AHFS Final Determination of Medical Acceptance: Off-label Use of Zoledronic Acid in Combination with Systemic Therapy for the Adjuvant Treatment of Early or Locally Advanced Breast Cancer

Drug/Drug Combination: Zoledronic acid

Off-label Use: Adjuvant treatment of early or locally advanced breast cancer in postmenopausal women

Criteria Used in Selection of Off-label Use for Review:

- Clinical results from two phase 3 randomized open-label trials and supportive data from a meta-analysis and three phase 3 randomized open-label trials

Strength of Evidence: Level 2 (Moderate strength/quality)

Strength of Study End Point(s): Disease-free survival

Grade of Recommendation: Reasonable choice (Accepted)

Narrative Summary:

Efficacy and safety of zoledronic acid in combination with adjuvant systemic therapy in postmenopausal women with early or locally advanced breast cancer have been studied in 2 open-label, randomized phase 3 studies (Austrian Breast and Colorectal Cancer Study Group-12 [ABCSG-12] and Adjuvant Zoledronic Acid to Reduce Recurrence [AZURE]-BIG 01/04 study),[10024, 10030] with supportive data from a meta-analysis and 3 open-label, randomized phase 3 studies evaluating the use of zoledronic acid for prevention of aromatase inhibitor-associated bone loss.[10001, 10017, 10018, 10019, 10022, 10032]

In the ABCSG-12 study, 1803 premenopausal women with estrogen receptor-positive and/or progesterone receptor-positive stage I or II breast cancer were randomized in a 1:1:1:1 ratio to receive hormonal therapy with tamoxifen (20 mg orally daily) or anastrozole (1 mg orally daily) plus a gonadotropin-releasing hormone (GnRH) agonist (goserelin acetate 3.6 mg by subcutaneous injection every 28 days) to induce ovarian suppression with or without zoledronic acid.[10023] An initial zoledronic acid dosage of 8 mg IV every 6 months was used; the protocol was subsequently amended to reduce the dosage to 4 mg by IV infusion over 15 minutes every 6 months following reports of increased toxicity (e.g., nephrotoxicity) with the higher dose.[10004] Therapy was continued for a duration of 3 years in all treatment groups.[10023] In this study, the primary measure of efficacy was disease-free survival.[10023] The median age of patients enrolled in the study was 45 years (range: 25–58); 31% had positive lymph node involvement and 85% did not receive neoadjuvant chemotherapy.[10023] All patients enrolled in the study had hormone receptor-positive tumors.[10023] At a median follow-up of 62 months, addition of zoledronic acid to hormonal therapy improved the rate of disease-free survival compared with hormonal therapy (92 versus 88%; hazard ratio of 0.68).[10023] Similar results were observed but predefined statistical significance was not achieved at a median follow-up of 94.4 months.[10024] Zoledronic acid administered concurrently with hormonal therapy was associated with numerically, but not significantly,

improved overall survival compared with hormonal therapy alone (96.7 versus 94.5%).[10024] A subset analysis of disease-free survival and overall survival based on clinically relevant baseline patient and disease characteristics demonstrated consistent treatment benefit with zoledronic acid regardless of lymph node status and disease stage (T1 or T2/3), but no difference in disease-free survival or overall survival was apparent in patients 40 years of age or younger receiving zoledronic acid compared with those receiving hormonal therapy alone.[10024] Adverse effects generally were consistent with known safety profiles of each agent, although arthralgia (24 versus 18%), bone pain (35 versus 25%), nausea/vomiting (8.6 versus 6.1%), pyrexia (8.9 versus 2.2%), dermatologic effects (6.5 versus 4.3%), peripheral nerve disease (5.7 versus 3.4%), tachycardia (2.1 versus 0.8%), cognitive disorder (1.4 versus 0.3%), and hypocalcemia (0.4 versus 0%) occurred more frequently in women receiving zoledronic acid concurrently with hormonal therapy compared with those receiving hormonal therapy alone.[10033] No confirmed cases of osteonecrosis of the jaw were reported.[10024]

