mg q3m iv (prevention or treatment)			• 60 mg q6m (treatment)
US Food and Drug Administration ([4]	•5 mg iv q1y (treatment) or q2y (prevention)	•5 mg/d or 35 mg/wk po for prevention •10 mg/d or 70 mg/wk po for treatment	•5 mg/d po •35 mg/wk po	• 150 mg/month po for prevention or treatment • 3 mg q3m iv for treatment			• 60 mg q6m sc
National Osteoporosis Guideline Group, UK [2] [3]	•5 mg iv q1y •Review after 3 y	•20 mg/d or 70 mg/wk treatment •5 mg/d prevention •Preferred due to lower cost •Review after 5 y	•5 mg/d or 35 mg/wk •Review after 5 y	• 150 mg/m oral • 3 mg q3m iv • Review after 5 y	Give in 90d cycles: 400 mg/d for 14d then calcium for 76 d		• 60 mg q6m sc
Europe [180][4]	•5 mg/y	•70 mg/wk	•35 mg/wk	• 2.5 mg/d • 150 mg q1m po • 3 mg q3 m iv		[Licenced for osteoporosis in only a few countries]	• 60 mg q6m

Abbreviations: iv, intravenously; po, per os (orally); sc, subcutaneously

[1] Drugs such as estrogens, teriparatide, and tibolone have also been used for osteoporosis, but should not be used as adjuvant therapy in patients with breast cancer.

[2] Evidence for efficacy of ibandronate is weaker than for the other agents. It has been found to reduce vertebral fractures; evidence is limited for non-vertebral fractures.

[3] In a single dose or in two 75 mg does on consecutive days

[4] Drug doses are those most commonly used or found equivalent, not a recommendation.

(50% vs. 58%). The overall evidence is sufficient to conclude that clodronate has benefit as adjuvant treatment in postmenopausal women with breast cancer.

Zoledronic Acid

In the EBCTCG meta-analysis [11], zoledronic acid for three to five years decreased bone recurrence and improved survival. As mentioned in the results, data is quite limited for use of aminobisphosphonates for less than three years and no conclusions other than as discussed for the GAIN trial above can be made for shorter periods of administration. There are studies that suggest that even a single dose of zoledronic acid may have a sustained benefit on BMD and corresponding decrease in bone resorption [78,181]. It is therefore considered possible that shorter duration may also have some benefit in the adjuvant setting and further research regarding treatment duration is needed.

All the trials in the EBCTCG category ">2 years aminobisphosphonate" (except the DBCG 89D trial of pamidronate) administered zoledronic acid for three to five years. There is a small but clear benefit of zoledronic acid in preventing bone recurrence in postmenopausal women and possible benefit in premenopausal women. Unfortunately, the EBCTCG does not report information on the premenopausal group, but calculations without the DBCG 89D trial of pamidronate indicate bone recurrence rates of 8.1% versus 9.5%, based on 1890 non-menopausal patients, compared with rates of 3.4% versus 4.6% based on 6868 postmenopausal patients. The premenopausal patients come from a portion of patients from the AZURE/BIG1-04 trial. In the AZURE/BIG 1-04 trial [46], bone metastasis was improved overall (8.0% vs. 10.1%, HR=0.81, p=0.022), in postmenopausal patients (7.0% vs. 9.7%), and appears to be improved in other patients (9.0% vs. 10.6%) (calculated from EBCTCG data). The publication of the trial [46] reports improved DFS for postmenopausal patients (HR=0.78, p=0.02). For OS, patients at least five years postmenopausal had benefit (HR=0.81, 95% CI 0.63 to 1.04) while there was no effect on OS for other patients (HR=1.04). Overall there is insufficient data to determine whether the possible benefit on bone events in premenopausal patients is offset by other recurrences. There is sufficient evidence for use of zoledronic acid for three to five years as adjuvant therapy in postmenopausal women. Shorter duration may be effective but data is limited.

Ibandronate

Intensive ibandronate (50 mg/day) was used in the GAIN trial [51], however this trial did not find significant differences in OS or DFS. In the EBCTCG meta-analysis of ibandronate based on this trial, the only outcome for which ibandronate appeared to have benefit was bone recurrence (p=0.07 in postmenopausal patients). The only other completed trial with ibandronate is the ARIBON trial which was small (50 patients randomized) and used a lower dosage (150 mg every 28 days); no cases of recurrence or death were reported. The SWOG S0307 trial, reported only as abstracts [14,15], suggests clodronate, ibandronate (50 mg/day for three years), and zoledronic acid have similar DFS and full publication is awaited. The TEAM IIb trial is an ongoing trial evaluating ibandronate [16]. Both these trials use relatively intense doses of ibandronate as used in metastatic cancer trials. At this time, evidence for adjuvant use of ibandronate is considered weak.

Pamidronate and Risedronate

The DBCG 89D trial [52,53] is the only one evaluating pamidronate and both bisphosphonate and control group bone recurrence rates were much higher than for other trials. The trial found no difference in bone recurrence or OS. N02C1, ARBI, and SABRE used risedronate, but were primarily studies of BMD. These were small studies with few reported events (seven deaths and two cases of bone recurrence in all studies combined) and no conclusions can be made.

Denosumab

The role of denosumab in adjuvant therapy of breast cancer is the subject of the ABCSG-18 and D-CARE trials which are ongoing. The ABCSG-18 trial reported a 50% decrease in fractures. The recent presentation at the SABCS 2015 conference reported seven-year DFS of 83.5% versus 80.4%, HR=0.816, 95% CI 0.66-1.00, p=0.051. While longer and more complete follow-up is desirable, due to the dramatic benefit in terms of fractures the independent data monitoring committee recommended patient choice of unblinding with optional start of denosumab (three years, seven doses of 60 mg) for patients on placebo, starting in 2016. This decision will complicate any further analysis and interpretation of longer-term data. It is hoped that there will be a full publication of the trial with all data collected right up until unblinding. The D-CARE trial is being conducted in a subset of women with high risk for recurrence, and administering denosumab at 120 mg monthly for six months and then every three months thereafter for five years. Due to this higher intensity treatment, it will not answer the question of whether denosumab at levels suggested by the ABCSG-18 and osteoporosis trials is beneficial.

