CANCERCare
A PROGRAM OF EASTERN HEALTH

Clinical Practice Guidelines - Breast Disease Site

Guideline Title:	Adjuvant Bisphosphonate Therapy in Primary Breast Cancer	**Date:** **(O):** **(R):**	Jan 18, 2018
Tumor Group:	Breast Disease Site Group	**Page:**	1 of 11
Issuing Authority:	Dr. Jehan Siddiqui Clinical Chief, Cancer Care Program	**Date Signed:**	Aug 30, 2019
Adapted From:	Joint Cancer Care Ontario and American Society of Clinical Oncology "Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer" guideline, June 2017 (28).		

Introduction:

Bisphosphonates have been found to be highly efficacious in the treatment of osteopenia and osteoporosis, as well as in the treatment of metastatic cancer-related bone disease for many years. Recent evidence however, suggests that bisphosphonates may also positively affect breast cancer outcomes in the adjuvant setting. There are a number of bisphosphonates and bone modifying agents on the market today which adds to the complexity of the decision-making process, when deciding the appropriate drug choice for the existing medical condition.

Questions:

1. What evidence supports the use of bisphosphonates in the adjuvant setting?
2. What is the appropriate choice of bisphosphonate to use in the adjuvant setting?
3. What criteria must be met to allow a patient with early stage breast cancer to be eligible for adjuvant bisphosphonate therapy?

Target Population:

These recommendations apply to patients with early stage breast cancer who may benefit from bisphosphonate therapy in the adjuvant setting.

Supporting Evidence:

Bone health among patients diagnosed with breast cancer has become an important aspect for consideration within the survivorship realm. Bone loss has been known to be attributed to risk factors such as increased age (> 65 years), Caucasian race, low body mass index (BMI) of < 20 kg/m^2, history of fractures or osteoporosis, corticosteroid use, menopausal status, and smoking (1). In addition, patients diagnosed with breast cancer are also at an increased risk of bone loss related to the use of curative adjuvant therapies. The use of aromatase inhibitors (AIs) in postmenopausal women and the suppression, or elimination of ovarian function in

premenopausal women are extremely effective therapies to combat the recurrence of breast cancer by reducing the serum estradiol levels. However, the resulting decline in estradiol level has been found to result in an increased rate of bone demineralization and resorption which in turn, increases the risk of low bone mass and osteoporosis-related fractures in patients receiving such treatments (2,3).

Bisphosphonates act as anti-resorptive therapy by inhibiting osteoclast activity of bone and thus promoting an increase in bone mineral density. Bisphosphonates have been shown to decrease the rate of osteoporotic fractures therein reducing the associated patient-related morbidities and economic costs to the health care system (4). In the oncology setting, bisphosphonates are indicated in prevention of bone loss and reduction of skeletal-related events in patients with metastatic bony disease, and more recently an indication in improving outcomes in women with early-stage breast cancer. Zoledronic acid has been found to be effective in improving bone loss in premenopausal women undergoing adjuvant chemotherapy, premenopausal women who had undergone ovarian suppression and are receiving tamoxifen or an AI, and postmenopausal women receiving an AI (5-7). A joint Cancer Care Ontario (CCO) and American Society of Clinical Oncology (ASCO) guideline recommends the use of zoledronic acid, or an alternative clodronate, for treatment in this setting (28). Further research has been conducted on the use of human monoclonal antibodies such as the anti-RANK-ligand, denosumab. This drug has also been shown in clinical trials to preserve bone mass in those patients receiving an AI compared to placebo (8,9). However, the joint CCO/ASCO guideline suggested that there are insufficient data at this time to propose the use of denosumab in the adjuvant setting but did recommend further research.

In recent years, researchers have suspected that in addition to the benefit to bone health, adjuvant bisphosphonates may also have an anti-cancer benefit for patients diagnosed with breast cancer. However, clinical trials performed to investigate the effect of bisphosphonates on breast cancer outcomes provided conflicting results. A 2010 meta-analysis of adjuvant clinical trials which compared bisphosphonates with placebo in patients with breast cancer who received either bisphosphonate treatment vs no treatment vs delayed treatment and investigated the primary outcomes of overall survival (OS), disease recurrences, and occurrences of bone metastases (10). However, the study results were not statistically significant between the bisphosphonate arm and the control arm in terms of any of the primary outcomes investigated. Another meta-analysis conducted in 2013 in the same manner investigated the impact of bisphosphonates on OS and fracture rates (11). In this case, the authors found that bisphosphonates did result in statistically significant increase in OS improvements and reductions in fracture risk but did not reveal significant differences in incidence of bone metastases between both arms.