In the AZURE-BIG 01/04 study, 3360 patients with stage II or III invasive breast cancer were randomized to receive zoledronic acid in addition to adjuvant antineoplastic therapy (i.e., hormonal therapy, chemotherapy, or both) or adjuvant antineoplastic therapy alone.[10030] Patients randomized to receive zoledronic acid received 4 mg by IV infusion every 3–4 weeks for 6 doses, then every 3 months for 8 doses, followed by every 6 months for 5 doses (for a total duration of 5 years).[10030] The majority of patients had positive lymph node involvement (98%), 78% had estrogen receptor-positive tumors, 45% were premenopausal, 31% had been postmenopausal for greater than 5 years, and 15% had been postmenopausal for 5 years or less.[10029] Most patients (74%) enrolled in the study planned to receive hormonal therapy in combination with chemotherapy.[10030] The majority of patients enrolled in the study planned to receive an anthracycline-containing regimen (93%) and 23% planned to receive a taxane-containing regimen.[10030] In this study, the primary measure of efficacy was disease-free survival.[10030] At median follow-up times of 59 and 84 months, no significant difference in disease-free survival (hazard ratios of 0.98 and 0.94, respectively) or overall survival (hazard ratios of 0.85 and 0.93, respectively) was observed between patients receiving zoledronic acid and antineoplastic therapy and those receiving antineoplastic therapy alone;[10029, 10030] however, zoledronic acid substantially reduced the incidence of bone fractures and bone metastasis by 31 and 19–22%, respectively, compared with antineoplastic therapy alone.[10030] A preplanned subset analysis of invasive disease-free survival based on menopausal status suggested a treatment benefit, primarily a reduction in extraskeletal invasive disease-free events, with the addition of zoledronic acid to antineoplastic therapy in women who had experienced menopause at least 5 years before study entry (hazard ratio of 0.77), but not in women in other menopausal groups (e.g., premenopausal, perimenopausal, unknown menopausal status) (hazard ratio of 1.03).[10030] Adverse effects were similar between both treatment groups, although 33 cases (confirmed in 26 cases) of potential osteonecrosis of the jaw occurred in women receiving zoledronic acid plus antineoplastic therapy compared with no cases in those receiving antineoplastic therapy alone.[10030]

Use of zoledronic acid in combination with adjuvant endocrine therapy in postmenopausal women also has been evaluated in several phase 3, open-label, randomized bone mineral density studies (Z-FAST, ZO-FAST, and E-ZO-FAST).[10001, 10017, 10018, 10019, 10022] (See Final Determination of Medical Acceptance: Off-Label Use of Zoledronic Acid for the Prevention of Aromatase Inhibitor-associated Bone Loss.) Women enrolled in these studies were postmenopausal with stage I to IIIa estrogen receptor-positive and/or progesterone receptor-positive breast cancer.[10001, 10018, 10022] Patients enrolled in these studies were randomized to receive zoledronic acid as either upfront therapy or delayed therapy (based on decline in BMD).[10001, 10018, 10022] Patients received zoledronic acid 4 mg by IV infusion over 15 minutes every 6 months for 5 years.[10001, 10018, 10022] All patients received letrozole 2.5 mg orally daily for 5 years.[10001, 10018, 10022] In the E-ZO-FAST study at a median follow-up of 12 months, no difference in disease-free survival rate was observed between women receiving upfront or

delayed zoledronic acid (97.2 versus 98.1%, respectively).[10022] Although no difference in disease-free survival was observed between the 2 treatment groups in the Z-FAST study at a median follow-up of 61 months (absolute difference of 0.7%),[10017] upfront administration of zoledronic acid therapy prolonged disease-free survival compared with delayed administration of the drug (hazard ratio of 0.66) in the ZO-FAST study.[10019] In the ZO-FAST study, breast cancer-related events in patients receiving upfront administration versus delayed administration of zoledronic acid included locoregional recurrence (0.9 versus 2.3%), distant recurrence (5.5 versus 7.7%), and bone metastases (2.6 versus 4.5%).[10019] No difference in overall survival was observed between the 2 treatment groups in the Z-FAST and ZO-FAST studies.[10017, 10019] At the time of analysis in the Z-FAST, ZO-FAST, and E-ZO-FAST studies, 25, 27, and 13%, respectively, of women in the delayed treatment group had begun treatment with zoledronic acid.[10017, 10019, 10022]