Routes of Administration

The bone-modifying agents under consideration may be administered orally, intravenously, or subcutaneously. Oral bisphosphonates (clodronate, alendronate, risedronate, ibandronate) are more likely to cause gastrointestinal adverse effects and can be difficult to swallow for some patients. To reduce adverse effects and maximize absorption patients need to remain upright for 30 to 60 min and take medication with water on an empty stomach. These requirements and adverse effects may be especially important in elderly patients or those who have other gastrointestinal problems. Frequency of administration may be a factor, as clodronate is taken daily (or twice a day), while other oral bisphosphonates may be administered less frequently (weekly or monthly) and thus there may be different effects on quality of life and compliance. Studies in postmenopausal osteoporosis have found greater compliance to oral medications which need to be taken less frequently [17,54,70]. Oral ibandronate (150 mg) monthly was found comparable to weekly alendronate and superior to daily ibandronate (2.5 mg). Some patients prefer oral medication because a hospital visit is not required. Clodronate had a high rate of non-compliance in several studies [71], although in the SWOG S0307 trial [15] 76% of patients indicated a preference for daily oral medication compared with intravenous therapy (zoledronic acid every four weeks for six months then every three months for two and a half years). Preference compared with zoledronic acid at longer intervals of every six months was not reported.

Zoledronic acid is administered intravenously and is relatively long-lasting; while it is generally administered monthly in the metastatic setting, for adjuvant use administration every six months is common, and yearly administration is used in osteoporosis treatment. The short-term side effect profile is different than for oral bisphosphonates. While there are fewer gastrointestinal effects, acute-phase response resulting in mild to moderate flu-like symptoms may occur after intravenous administration. The less frequent administration compared with the oral bisphosphonates is considered desirable for some patients. This must be balanced against the required hospital visit required for intravenous administration. Travel time, cost, and inconvenience, as well as a general dislike of hospitals may be important considerations.

Denosumab is generally administered by subcutaneous injection every six months in osteoporosis treatment and this frequency was also used in the ABCSG-18 adjuvant trial. This timing shares the same advantage as for zoledronic acid with respect to infrequent administration, without requiring intravenous use.

Dose, Frequency, and Timing of Administration

There is much uncertainty regarding minimal and optimum dose and frequency of administration. There is no data available from within-study comparisons in the adjuvant setting. Lower doses and less frequent administration are used in prevention or treatment of osteoporosis (see Table 4-6), and some of the adjuvant trials had similar administration to these studies, while others gave bisphosphonates or denosumab at higher doses and frequency as is used in metastatic trials and regimens. The meta-analysis did not find a significant difference between low (osteoporosis) and high (cancer metastasis) dose/frequency, but did not subdivide results according to bisphosphonate used (clodronate or other). At higher dosages the adverse effects are much greater, so it is desirable to give the lowest effective dosage. At this time there is insufficient evidence that higher doses are more effective, although it is plausible there may be a difference depending on stage of disease.

There are studies that suggest that even a single dose of zoledronic acid may have a sustained benefit on BMD and corresponding decrease in bone resorption [78,181]. In osteoporosis regimens, zoledronic acid is generally administered at 5 mg once a year. The US FDA labeling for zoledronic acid is 5 mg yearly for treatment of postmenopausal osteoporosis and every two years when used for osteoporosis prevention. Discontinuation or drug holiday for patients not at high risk of vertebral fractures has been suggested, but data is limited. This will depend to some extent on the agent used, as residual effects vary, and are believed to be longest with zoledronic acid.

Weekly alendronate or risedronate or weekly or monthly ibandronate (see Table 4-6) have been found to have positive bone effects, and may be more convenient than daily oral clodronate. As noted, these have not been sufficiently tested in adjuvant trials. Additional trials comparing these agents and various doses are urgently needed.

Especially due to a trend to give endocrine therapy for longer periods (up to 10 years), the question arises as to whether bone-modifying agents should be administered for the same period. Zoledronic acid was administered for the duration of endocrine therapy in the ABCSG-12 trial (three years) [44] and Z-FAST/ZO-FAST/E-ZO-FAST trials (five years) [55,56,60]. These trials all administered zoledronic acid at 4 mg every six months and accounted for almost all the bone recurrence events in the EBCTCG meta-analysis [11] using this administration frequency. At this time there is no evidence for which to evaluate longer periods of administration.

The AZURE / BIG 1-04 trial [45,46,61,62] accounted for almost all events in the EBCTCG meta-analysis for trials administering zoledronic acid at greater frequency (4 mg every three to four weeks). In the AZURE trial, after six doses the frequency of administration was reduced (every three months for eight doses then every six months for five doses). These patients had more advanced disease, and this is reflected in higher bone recurrence rates for the postmenopausal patients in both zoledronic acid and control groups (7.0% vs. 9.7%, respectively) compared with the trials administering zoledronic acid less frequently (2.9% vs. 3.7%) (calculated from EBCTCG data). Adverse events, including ONJ were greater with more frequent administration.

In most trials, bisphosphonate were started soon after surgery or chemotherapy: Royal Marsden within six months from primary treatment [48]; NSABP B-34 within two weeks of randomization after surgery [https://clinicaltrials.gov/ct2/show/NCT00009945]; AZURE together with adjuvant chemotherapy [within sixty days of surgery] or within thirty days of starting neoadjuvant chemotherapy [http://www.controlled-trials.com/ISRCTN79831382], Z-FAST within twelve weeks of completing surgery, radiotherapy, or chemotherapy [118]; SWOG 0307 within twelve weeks of surgery or eight weeks of chemotherapy [https://clinicaltrials.gov/ct2/show/NCT00127205]). In the ZO-FAST trial [56,63] of immediate versus delayed administration of zoledronic acid (until decline in bone density or fracture), DFS

and BMD were better with immediate administration, although there was still a DFS benefit (HR=0.46, p=0.0334) of starting later compared with none at all [56].

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

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel (see Appendix 1), the PEBC Report Approval Panel (RAP), and the ASCO Clinical Practice Guidelines Committee (CPGC). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 19 members of the GDG Expert Panel, 17 members cast votes and 2 abstained, for a total of 89% response in May 2016. Of those that cast votes, all approved the document. The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. It should be clarified that RCTs were not designed to test the hypothesis that bone modifying agents would have different efficacy based on age/hormonal status. Describe subset analysis/meta-analysis difference.	Some more details have been added to the background.
2. Uncommon/rare adverse effects other than ONJ, such as atypical fractures, and renal and ophthalmologic toxicities, should be mentioned. Advocate for post-marketing reporting of adverse events.	This has been added to the preamble, Recommendation 6, and the systematic review. Statements have also been added that the user should refer to other prescribing information.
3. National Comprehensive Cancer Network (NCCN) guidelines remain silent on bisphosphonates in women with normal bone density and insurers sometimes reject zoledronic acid use. Clodronate is not available in the USA. Zoledronic acid is approved in the USA at different dosage and indications than in the guideline.	There are differences between the USA and Canada systems. In Canada guidelines are sometimes required prior to approval or funding, and are seen as guidelines without legal authority. A discussion of availability, approval, and different jurisdictions has been added to the preamble and implementation considerations. It was explained that there may need to be some additional wording /comment in the ASCO version; the current format will appear on the CCO website. This is beyond the current Working Group's mandate or expertise.
4. Include patient-reported toxicities in future trials.	These have been included as outcomes in Table 2-2.
5. Should recommend dental assessment before bisphosphonate therapy.	Consensus could not be reached on this point, and this is indicated in the Interpretation of Evidence for Recommendation 6. Additional information referring to position statements or recommendations of dental organizations has been added to qualifying statements.