In 2015, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a meta-analysis of 26 clinical trials involving patients with early breast cancer who randomly received two to five years of either bisphosphonate or placebo treatment (12). The results showed an overall statistically significant reduction in the 10-year risk of bone recurrence with the addition of adjuvant bisphosphonates compared to control (7.8% vs 9.0%) (13). The subgroup analysis found that bisphosphonate treatment had no effect on premenopausal women however, there were small but significant reductions in risk for the postmenopausal women in terms of all recurrences, distant recurrences, bone recurrences, and breast cancer mortality. The risk for bone fractures was also reduced with a five-year fracture risk of 5.1% in the bisphosphonate

arm compared to 6.3% in the control arm (13). A 2017 Cochrane review confirmed that the use of bisphosphonates was associated with a lower risk of bone metastases compared to placebo/no bisphosphonate (14). The results also confirmed that no survival benefit was found for premenopausal women. However, an OS and a disease-free survival (DFS) benefit was found for postmenopausal women with the addition of bisphosphonate treatment. This review did not detect a significant reduction in the incidence of fractures between the two study arms.

Cost analyses have been performed to determine whether adjuvant bisphosphonates were effective in reducing skeletal-related events which improved quality-adjusted life-years (QALY) and reduced costs to the health care system. A Canadian study found using a probabilistic sensitivity analysis that there was a 100% probability that adjuvant zoledronic acid was cost-effective in terms of gains to QALY for the patient and reduction of costs to the health care system (15). American studies have also found that a less frequent dosing schedule of zoledronic acid has a similar efficacy with that of a more frequent dosing schedule therefore improving the cost-effectiveness (16-18).

Since CCO and ASCO published their joint guideline on evidence-based recommendations for the use of bisphosphonates in June of 2017, several other reputable international cancer care organizations have released their own adjuvant bisphosphonate guidelines (32-35). The BC Cancer Agency (BCCA) released a systemic therapy update in December of the same year which included an announcement of the launch of the use of adjuvant bisphosphonates in the treatment of early stage breast cancer, followed by a new guideline from Alberta Health Services (AHS) in April 2018 (30,31). Both BCCA and AHS stipulate that adjuvant bisphosphonate therapy should be offered to only those post-menopausal women (including those pre-menopausal women who have treatment-related amenorrhea through ovarian suppression or ablation) who are at high risk of breast cancer recurrence. These would include all women who presently have been diagnosed with lymph node-positive, or high-risk lymph node-negative breast cancer, with BCCA restricting its eligibility criteria to those women diagnosed with stage II and III breast cancer only.

The Eastern Health Breast Disease Site Group (BDSG) has determined that there is sufficient evidence to support the use of adjuvant bisphosphonates in the treatment of post-menopausal women with early stage breast cancer going forward. Natural menopause is defined as at least 12 consecutive months of amenorrhea prior to the initiation of chemotherapy, and not due to chemotherapy-induced cessation of menses alone. Treatment-induced menopause is defined as amenorrhea brought on with the intentional use of pharmaceutical, surgical or radiation treatment to temporarily suppress or permanently remove/ablate ovarian function in pre-menopausal women. The BDSG considers both of these populations of women to be eligible for adjuvant bisphosphonate therapy in this province when their risk of breast cancer recurrence is high enough to warrant adjuvant systemic treatment as per the joint CCO/ASCO guideline (28). This risk category would include having disease features such as lymph node involvement or high-risk patient/tumor features in the absence of lymph node spread, such as patient age of less than 35 years of age and the presence of disease with lymphovascular invasion, grade 3 disease, hormone receptor-negative, HER2 over-expression (HER2 positive), and/or has a “high risk” test score on Oncotype DX. Medical oncologists may offer adjuvant bisphosphonate therapy to some patients with intermediate-risk, on a case-by-case basis, who despite being outside the eligibility criteria, may have a health history which deems this therapy appropriate. Adjuvant bisphosphonate therapy can commence at the end of the prescribed chemotherapy

regimen for women with hormone receptor-negative breast cancer or during the first two to three months of hormonal therapy for those with hormone receptor-positive disease. For those women who have undergone treatment-induced menopause, adjuvant bisphosphonate therapy will commence once ovarian function has been eliminated.