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a meta-analysis of individual patient data from 26 randomized clinical trials evaluating addition of bisphosphonate (any drug, dose, and schedule) therapy to standard adjuvant systemic therapy in women with early-stage breast cancer. [10031, 10032] This meta-analysis indicated that addition of bisphosphonate therapy to standard systemic therapy (median duration of therapy of 3.4 years) modestly reduced the risk of bone recurrence (rate ratio of 0.83) and bone fractures (rate ratio of 0.85) at 10 years compared with standard systemic therapy alone.[10031, 10032] Addition of bisphosphonate therapy to adjuvant systemic therapy also resulted in small reductions in the risk of recurrence (rate ratio of 0.94, which corresponded to an absolute difference in recurrence rate of 1.1% at 10 years), distant recurrence (rate ratio of 0.92, which corresponded to an absolute difference in rate of distance recurrence of 1.4% at 10 years), and breast cancer mortality (rate ratio 0.91, which corresponded to an absolute difference in breast cancer mortality rate of 1.7% at 10 years).[10032] However, consistent with data from the ABCSG-12 and AZURE-BIG 01/04 studies, subset analysis based on menopausal status suggested clinical benefit with adjuvant bisphosphonate therapy in postmenopausal women but not in premenopausal women.[10031, 10032, 10033] In postmenopausal women, the addition of bisphosphonate therapy to adjuvant systemic therapy reduced the risk of bone recurrence (rate ratio of 0.72, which corresponded to an absolute difference in bone recurrence rate of 2.2% at 10 years) and breast cancer mortality (rate ratio of 0.82, which corresponded to an absolute difference in breast cancer mortality rate of 3.3% at 10 years).[10032]

Based on current evidence,[10001, 10017, 10018, 10019,10022, 10024, 10030, 10032] use of zoledronic acid in combination with adjuvant systemic therapy may be considered a reasonable choice (accepted) in postmenopausal women with early or locally advanced breast cancer. The American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) state that postmenopausal women who are candidates for adjuvant systemic therapy for the treatment of breast cancer should consider receiving a bisphosphonate (i.e., zoledronic acid) during the course of adjuvant therapy for up to 5 years.[10031] Although some clinicians state that any bone-modifying agent that has demonstrated a reduction in the risk of fragility fractures in at-risk populations (e.g., postmenopausal women, drug-induced osteoporosis) may be effective as adjuvant therapy for breast cancer, sufficient data are only available from clinical trials evaluating zoledronic acid or clodronate (not commercially available in the US); additional data are needed to further elucidate clinical benefit of other bone-modifying agents.[10031] The optimal time for initiating bisphosphonates is not known; however, bisphosphonate therapy was generally initiated soon after surgery or chemotherapy in most clinical trials.[10031] The optimal duration of adjuvant bisphosphonate therapy is not known; however, the duration should not exceed 5 years since toxicity of long-term (e.g., beyond 5 years) use of bisphosphonates, including zoledronic acid, has not been determined.[10031]ASCO states that clinicians should consider patient and disease characteristics (e.g., risk of recurrence) and adverse effects when deciding whether bisphosphonate therapy should be added to adjuvant systemic therapy.[10031]

Dosage:

When zoledronic acid has been used in combination with adjuvant systemic therapy in postmenopausal women with early or locally advanced breast cancer, zoledronic acid 4 mg has been administered by IV infusion over 15 minutes every 6 months for 3–5 years.[10001, 10004, 10019, 10022, 10023] In clinical trials, patients were encouraged to take supplemental oral calcium (400 mg to 1.2 g daily) and vitamin D (200–800 units daily).[10001, 10019, 10022, 10029]

References:

10001. Brufsky A, Harker WG, Beck JT et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol*. 2007; 25:829-36.

10004. Gnant MF, Mlineritsch B, Luschin-Ebengreith G et al. Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. *J Clin Oncol*. 2007; 25:820-8.

10017. Brufsky AM, Harker WG, Beck JT et al. Final 5-year results of Z-FAST trial: adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole. *Cancer*. 2012; 118:1192-201.

10018. Bundred NJ, Campbell ID, Davidson N et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. *Cancer*. 2008; 112:1001-10.

10019. Coleman R, de Boer R, Eidtmann H et al. Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results. *Ann Oncol*. 2013; 24:398-405.

10022. Llombart A, Frassoldati A, Paija O et al. Immediate administration of zoledronic acid reduces aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer: 12-month analysis of the E-ZO-FAST trial. *Clin Breast Cancer*. 2012; 12:40-8.