6. Is there information about when ABCSG-18 and D-CARE will have data? Will it change the guideline?	Further information about the D-CARE timeline has been added; while enrolment is complete, follow-up will not be complete until 2022. If ABCSG-18 is published prior to the current guideline completion, it will be looked at again. The Working Group's impression at this time as it is unlikely to change the recommendations.
7. There were several requests for verification or clarification of statements.	Language was altered to make the meaning clearer in several statements.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in June 2016. The RAP approved the document on June 15, 2016, with the requirements that (a) the systematic review methods and literature search results be revised to more clearly indicate the overlap and difference between the EBCTCG meta-analysis and the current literature search; and (b) Section 2 and 4 be revised to ensure individual trial data already in the meta-analysis was not repeated separately without explanation. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. Consider making the key evidence following recommendations more succinct.	Some discussion of key evidence has been moved to the evidence review (Section 4) and cross-referenced. Other wording has been revised.
2. Clarify the literature search results so it is easier to understand the overlap and differences between the EBCTCG meta-analysis trials and trials found in the literature search. Consider including more details in Figure 4-1.	Section 3 (Guideline Methods Overview) and the methods and results of Section 4 (Evidence Review) have been revised to indicate the actual process and rationale used in conducting the search and the results obtained. Additional limitations to the EBCTCG meta-analysis have been noted. Some headings and Figure 4-1 (flowchart) have been revised.
3. Be careful not to repeat data from individual trials already considered in the EBCTCG meta-analysis. Use of trials already in the meta-analysis should focus on additional information not addressed by the meta-analysis.	Some details of ABCSG-12 and AZURE results were removed, and more focus placed on adverse events and other details not covered in the meta-analysis. Wording has been altered to more clearly indicate that data from the meta-analysis is being used, but comes from only specific trials.
4. There is explicit agreement between recommendations and evidence but not research questions. Question 1 is not addressed separately, but is in the body of the guideline. Consider rewording Question 1 or recommendations.	The research questions shaped the search strategy and systematic review. The recommendations were made based on the data in the review and influenced by the questions, but there was no attempt to correspond directly to the questions. As listing the questions in Section 2 is considered optional, and maybe confusing in this particular guideline, the questions have been retained only in Section 4.
5. Recommendations 2-4 could be combined as one recommendation.	While the authors agree the recommendations themselves could be combined, there are differences in key evidence, qualifying statements, and interpretation such that merging these may make the information more difficult to read. We therefore chose to keep these as separate recommendations.

ASCO CPGC Review and Approval

Members of the ASCO CPGC were eligible to review and vote for approval of the guideline if they had no relevant conflicts of interest (COI) according to the ASCO COI policy. One member of the committee reviewed the document and presented it to the other thirteen eligible committee members. The following comments and the authors' responses are indicated in the table below. Final ASCO CPGC approval was received September 15, 2016.

Table 5-3. Summary of the Working Group's responses to comments from the ASCO CPGC.

Comments	Responses
1. The guideline should be clear that it is talking about women with normal bone mineral density.	In the development of the guideline, the authors did not restrict the target audience to patients with normal bone mineral density, and the studies in the evidence based did not generally exclude patients based on their bone mineral density. The determination of "normal" was considered outside the scope of the guideline and was not dealt with explicitly (the readers are referred to other guidelines on this topic). Also, bone-modifying agents may be recommended for multiple purposes, so the authors did not want to override the use of bone-modifying agents prescribed for other (non-adjuvant) reasons. The authors agree this was unclear in summary materials in the ASCO version, and have revised the abstract and T*he Bottom Line* to add sentences that were in the full version.
2. The dental screening statement should be revised to indicate it is an option if patients can afford it. One reviewer wrote: "Dental screening is often a financial and logistic sticking point for underinsured patients."	During preparation of the recommendations, most of the panel members indicated that an assessment (and treatment if required) was essential and preferred a stronger recommendation to that effect. However, there was dissent about mandating it and a compromise was made to state "a dental assessment should be considered" and to also cite the policies of other organizations. Part of the consideration could be cost. To be more explicit and address the ASCO committee concerns, the recommendation was revised as follows: "a dental assessment is recommended where feasible".
3. For Recommendation 4, lack of availability of the recommended drugs and doses in the United States was a concern.	Issues of availability (approval and funding) are discussed both in "Preamble and Implementation Considerations" and "Other Implementation Considerations", immediately before and after the main recommendations, respectively. The guideline may serve as an impetus to improve access. The majority of authors believed that the recommendation was based on the evidence and should not be changed, and that issues of

	availability were adequately addressed. However, to address the concern an additional qualifying statement was added: "In jurisdictions where the recommendation cannot be followed due to availability, similar doses and schedules of zoledronic acid or clodronate are considered reasonable".

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Two targeted peer reviewers from Ontario, one from Alberta, and six from the United States who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group and the ASCO CPGC. Five agreed to be the reviewers and four responses were received. Results of the feedback survey are summarized in Table 5-4. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-5.

Table 5-4. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=4)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	3
2. Rate the guideline presentation.			1	1	2
3. Rate the guideline recommendations.			1		3
4. Rate the completeness of reporting.			1	1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				2	2
6. Rate the overall quality of the guideline report.				2	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			1		3
8. I would recommend this guideline for use in practice.				1	3
9. What are the barriers or enablers to the implementation of this guideline report?	Awareness of it by clinicians, scepticism that bisphosphonates can work, funding (including time and effort to make applications), incorporation into CCO Systemic Treatment Program–Quality-Based Procedures (ST-QBP), cost to patients				
10. Other comments	Denosumab and ibandronate may need to be included soon.				