Presently, the joint CCO/ASCO guideline recommends either zoledronic acid intravenously or oral clodronate for treatment options, it remains unclear which pharmaceutical bisphosphonate agent is most suitable in the adjuvant setting (28). The vast majority of recent clinical trials were conducted using zoledronic acid in this clinical setting which was reflected in the 2015 EBCTCG meta-analyses as well (19-25). Older studies using clodronate provided mixed results while a recent NSABP B-34 study comparing clodronate to placebo indicated that clodronate provided bone-metastasis-free interval benefits but no DFS or OS benefits (26). In addition, clodronate has never been studied specifically in the patient population receiving AIs (28). A 2014 Southwest Oncology Group (SWOG) S0307 clinical trial compared several types of bisphosphonate therapies however, it was only ever published in abstract form and therefore unsuitable to base recommendations upon (27). The out-of-pocket cost of clodronate will be prohibitive for many breast cancer patients and historically has been reported to be associated with poor treatment adherence (26,29). Therefore, the Eastern Health BDSG recommends that the zoledronic acid should be the drug of choice however, in the event where the patient is intolerant to zoledronic acid then clodronate is an acceptable alternative.

The joint CCO/ASCO guideline recommends that zoledronic acid 4 mg should be given intravenously every six months for three to five years while clodronate 1600 mg can be taken orally daily for two to three years. Baseline bloodwork of luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol levels should be obtained to establish the menopausal status of patients who are younger than 60 years of age. In addition, a baseline serum calcium should be obtained and renal function should be monitored during zoledronic acid treatment. A baseline dual-energy x-ray absorptiometry (DEXA) or bone mineral density test should also be performed prior to commencing adjuvant bisphosphonate therapy. All eligible patients should also be advised to take calcium and vitamin D supplements daily and be encouraged to perform weight-bearing exercise to promote bone health. Oncologists must inform patients about the common side effects associated with bisphosphonates including fatigue, fever, and joint pain, and the potential for more serious adverse events, such as hypocalcemia, renal impairment and in rare cases, the development of osteonecrosis of the jaw (ONJ). All patients should be advised to undergo a dental assessment, where feasible, and any necessary dental or oral health issues addressed prior to beginning bisphosphonate therapy.

Recommendations:

The following recommendations of the Eastern Health Breast Disease Site Group apply to patients diagnosed with early stage (non-metastatic) breast cancer:

1. All women diagnosed with early-stage (stage I, II or III) lymph node-positive or high-risk lymph node-negative breast cancer, regardless of molecular biomarker profile who lack ovarian function should be offered adjuvant bisphosphonate therapy. In the case of:
    - ***Premenopausal women*** – consider the use of adjuvant bisphosphonate treatment as a part of adjuvant systemic therapy for those who have menopause induced by ovarian ablation or suppression (NOT chemotherapy-induced menses cessation alone);

- ***Postmenopausal women*** – consider the use of adjuvant bisphosphonate treatment as a part of adjuvant systemic therapy for those having natural menopause (at least 12 months of amenorrhea prior to initiation of chemotherapy or endocrine therapy);

2. High-risk lymph node-negative breast cancer includes any or a combination of these patient and tumor-related features which include;
   - patient age of less than 35 years of age
   - presence of disease with lymphovascular invasion
   - grade 3 histology
   - hormone receptor-negative
   - HER2 over-expression (HER2 positive), and/or
   - has obtained a “high risk” test score on Oncotype DX;
3. When menopausal status is in question, women ≤ 60 years should have serum luteinizing hormone (LH), follicle-stimulating hormone (FSH) and estradiol levels performed prior to initiation of adjuvant bisphosphonate treatment;
4. For patients eligible for adjuvant bisphosphonate treatment, the recommended bisphosphonate is zoledronic acid 4mg IV over 15 minutes every six months for three to five years OR in the event, where a patient is intolerant to zoledronic acid then clodronate, orally 1600mg daily for two to three years, is an acceptable alternative;
5. All patients should be advised of the potential adverse events of bisphosphonate treatment including the risk of developing osteonecrosis of the jaw (ONJ). All patients being considered for adjuvant bisphosphonate treatment should have a dental assessment performed, where feasible, and any necessary dental or oral health issues addressed prior to commencement of adjuvant bisphosphonate treatment;
6. All patients being considered for adjuvant bisphosphonate treatment should undergo a serum calcium prior to commencement and monitored for renal function when receiving zoledronic acid;
7. All patients are advised to take calcium and vitamin D supplements unless contraindicated.