10023. Gnant M, Mlineritsch B, Stoeger H et al. 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*. 2011; 12:631-41.

10024. Gnant M, Mlineritsch B, Stoeger H et al. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. *Ann Oncol*. 2015; 26:313-20.

10029. Coleman RE, Marshall H, Cameron D et al. Breast-cancer adjuvant therapy with zoledronic acid. *N Engl J Med*. 2011; 365:1396-405.

10030. Coleman R, Cameron D, Dodwell D et al. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. *Lancet Oncol*. 2014; 15:997-1006.

10031. Dhesy-Thind S, Fletcher GG, Blanchette PS 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*. 2017; 35:2062-81.

10032. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet*. 2015; 386:1353-61.

10033. Dhesy-Thind S, Fletcher GG, Blanchette PS et al. Cancer Care Ontario and ASCO guidelines data supplement: Use of adjuvant bisphosphonates and other bone modifying agents in breast cancer: a systematic review. From ASCO website. Accessed on 2018 Oct 31.

Oncology Expert Committee Voting Results:

Proposed Level of Evidence: Level 2 (Moderate strength/quality); disease-free survival

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 0 votes

Reasonable choice (Accepted, treatment option): 4 votes

Not fully established (Unclear risk/benefit or equivocal): 1 vote

Not recommended (Unaccepted): 0 votes

Proposed Consensus Recommendation:

Based on current evidence,[10001, 10017, 10018, 10019,10022, 10024, 10030, 10032] use of zoledronic acid in combination with adjuvant systemic therapy may be considered a reasonable choice (accepted) in postmenopausal women with early or locally advanced breast cancer. The American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) state that postmenopausal women who are candidates for adjuvant systemic therapy for the treatment of breast cancer should consider receiving a bisphosphonate (i.e., zoledronic acid) during the course of adjuvant therapy for up to 5 years.[10031] Although some clinicians state that any bone-modifying agent that has demonstrated a reduction in the risk of fragility fractures in at-risk populations (e.g., postmenopausal women, drug-induced osteoporosis) may be effective as adjuvant therapy for breast cancer, sufficient data has only been demonstrated in clinical trials evaluating zoledronic acid or clodronate (not commercially available in the US); additional data are needed to further elucidate clinical benefit of other bone-modifying agents.[10031] The optimal time for initiating bisphosphonates is not known; however, bisphosphonate therapy was generally initiated soon after surgery or chemotherapy in most clinical trials.[10031] The duration of adjuvant bisphosphonate therapy should not exceed 5 years, since toxicity of long-term (e.g., beyond 5 years) use of bisphosphonates, including zoledronic acid, has not been determined.[10031] The optimal duration of adjuvant bisphosphonate therapy is not known.[10031] ASCO states that clinicians should consider patient and disease characteristics (e.g., risk of recurrence) and adverse effects when deciding whether bisphosphonate therapy should be added to adjuvant systemic therapy.[10031]

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

Oncology Expert Committee Members' Comments:

Comments in Support of Vote on Level of Evidence and Grade of Recommendation:

Reviewer #1: [Specific patient population] Limited to postmenopausal women or those premenopausal women >40 years of age.

Reviewer #1: Should not exceed 5 years of therapy and should be given with calcium and vitamin D.

Reviewer #2: [Specific patient population] Postmenopausal women.

Reviewer #3: Agree with ASCO's carefully chosen recommendations of "consideration", drugs/agents, promising but insufficient data for denosumab, duration, definition of menopause, and dental assessment.

Reviewer #5: [Specific patient population] Postmenopausal patients (either natural or via ovarian suppression).

Comments on Draft Narrative Summary:

Reviewer #2: Benefit in premenopausal and perimenopausal not verified.

Comments on Proposed Consensus Recommendation:
None.

Participants:

AHFS Staff Members (writing and editing): Lily Leu, Pharm.D., BCOP

AHFS Oncology Expert Committee Members (reviewing and voting): Raymond Hohl, M.D., Ph.D.; Ron Walters, M.D., MBA, MHA, MS; LeAnn Norris, Pharm.D., BCPS, BCOP; Mandy Gatesman, Pharm.D., BCOP; Sandra Kurtin, RN, MS, AOCN, ANP-C

External Consultants: None

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

Publication Date: November 25, 2019