Table 5-5. Responses to comments from targeted peer reviewers.

Comments	Responses
1. There is a lot of repetition and redundancy, especially between Sections 1 and 2.	This was a style decided upon by the PEBC/CCO leadership and outside the control of the authors.
2. Limitations of the EBCTCG were not discussed in detail, the most important being age >55 years was a surrogate for menopausal status when actual menopausal status was unavailable.	Some strengths and limitation were included in the systematic review. It was noted that there was alternate analysis by age as menopausal status was not available, and results are given in Table 4-5 by both age and menopausal status. A sentence has been added to be more explicit "For patients of unknown menopausal status, those less than age 45 years were classified as premenopausal, those age 45-54 years classified as perimenopausal, and those age ≥55 years as postmenopausal". As perimenopausal patients have been excluded from the analyses, the risk of misclassification exists only for a small portion of patients undergoing early (before age 45) or late (after age 55) menopause.
3. Overall, the recommendations are reasonable except for pre-menopausal women receiving GnRH analogues with an AI. Data supporting bone targeted therapy in this group are based predominantly on the ABCSG-12 trial which comprised a very different patient population than the SOFT/TEXT population that are treated with GNRH analogues and AI. Specifically, <10% of patients in ABCSG-12 received chemotherapy (unlike SOFT/TEXT where benefit was seen only in women receiving chemotherapy). Additionally, duration of endocrine therapy was only 3 years which is non-standard and makes interpretation of data from ABCSG-12 more challenging. This warrants a recommendation for additional discussion with patients about these uncertainties. Finally, there are very limited data to support bone-targeted therapy in the setting of extended adjuvant endocrine therapy.	It is stated in Recommendation 5 that evidence is weaker in patients with induced menopause as it is derived mostly from one trial (ABCSG-12). SOFT and TEXT are not randomized trials of bone-modifying agents, and therefore not part of the systematic review. Duration of bisphosphonate use is discussed in Recommendation 4. During preparation of the guideline there was discussion whether bisphosphonate duration should extend to the duration of endocrine therapy (up to 10 years). It was decided that while there may be benefit, evidence was not available. The recommendation therefore is based on durations studied in adjuvant trials, with a secondary recommendation that different durations may be considered and more research is needed.
4. Strength of recommendations would be useful, as data for some subgroups are stronger than others.	Instead of giving explicit strength of recommendations, this is indicated by the wording of the recommendation, qualifying statements, and interpretation of evidence. We believe sufficient detail is given that the reader should be able to distinguish recommendation strength.
5. A panel item regarding areas of uncertainty would be important to include. Some are addressed in other comments and in the body of the guideline.	Areas of uncertainty regarding recommendations and evidence are addressed throughout the guidelines. A table of proposed future clinical trials was also included. Therefore, the authors agreed not to repeat under a separate panel.

6. For patients already on bisphosphonates for osteopenia/osteoporosis, they should not be required to switch.	We have indicated in the preamble of the recommendations that "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." Whether to switch or not would be an individual decision.
7. The RMH and NSABP-34 trials gave clearer efficacy results with less toxicity but were not discussed as much as the zoledronate trials.	Trials for clodronate are complete with long-term follow-up and addressed sufficiently by the EBCTCG meta-analysis. We therefore deemed it most appropriate to not discuss the individual trials in detail.
8. For oral bisphosphonates, calcium and vitamin D should be taken at least 4 hours away from the bisphosphonate	Several sources indicate not to take concurrently, however 2 hours appears a more common recommendation (see BC and CCO monograph), and no reference to a 4-hour delay was found. An addition to Recommendation 6 has been made to indicate that "oral bisphosphonates and calcium should not be taken concurrently; several monographs suggest an interval of at least two hours to allow maximum absorption."
9. Clodronate (unlike amino-bisphosphonates) does not require an upright posture as its main gastrointestinal toxicity is diarrhea. Oral risedronate, alendronate, and ibandronate do require the 30-minute gastric cleansing time	We are unable to verify this. While diarrhea is the most frequent adverse effect, dyspepsia and other gastrointestinal effects have been reported. These may be minimized with appropriate administration; details of patient instructions and compliance are not available for the trials cited. Drug monographs (CCO) and patient information (e.g., myhealth.alberta.ca) indicate patients should remain upright and we defer to these documents.
10. Unlike AIs, there is no danger of bisphosphonate doing harm. There is a trend towards benefit in premenopausal women as well, so give bisphosphonates to all (pre- or post-menopausal) if in doubt.	We disagree that there is no potential harm, as adverse effects have been documented in trials and mentioned in the review; we agree that these are small in comparison to that for some other therapeutic agents. The balance of harm and benefit must be considered, and varies depending on patient and disease characteristics. While the trends suggest a possible benefit for premenopausal women, differences are not statistically significant and therefore data is not considered sufficient to recommend use in these patients.
11. Subset analysis of the EBCTCG data regarding pamidronate is contrary to EBCTCG way of interpretation, and they would say that pamidronate does not differ from the overall group.	We believe the subset analysis to be valid. The EBCTCG publication also concludes that "there was no apparent benefit in the smaller oral pamidronate group" and there is an "apparent lack of benefit from pamidronate".
12. In Recommendations 1 ad 5 it is not clear whether survival benefit at 76 months and 94 months refer to a time point or the whole curve.	The publications are unclear, but convention is that the survival numbers (88.4% vs 85.0%) refer to a time-point, while the statistical calculations for significance and confidence intervals refer to the entire curve. The reader is directed to the cited publications.

13. Given the limited data for denosumab, it should not be assumed or implied it may be an okay substitute.	We have clearly stated that data is insufficient to make a recommendation regarding adjuvant use.
14. Recommendation 3. Suggest adding "in the adjuvant setting" to the recommendation	This change has been made.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All medical oncologists in the PEBC database with an interest in breast cancer were contacted by email to inform them of the survey. Fifty-six oncologists were contacted, of which 51 practice in Ontario and 5 elsewhere. Fifteen responses (27%) were received. Six stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from nine people are summarized in Table 5-6. The main comments from the consultation and the Working Group's responses are summarized in Table 5-7.

Table 5-6. Responses to four items on the professional consultation survey.