Search Strategy:

Literature searches were conducted in PubMed, Embase, and the Cochrane Library, using keywords “diphosphonates” AND “breast neoplasms” AND “adjuvant therapy”. Guideline searches were also carried out on the websites of the world’s most highly respected cancer organizations and agencies. All selected literature articles were in English and dated after the year 2008 (unless the selection was an earlier landmark study) up to and including January 18, 2018. All chosen source guidelines were in English and dated from 2015 onward and were ensured to have incorporated the results of the landmark 2015 EBCTCG meta-analysis. The inclusion/exclusion process consisted of selecting guidelines from reputable cancer organizations with preference given to those from Canadian sources where possible. Seven source guidelines were identified and conformed to our search criteria were selected due to currency, quality of content and/or were Canadian in origin (28, 30 - 35).

The seven identified source guidelines (28, 30 - 35) were put through the ADAPTE process (36) with an AGREE II assessment (37), and the joint CCO/ASCO guideline was chosen to be adapted for use in our guideline (28). The “use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer” guideline was selected as the optimal choice due to its applicability, quality and currency of content.

There has been much debate but no consensus on the 'grading of evidence' in Canada. Presently, Canadian experts in the field of guideline development are involved in an ongoing in-depth analysis of the functionality of grading. Until such time as a report is released of their findings, and a consensus reached on whether to assign a grade of recommendation to a guideline, this group has decided to forgo the use of grading.

No competing or conflicts of interest were declared.

Disclaimer:

These guidelines are a statement of consensus of the Breast Disease Site Group regarding their views of currently accepted approaches to diagnosis and treatment. Any clinician seeking to apply or consult the guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

Contact Information:

For more information on this guideline, please contact Dr. Joy McCarthy MD FRCPC, Dr. H. Bliss Murphy Cancer Center, St. John's, NL; Telephone 709-777-7436. For access to any of our guidelines, please visit our Cancer Care Program website at www.easternhealth.ca

Literature Support:

1. Robbins, J., Aragaki, A. K., et al. (2007). Factors associated with a 5-year risk of hip fracture in postmenopausal women. *JAMA, 298*(20), 2389-2398.
2. Body, J. J. (2011). Increased fracture risk in women with breast cancer: A review of the hidden risk. *BMC Cancer, 11,* 384. Retrieved from: http://www.biomedcentral.com/1471-2407/11/384
3. Bouvard, B., Soulie, P., et al. (2014). Fracture incidence after 3 years of aromatase inhibitor therapy. *Annals of Oncology, 25*(4), 843-847. Doi: 10.1093/annonc/mdu008
4. Delea, T. E., Taneja, C. et al. (2010). Cost-effectiveness of zoledronic acid plus endocrine therapy in premenopausal women with hormone-responsive early breast cancer. *Clinical Breast Cancer, 10*(4), 267-274. Doi: 10.3816/CBC.2010.n.034.
5. Hershman, D. L., McMahon, D. J., et al. (2010). Prevention of bone loss by zoledronic acid in premenopausal women undergoing adjuvant chemotherapy persist up to one year following discontinuing treatment. *Journal of the Clinical Endocrinology and Metabolism, 95*(2), 559-566. Doi: 10.1210/jc.2009-1366.
6. Gnant, M., Mlineritsch, B., et al. (2009). Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *New England Journal of Medicine, 360*(7), 679-691.
7. Safra, T., Bernstein-Molho, R., et al. (2011). The protective effect of zoledronic acid on bone loss in postmenopausal women with early breast cancer treated with sequential tamoxifen and letrozole: A prospective, randomized, phase II trial. *Oncology, 81,* 298-305. Doi: 10.1159/000334456
8. Ellis, G. K., Bone, H. G., et al. (2009). Effect of denosumab on bone mineral density in women receiving adjuvant aromatase inhibitors for non-metastatic breast cancer: Subgroup analysis of a phase 3 study. *Breast Cancer Research and Treatment, 118,* 81-87. Doi: 10.1007/s10549-009-0352-y.