	Number				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				1	8
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.		1		1	7
3. I would recommend this guideline for use in practice.			1	1	7
4. What are the barriers or enablers to the implementation of this guideline report?	Approval and funding, cost (adjuvant clodronate not covered in Ontario), common (flu-like) and severe (ONJ) adverse effects. Guidelines built on weak evidence will be (inherently) weak guidelines				

Table 5-7. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	Responses
1. Statement regarding chemotherapy is confusing/not helpful. The thresholds for chemotherapy benefit are patient specific - many patients with a (for instance) node positive ER positive breast cancer at 65 may not feel the marginal benefit of chemotherapy is worth it, but bisphosphonates every 6 months are. Using 'would you give chemotherapy?' as a benchmark	We believe the recommendation is valid. Recommendation 1 indicates bisphosphonates be considered for patients deemed candidates for adjuvant systemic therapy. It makes no mention of whether or not the patient actually accepts taking systemic therapy. The second part of the recommendation notes the final decision is to be made in consultation

is a problem when benchmarks change (e.g., RxPonder study).	between the patient and oncologist, considering potential risks and benefits.
2. Remove the Qualifying Statement to Recommendation 2 regarding the hypothesis that that any agent proven to reduce the risk of fragility fractures in at risk populations may be effective as adjuvant therapy for breast cancer. This does not belong in an evidence-based guideline.	The recommendation for zoledronic acid and clodronate is very clear. However, there are limitations to their use, and we state the need for further trials of other different doses and agents. While the hypothesis stated appears to be the framework for the EBCTCG meta-analysis (see the literature review), it is not meant to be a recommendation in the current guideline. The wording has been revised to clarify that the hypothesis comes from other publications, we are referring to osteoporosis trials, and evidence from adjuvant trials is needed.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel, the PEBC RAP, and the ASCO CPGC.

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Appendix 1: Members of the Adjuvant Bisphosphonates in Breast Cancer Guideline Development Group

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*Members of the Working Group

Appendix 2: Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors (Working Group and Expert Panel members), and internal and external reviewers were asked to disclose potential conflicts of interest. Three members of the Working Group declared no conflicts and five declared potential conflicts. BDT published an editorial on screening for osteoporosis and PSB published an opinion/review on the role of bisphosphonates. RG received a travel grant from Roche and Astra Zeneca and speaker fees from Roche, Novartis, Astra Zeneca, and Janssen. MJC is the Canadian lead and TV a local principal investigator for the SWOG S0307 trial. MJC has multiple publications in the area of bone health, managerial responsibility for grants from Amgen for the Annual Bone Meeting in Ottawa, and received travel support from Novartis for the IMPACT meeting.

For the Expert Panel, 14 members declared they had no conflicts of interest, and 5 declared conflicts. CHVP received grants from Amgen and Novartis for clinical trials and salary support; is involved as a principal investigator for SWOG 0307 and D-CARE trials, and published opinions/editorials/commentaries regarding use of adjuvant osteoclast inhibitors. She is also on the Cancer and Bone Advisory Committee of the International Bone & Mineral Society (IBMS) and on the Board of Directors for the Paget Foundation and the Bone and Cancer Foundation. SFD received support for clinical trials from Amgen. DM declared stocks in Johnson and Johnson. CH holds a consulting position with CCO's Disease Pathway Management and Diagnostic Assessment Programs. MET is principle investigator for the CTC MAC8 (Belle-2) trial sponsored by Novartis and had managerial responsibility for a grant received from AMGEN for the Patients for GCSF through Victory program.

Members of the RAP declared they had no conflicts of interest.

One targeted peer reviewer indicated no interests to declare, and three declared potential conflicts of interest. EA declared publication of commentaries on this topic. SP previously acted as a consultant for Amgen regarding denosumab, received per patient payments from Amgen as part of the D-CARE trial, and is an investigator for the D-CARE trial. KP has received consulting fees as part of the advisory boards for Novartis and Pfizer and travel support to attend a meeting from Eisai. KP received grants from Roche, Eisai, and Novartis in support of the Sunnybrook breast fellowship program, and published a commentary on a related topic.

The COIs declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy.

To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca

Appendix 3: Literature Search Strategy

Final Search September 15, 2015

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials August 2015, Embase 1996 to 2015 Week 37, Ovid MEDLINE® without Revisions 1996 to September Week 1 2015, Ovid MEDLINE® Daily Update September 14, 2015, Ovid MEDLINE® In-Process & Other Non-Indexed Citations September 14, 2015

Search Strategy:

#	Searches	Results
1	exp Breast Neoplasms/ or exp breast tumor/ or exp breast cancer/ or breast cancer.mp. or breast neoplasm:.mp. or ((cancer: or neoplasm: or tumo?r: or carcinom: or malignan:) and (breast or mammar:)).mp.	620779
2	limit 1 to yr="2005-current"	442552
3	exp Diphosphonates/ or exp bisphosphonic acid derivative/ or (diphosphonate: or bisphosphonate: or zoledron: or ibandron: or pamidron: or risedron: or alendron: or neridron: or olpadron: or clodron: or tiludron: or etidron: or reclast or zometa or aclasta or boniva or aredia or actonel or fosamax or nerixia or bonefos or loron or skelid or didronel).mp.	74542
4	exp Bone Density Conservation Agents/ or exp Endothelin A Receptor Antagonists/ or Receptor, Endothelin A/ag or exp denosumab/ or exp calcitonin/ or exp endothelin A receptor antagonist/ or exp dasatinib/ or exp rilotumumab/ or exp cabozantinib/ or (bone-modifying agent: or bone modifying agent: or denosumab or calcitonin or endothelin A receptor antagonist or atrasentan or zibotentan or dasatinib or rilotumumab or AMG102 or cabozantinib or Prolia or Xgeva or Fortical or Miacalicin or Evista).mp.	135211
5	2 and 3	7286
6	2 and (4 not 3)	7417
7	exp phase 3 clinical trial/ or exp "phase 3 clinical trial (topic)"/ or exp clinical trial, phase iii/ or exp clinical trials, phase iii as topic/ or exp phase 4 clinical trial/ or exp "phase 4 clinical trial (topic)"/ or exp clinical trial, phase iv/ or exp clinical trials, phase iv as topic/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or exp controlled clinical trial/ or exp randomized controlled trials as topic/ or exp randomization/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/ or exp placebos/ or exp placebo/ or ((exp phase 2 clinical trial/ or exp "phase 2 clinical trial (topic)"/ or exp clinical trial, phase ii/ or exp clinical trials, phase ii as topic/ or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/) and random$.tw.) or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or ((singl$ or doubl$ or treple$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw. or placebo?.tw. or (allocat: adj2 random:).tw. or	1994241

	(random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.	
8	exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw. or (medline or med-line or pubmed or pub-med or embase or cochrane or cancerlit).ab.	477369
9	exp evidence based practice/ or exp practice guideline/ or exp consensus development conference/ or guideline.pt. or practice parameter$.tw. or practice guideline$.mp. or (guideline: or recommend: or consensus or standards).ti. or (guideline: or recommend: or consensus or standards).kw.	1317329
10	5 and 7	2324
11	5 and (8 not 7)	188
12	5 and (9 not (8 or 7))	323
13	6 and 7	1812
14	6 and (8 not 7)	123
15	6 and (9 not (8 or 7))	135
16	remove duplicates from 10	1847
17	remove duplicates from 11	168
18	remove duplicates from 12	302
19	remove duplicates from 13	1452
20	remove duplicates from 14	120
21	remove duplicates from 15	132

Total 4021

After removing additional duplicates: 3851

Appendix 4: Excluded Bisphosphonate Trials

EBCTCG	Trial name(s) or location, enrolment	NCT number (other number if no NCT)	Source	Number of patients	Patient characteristic	Arms or comparison	Outcome	Notes
Listed (no data)	Wisconsin, Ohio 2000-2007	NCT00213980	Leal, 2010 [141]	68 (target 74)	Postmenopausal, stage II/III N+ or stage III	ZOL (4 mg q12w ×4) vs. observation	Primary: BMD, Secondary: BMD, DFS, OS, toxicity No cases of ONJ in retrospective chart review.	Exclude Powered only for BMD, survival not reported by arm, median 8 y follow-up (full text)
Listed (no data)	REBBeCA, 2003-2005	NCT00118508	Greenspan, 2007, 2008 [142,143] Van Londen, 2008 [144]	87	Newly menopausal (<8 y) after treatment with chemotherapy (with or without tamoxifen or AIs), stage I-III, non-metastatic BC	Risedronate vs. placebo for 12 m with 12 m extension	Primary: change in spine and hip BMD Secondary: bone resorption and formation; tolerability. Primarily bone loss study	After two years: 2 fractures in the placebo and 3 in the risedronate group Exclude, no outcomes of interest
Listed (no data)	REBBeCA II; REBBeCA2 2003-2004	NCT00485953	Greenspan, 2015 [145]	109	Age >55 y; on an AI, low bone mass, HR+	Risedronate vs. placebo for 24 m	Primary: BMD, Secondary: bone turnover markers (BTM), safety Primarily bone loss study	24% had a serious adverse event, and 94 % had a non-serious adverse event. Exclude, no outcomes of interest
Listed (no data)	FEMZONE EUCTR2004-004007-37-DE 2006-2010	NCT00375752	Fasching, 2014 [146]	168 (131 assessed)	Postmenopausal Exclude if current dental problems	Neoadjuvant letrozole ± ZOL for 6 m	Primary: clinical response rate by mammography, MRI, or sonography Other: safety (adverse events)	Exclude: no outcomes of interest; terminated early due to insufficient recruitment (full text)
Listed (no data)	NEOZOTAC BOOG 2010-01	NCT01099436	Charehbil, 2014 [147]	250	Stage II/III, HER2- Exclude if poor dental health	Neoadjuvant TAC ± ZOL	Primary: pCR; grade III/IV toxicity	Exclude, no survival

EBCTCG	Trial name(s) or location, enrolment	NCT number (other number if no NCT)	Source	Number of patients	Patient characteristic	Arms or comparison	Outcome	Notes
	EudraCT 2009-016932-11 NL30600.058.09 2010-2012						Secondary: clinical response (MRI), tolerability/AEs No cases of ONJ.	outcomes (full text)
Listed (no data)	Columbia University, New York [listed in EBCTCG as Herbert Irving Cancer Center]		Hershman, 2010 [148]	101		ZOL vs. placebo	Primary: BMD, bone turnover markers	Exclude (full text) as no survival outcomes
Listed (no data)	EXPAND CFEM345DDE09 Germany 2006-2010	NCT00332709	Hellriegel, 2011 [149] [abstract] https://www.clinicaltrials.gov/ct2/show/study/NCT00332709	460 planned; 83 actual	HR+ and 4-6 y tamoxifen	Letrozole ± ZOL	BMD change Secondary: efficacy and tolerability (adverse effects), DFS	Exclude (abstract): no survival outcomes
Listed (no data)	New York [Columbia University in EBCTCG]		Cohen, 2008 [150]	11	Postmenopausal, after tamoxifen.	Alendronate vs. placebo	Primary: BMD	Exclude: low pt number, no survival outcome
Listed (no data)	Helsinki, Finland Helsinki University Hospital 1998-1999		Vehmanen, 2004 [151]	48	Premenopausal, operable T1-3 N0-2, age ≤55 y; CMF or CEF then tamoxifen if HR+	Intermittent iv clodronate vs. none. 1500 mg over 3 before chemotherapy for 7 consecutive cycles	Outcome: BMD, collagen metabolites, amenorrhea. Stopped early due to other clodronate trial results	Exclude, no outcome of interest
Listed (no data)	BATMAN Osteoporosis Australia 2005-2010	NCT00122356	Lomax, 2013 [152]	303	Early stage	Treatment with alendronate by an algorithm in preventing bone loss, not RCT		Exclude, not RCT
Listed (no data)	Manchester, Edinburgh, Sheffield, UK		Bundred, 2010 [153]	109	Postmenopausal, early	14 d letrozole ± zoledronic acid (2-4 d before surgical excision)	Primary: short-term biological effects (apoptosis, proliferation) as measured by fall in Ki67	Exclude, no outcome of interest