9. Ellis, G. K., Bone, H. G., et al. (2008). Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *Journal of Clinical Oncology, 26,* 4875-4882. Doi: 10.1200/JCO.2008.16.3832.
10. Mauri, D., Valachis, A., et al. (2010). Does adjuvant bisphosphonate in early breast cancer modify the natural course of the disease? A meta-analysis of randomized controlled trials. *Journal of the National Comprehensive Cancer Network, 8*(3), 279-286.
11. Valachis, A., Polyzos, N. P., et al. (2013). Adjuvant therapy with zoledronic acid in patients with breast cancer: A systematic review and meta-analysis. *The Oncologist, 18,* 353-361. Doi: http://dx.doi.org/10.1634/theoncologist.2012-0261.
12. Early Breast Cancer Trialists' Collaborative Group. (2015). Adjuvant bisphosphonate treatment in early breast cancer: Meta-analysis of individual patient data from randomized trials. *The Lancet, 386,* 1353-1361. Doi: http://dx.doi.org/10.1016/S0140-6736(15)60908-4
13. National Cancer Institute. (2015). Meta-analysis finds benefits of adjuvant bisphosphonates for postmenopausal breast cancer. Retrieved from: https://www.cancer.gov/types/breast/research/adjuvant-bisphosphonates-meta-analysis
14. O'Carrigan, B., Wong, M. H. F., et al. (2017). Bisphosphonates and other bone agents for breast cancer (Review). *Cochrane Database of Systematic Reviews,* Issue 10. Art. No.: CD003474. Doi: 10.1002/14651858.CD003474.pub4.
15. Lamond, N. W. D., Skedgel, C., et al. (2015). Cost-utility of adjuvant zoledronic acid in patients with breast cancer and low estrogen levels. *Current Oncology, 22*(4), e246-e253. Doi: http://dx.doi.org/10.3747/co.22.2383.
16. Tella, S. H., Kommalapati, A., & Singhi, R. K. (2018). Cost-effectiveness in managing skeletal related events in breast cancer: A strategy of less-intense dosing schedule of bone modifying agents. *Translational Cancer Research, 7*(Suppl. 1), S81-S84. Doi: 10.21037/tcr.2018.01.07.
17. Shapiro, C. L., Moriarty, J. P., et al. (2017). Cost-effectiveness analysis of monthly zoledronic acid, zoledronic acid every 3 months, and monthly denosumab in women with breast cancer and skeletal metastases: CALGB 70604 (alliance). *Journal of Clinical Oncology, 35*(35), 3949-3955. Doi: https://doi.org/10.1200/JCO.2017.73.7437.
18. Himelstein, A. L., Foster, J. C., et al. (2017). Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases: A randomized clinical trial. *JAMA, 317*(1), 48-58. DOI: 10.1001/jama.2016.19425.
19. Majithia, N., Atherton, P. J., et al. (2016). Zoledronic acid for treatment of osteopenia and osteoporosis in women with primary breast cancer undergoing adjuvant aromatase inhibitor therapy: A 5-year follow-up. *Support Care Cancer, 24,* 1219-1226. Doi: 10.1007/s00520-015-2915-2
20. Coleman, R., Cameron, D., et al. (2014). Adjuvant zoledronic acid in patients with early breast cancer: Final efficacy of the AZURE (BIG 01/04) randomised open-label phase 3 trial. *Lancet Oncology, 15,* 997-1006. Retrieved from: http://dx.doi.org/10.1016/S1470-2045(14)70302-X
21. Coleman, R., de Boer, R., et al. (2013). Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): Final 60-month results. *Ann Oncol, 24*(2), 398-405. Doi: 10.1093/annonc/mds277
22. Llombart, A., Frassoldati, A., et al. (2012). Immediate administration of zoledronic acid reduces aromatase inhibitor-associated bone loss in premenopausal women with early