EBCTCG	Trial name(s) or location, enrolment	NCT number (other number if no NCT)	Source	Number of patients	Patient characteristic	Arms or comparison	Outcome	Notes
Listed (no data)	RISAROS EudraCT 2006-006943-29 2009-2013	NCT00859703	https://www.clinicaltrials.gov/ct2/show/NCT00859703	20 (206 planned)	Postmenopausal, AI	Risedronate vs. placebo	Primary: BMD Secondary: BMD, bone resorption/ formation markers, fractures	Follow-up ongoing, no publications Exclude, only 20 pts
Listed (no data)	USA/Canada [EBCTCG lists as Seattle/AMGEN]	NCT00089661	Ellis, 2008, 2009 [154,155] http://www.amgentrials.com/amgen/trialsummary.aspx?studyid=20040135#evnt	252	HR+, non-metastatic, AI, low bone mass excluding osteoporosis	Denosumab vs. placebo, q6m×4 then 2 y follow-up	Primary: change in BMD Secondary: BMD Exploratory: BMD, fractures, OS Primarily BMD study	Survival not reported due to small number of deaths Exclude, no outcomes of interest
Listed, states no recurrence data	CALGB 79809	NCT00022087	Shapiro, 2011 [156]	439	Premenopausal, age 40+	ZOL for 2 y	Differences in BMD In all pts and those with chemotherapy-induced ovarian failure. No cases of ONJ observed	Exclude (full text) as no survival outcomes
Not listed	INSERM, Lyon, France		Delmas, 1997 [103] (found from review)	53	Artificially induced menopause by chemotherapy, aged 36-55 y; stratified by tamoxifen use	Risedronate vs. placebo (8 cycles; daily for 2 weeks then 10 weeks no drug each cycle)	Primary: BMD, markers of bone turnover Other: safety (adverse events) Primarily bone loss study	Exclude, no outcome of interest
Not listed	Lebanon 2000-2002		Fuleihan, 2005 [157]	40	Premenopausal, newly diagnosed, non-metastatic	Chemo ± pamidronate vs. placebo, q3m for 1 y	Primary: BMD, amenorrhea Exploratory: metastasis, survival Primarily bone loss study	Mean 2-y follow-up from study entry (1-y from completion) Exclude, no outcome of interest
Not listed	BONADIUV	NCT02616744 https://www.clinicaltrials.g	Cecchini, 2013 [158] Scotti, 2014 [159]	202	Osteopenic women with breast cancer on aromatase inhibitors	Ibandronate (150 mg/m for 2 years) vs. placebo	Primary: BMD Secondary: compliance, FRAX® index evaluation,	Exclude because no survival

EBCTCG	Trial name(s) or location, enrolment	NCT number (other number if no NCT)	Source	Number of patients	Patient characteristic	Arms or comparison	Outcome	Notes
		ov/ct2/show/ NCT02616744	Livi, 2016 [182] [abstracts]				ibandronate safety and bone turn-over markers	outcomes (abstracts)
Not listed	Korea		Rhee, 2013 [160]	98	Postmenopausal, HR+, early, AI	Alendronate + calcitriol vs. placebo	Primary: BMD Other: AEs	Exclude (full text) as no survival outcomes
Not listed	NEOCAN Canada 2005-2007	NCT00247650	https://www.clinicaltrials.gov/ct2/show/study/NCT00247650	190	Age 65+, non-metastatic, operable	Neoadjuvant letrozole ZOL	Primary: clinical response Secondary: BCS, pCR, biomarkers	No publications; terminated early; exclude
Not listed	Japan 2008-2010		Saito, 2015 [161] [abstract]	58	AI, postmenopausal, low bone density	Alfacalcidol ± alendronate	Primary: BMD Secondary: AEs, bone health markers	Exclude (abstract): no survival outcomes
Not listed	German Breast Group GBG 32 ICE 2004-2008		Sullivan, 2015; Reimer, 2009a, 2009b; Von Minckwitz, 2015 [162-165] [abstracts]	1049	Female >+ 65 y	Ibandronate ± capecitabine	Primary: DFS Secondary: OS, safety, QoL	Exclude (abstracts): trial of capecitabine, not ibandronate
Listed, excluded (prevention trial)	IBIS-II UK/Australia		Singh, 2011 [166] [abstract]	194	Healthy postmenopausal, high risk of breast cancer	Risedronate vs. placebo		Exclude, cancer prevention study
Listed, excluded (prevention trial)	GISS, Germany 2001-2003		Von Minckwitz, 2011 [183]	30	Premenopausal women at increased risk of breast cancer	(Goserelin + ibandronate + screening) vs. screening	Discontinuation, safety, quality of life	Exclude, cancer prevention study

Abbreviations: AEs, adverse effects; AI, aromatase inhibitor; BCS, breast conserving surgery; BMD, bone mineral density; DFS, disease-free survival; ER–, estrogen receptor negative; HER2, human epidermal growth factor receptor 2; HR+, hormone-receptor positive; iv, intravenously; MRI, magnetic resonance imaging; N+, node-positive; N0, node negative; ONJ, osteonecrosis of the jaw; OS, overall survival; pCR, pathologically complete response; pts, patients; QoL, quality of life; RCT, randomized controlled trial; RT, radiation therapy; ZOL, zoledronic acid

Appendix 5. Quality Assessment of Included Trials

Trial name and source	Design	Reported Allocation Sequence	Allocation Concealed	Blinded	Balanced Baseline Characteristics	Industry Funding	Statistical Power and Target Sample Size	ITT Analysis	Withdrawals Described	Reported Loss to Follow-up	Terminated Early
Z-Fast [60,118,119]	Prospective	Multicentre, randomized	Open label	No	Yes, stratified by chemotherapy (yes/no), baseline T-score (-2.0 to -1.0 or above -1.0),	Yes: Novartis	Power of 90% and a significance level of p=0.05 to detect a 3% difference in percent change in LS BMD with a standard deviation of 9% from baseline to 12 months between the groups. A sample size of 191 patients per treatment arm was required. To allow for a 25%dropout rate, at least 250 patients in each treatment arm were required; 301 patients per arm were enrolled. The study was not powered to detect a difference in the incidence of clinical fractures or breast cancer relapse	ITT based on all pts who received ≥1 dose letrozole or zoledronic acid and ≥1 post-baseline assessment	Yes	Yes	No. 16pts (5.4%) at 6m and 17 pts (5.7%) at 12 m in delayed group received zoledronic acid not according to protocol . Final 5-year results reported
ZO-FAST [56,63]	Prospective	Multicentre, randomized	Open label	No	Yes, stratified by chemotherapy (yes/no), baseline T-score (-2.0 to -1.0 or above -1.0), menopausal stage (resent, established)	Yes: Novartis	Primary outcome change in BMD; secondary outcome change in BMD, fractures, DFS, OS, safety. The study was designed and powered to evaluate the effect of immediate and delayed ZOL on change in BMD. All statistical tests used a p=0.05 significance level. Secondary malignancies not included in DFS definition	ITT for disease recurrence	Yes	Yes	Final 5-year results reported

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E-ZO-FAST [55]	Prospective	Multicentre. Centrally randomized, using an interactive voice response system	Open label	No	Yes, stratified by chemotherapy (yes/no), baseline T-score (-2.0 to -1.0 or above -1.0), menopausal stage (resent, established)	Yes: Novartis.	A sample size of 500 (527 randomized) was based on practical considerations, and no inferential analyses were planned. The study was not powered to detect a difference in the incidence of clinical fractures or recurrence of breast disease.	Yes	Yes	Yes	No, 12-month analysis only. Further follow-up required for fracture, disease recurrence, and survival rates.
AZURE (BIG 01/04) [45,46]	Prospective	Multicentre. Randomized by central computer-generated telephone minimization system.	Yes, prior to assignment. Open label		Yes. Randomization took into account number of involved lymph nodes (none, 1-3, ≥4), ER status, systemic therapy (chemotherapy ± endocrine, endocrine alone, taxane, anthracycline, adjuvant neoadjuvant, menopausal status (pre, within 5 y, >5 y), statins, treating centre	Yes: Novartis (role defined; not involved in data collection or analysis)	Primary analysis DFS; secondary endpoints IDFS, OS, time to bone metastases, time to distant recurrence, subgroup analyses. Final analysis planned after 940 DFS events to provide 80% power to detect a 17% reduction in the HR for DFS at 5% significance (about 3.7% absolute benefit). Assumed 3-y recruitment of 3300 pts, 75% DFS for control at 3 y, 5% annual loss to foll0w-up. Second interim analysis planned after ≥705 events and 0.5% probability of false positive results or 5% probability of declaring negative results. Independent statistician calculated efficacy boundary HR=0.833 and lack of efficacy boundary HR=0.936. Final analysis	Yes	Yes	Yes	Fully recruited, results released early (752 events (see statistical power entry); final analysis done at 966 events

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							was conducted with 752 events; lower threshold of efficacy boundary was crossed.				
ABCSG-12 [42-44]	Prospective	Computer-generated adaptive randomization via automated telephone service. 2×2 factorial design.	Open label	Only those evaluating recurrence from lab results.	Yes. Arms balanced prognostic variables: age (19–34 years vs. ≥35 years), neoadjuvant chemotherapy (no vs. yes with CR vs. yes without CR), pathological tumour stage (pT1 vs. pT2 vs. pT3), lymph-node involvement (0 vs. 1–3 vs. 4–9), type of surgery and radiation treatment, complete axillary dissection (yes vs. no), intraoperative radiation (yes vs. no), and geographical region	No [except donation of drugs by Novartis and Astra-Zeneca; not involved in data collection or analysis]	Primary endpoint DFS. Secondary endpoints RFS, OS, BMD. Exploratory endpoint BMFS. Originally powered with 1250 pts to detect DFS superiority of anastrozole versus tamoxifen. International advisory board recommended increase to 1800 pts (1803 enrolled), with 90% power for a hazard ratio of 1.8 with a two-sided alpha error of 0.05, to include approximately 124 events. 137 events had occurred at median 48 m follow-up and 251 evens at final report.	Yes	Not reported	Not reported	No. Final results at 94 months reported
ABCSG-18 [18,19]	Prospective	Multicentre, interactive voice response system,	Double-blind, placebo controlled	Patients, investigators, project manager,	Yes. Randomisation was stratified by: previous aromatase	Yes: Amgen. Role clearly defined	Primary outcome time to first clinical fracture. Originally 2800 pts to detect clinical fracture reduction with hazard	Yes	Yes	Yes	Due to large difference in fracture rate at interim analysis,

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		using a randomly permuted block design with block sizes 2 and 4.		data management team, clinical research associates, and statisticians were masked to the treatment group.	inhibitor use (yes/no), total lumbar spine bone mineral density score at baseline (T-score <-1.0 vs. ≥1.0), and type of hospital (preselected bone mineral density centres vs. others)		ratio of 0.6; revised to 3400 to detect HR=0.7. Based on a dropout rate of 3.6% per year, 247 patients would need to have a clinical fracture for this study to have 80% power to detect a hazard ratio of 0.70 (denosumab vs. control), with a two-sided significance level of 0.05. 102 pts/group to give 90% power to detect a mean 1.8% difference (SD 3.9%) in the percentage of change of lumbar spine BMD at 12 months. Secondary outcomes DFS, BMFS, OS 3425 enrolled.				control patients allowed to switch groups if they want. Analysis before that time was median 4 years and 370 DFS events. BMFS, OS will be analyzed during further study follow-up.
GAIN [51]	Prospective	Multicenter. Permutated block randomization 2×2 design	Open label	No	Yes Stratified for center, nodal status (one to three, four to nine, or 10 or more involved nodes), and receptor content (<10% positive stained cells for estrogen and progesterone receptor, or ≥10% for either one).	Yes: Amgen, Bristol-Myers Squibb, Roche	Primary outcome DFS; secondary outcome OS, safety, compliance, EFS in subgroups. 2,640 pts with 2:1 randomization (1,760 ibandronate, 880 control arm) and 5% dropout to give 728 events to detect increase in DFS at 5 years from 75% to 79.5% by ibandronate. Power reduced by interim analysis but as required more pts for chemotherapy question (3000 pts), the trial	Yes, if started chemo-therapy	Yes	Yes. Follow-up 76.8% at median 38.7 months	Early analysis after 50% of required DFS events due to low event rate and calculation of futility. Follow-up data required; unlikely to change overall conclusions but may influence subgroup data

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							maintained 80% power for ibandronate question. 3023 pts enrolled.				
SWOG S-0307 [14,15] https://clinicaltrials.gov/show/NCT00127205	Prospective	Multicentre, randomized	Open label	Not reported	Not reported	Not reported	Primary outcome DFS. 5400 pts to give >86% power to detect difference, p=0.05. 6097 pts accrued.	Not reported	Not reported	Not reported	At fourth interim analysis concluded no realistic chance of statistically significant difference and results released. Abstract only.
TEAM IIb [16] http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=785	Prospective	Multicentre, randomized	no	no	NA	No	Primary outcome is 3-year DFS, 80% power to detect increase from 92% to 95%	NA	NA	NA	Ongoing, no results, no publications
D-CARE [21]	Prospective	Global, randomized	Double-blind	Not reported	Not reported	Amgen	Primary outcome BMFS; secondary endpoint DFS, OS. 4500 pts enrolled. Power not reported	NA	NA	NA	Ongoing, no results, abstract only

Abbreviations: Abbreviations: BMFS, bone-metastasis-free survival; BMD, bone mineral density; CR, complete response; DFS, disease-free survival; EFS, event-free survival; ER, estrogen receptor; HR, hazard ratio; IDFS, invasive-disease-free survival; ITT, intention to treat; NA, not applicable; OS, overall survival; pts, patients; RFS, recurrence-free survival; ZOL, zoledronic acid