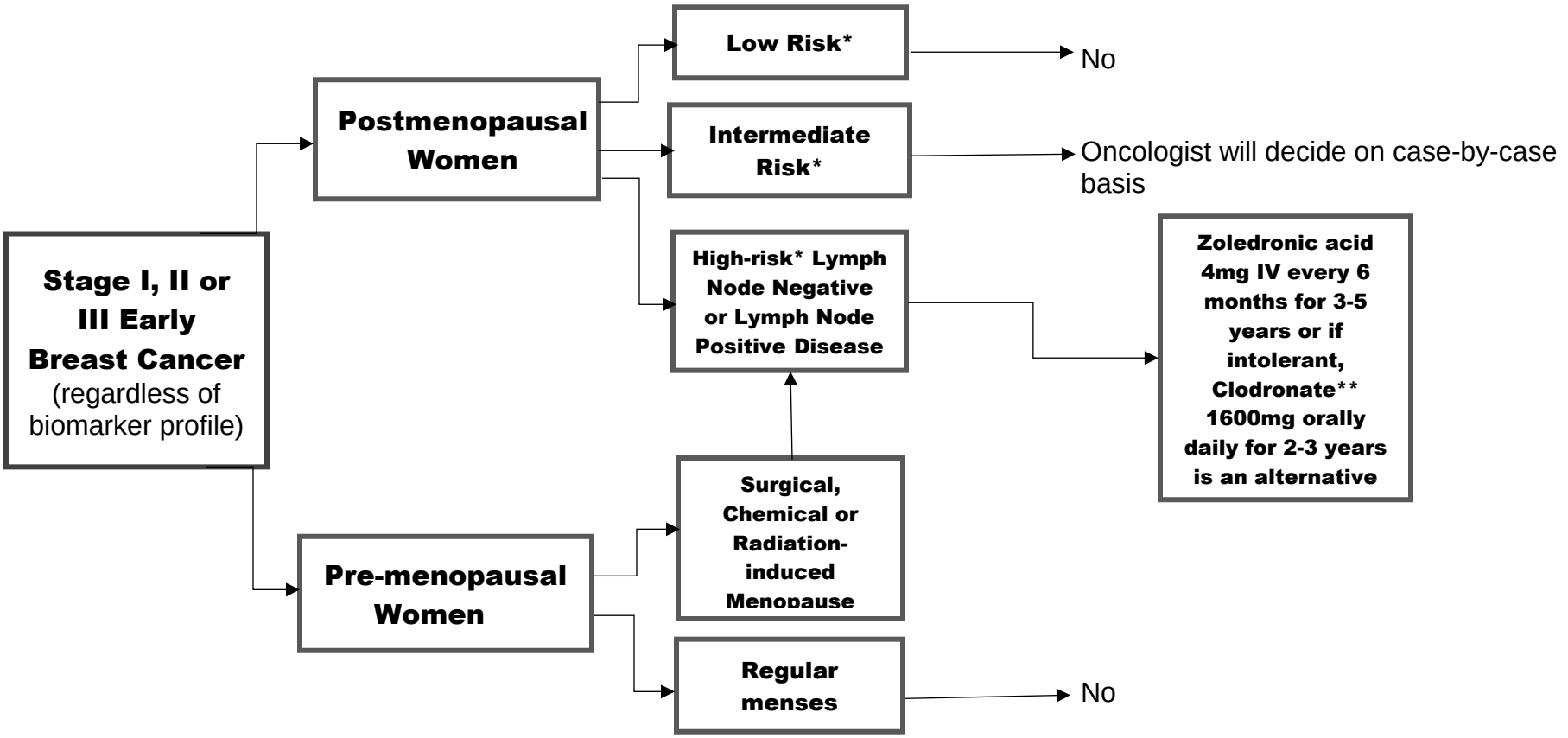
breast cancer: 12-Month analysis of the E-ZO-FAST trial. *Clinical Breast Cancer, 12(1),* 40-48. Doi: 10.1016/j.clbc.2011.08.002

23. Brutsky, A. M., Graydon Harker, W., et al. (2012). Final 5-year results of Z-FAST trial. *Cancer, 118,* 1192-1201. Doi: 10.1002/cncr.26313
24. Nuzzo, F., Gallo, C., et al. (2012). Bone effect of adjuvant tamoxifen, letrozole or letrozole plus zoledronic acid in early-stage breast cancer: The randomized phase 3 HOBOE study. *Ann Oncol, 23*(8), 2027-2033. Doi: 10.1093/annonc/mdr600
25. Gnant, M., Mlineritsch, B., et al. (2011). Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-Month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol, 12,* 631-641. Doi: 10.1016/S1470-2045(11)70122-X
26. Paterson, A. H. G., Anderson, S. J., et al. (2012). Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): A multicentre,placebo-controlled, randomised trial. *Lancet Oncol, 13,* 734-742. Doi: 10.1016/S1470-2045(12)70226-7
27. Gralow, J., Barlow, W. E., et al. Phase III trial of bisphosphonates as adjuvant therapy in primary breast cancer: SWOG/Alliance/ECOG-ACRIN/NCIC Clinical Trials Group/NRG Oncology Study S0307. *Clin J Oncol, 33,* 2015 (abstract 503).
28. Dhesy-Thind, S., Fletcher, G. G., et al. (June 2017). 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. Journal of Clinical Oncology, 35(18), 2062-2081. Doi: https://doi.org/10.1200/JCO.2016.70.7257.
29. Dhesy-Thind, S., Fletcher, G. G., … and the Adjuvant Bisphosphonates in Breast Cancer Guideline Development Group. (2016). Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer. Cancer Care Ontario. Retrieved from: https://archive.cancercare.on.ca/common/pages/UserFile.aspx?fileId=371866
30. Alberta Health Services. (April 2018). Adjuvant systemic therapy for early stage (lymph node negative and lymph node positive) breast cancer. Retrieved from : https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-adjuvant-systemic-therapy-breast.pdf
31. BC Cancer Agency. (December 2017). Adjuvant bisphosphonates for breast cancer. *Systemic Therapy Updates, 20*(12). Retrieved from: http://www.bccancer.bc.ca/systemic-therapy-site/Documents/2017%20ST%20Updates/ST%20Update_Dec%202017.pdf.
32. Hadji, P., Coleman, R. E., et al. (2016). Adjuvant bisphosphonates in early breast cancer: Consensus guidance for clinical practice from a European panel. *Annals of Oncology, 27*(3), 379-390. Doi: 10.1093/annonc/mdv617.
33. National Institute for Health and Care Excellence. (2017). Early breast cancer (preventing recurrence and improving survival): Adjuvant bisphosphonates. Retrieved from: https://www.nice.org.uk/advice/es15/chapter/Introduction-and-current-guidance.
34. National Comprehensive Cancer Network (NCCN). (2018). NCCN clinical practice guidelines in oncology: Breast cancer. Available at: www.nccn.org/patients
35. Up-To-Date. (2018). Overview of the use of osteoclast inhibitors in early breast cancer. Available at: www.uptodate.com
36. Brouwers M, Browman G, et al. Guideline adaptation: Enhancing efficiency in guideline development and utilization. www.adapte.org

37. Brouwers M, Kho ME, et al for the AGREE Next Steps Consortium. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. Can Med J. 2010.doi : 10.1503/cmaj.090449

Appendix

Figure 1: Algorithm for Adjuvant Bisphosphonate Therapy



* See next page for definitions of risk categories
** Level of evidence is weaker for Clodronate

Figure 2: Risk Categories for Lymph Node Negative Breast Cancer*

Risk Category	Risk Factor
Adverse Prognostic Factors	• Age < 35 years • HER2 over-expression (HER2+) • Presence of lymphovascular invasion • Grade 3 • Hormone receptor negative disease • Oncotype DX** test score: “higher risk”
Lower Risk	• ≤ 2 cm, grade 1, with no other adverse prognostic factors • < 0.5 cm with any other feature • Oncotype DX** test score: “lower risk”
Intermediate Risk	• All other combination of factors that do not fit into either the low or high risk criteria • Oncotype DX** test score: “intermediate risk”
Higher Risk	• > 1 cm with any 2 or more adverse prognostic factors • > 2 cm with any 1 or more adverse prognostic factors • > 3 cm +/- adverse prognostic factors • Special considerations for HER2+ breast cancer • Oncotype DX** test score: “higher risk”

* Adopted from Alberta Health Services “Adjuvant systemic therapy for early stage (lymph node negative and lymph node positive) breast cancer” guideline, April 2018 (30).
** Can include any other approved genomic biomarker assay as well.