AHFS Final Determination of Medical Acceptance: Off-label Use of Exemestane for Initial Adjuvant Treatment of Early-stage Breast Cancer

Drug/Drug Combination: Exemestane

Off-label Use: Initial adjuvant treatment of early-stage hormone receptor-positive 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

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

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

Grade of Recommendation: Reasonable choice (Accepted, with possible conditions)

Narrative Summary:

Use as Initial Adjuvant Therapy:

Data from two phase 3 randomized open-label clinical trials indicate that initial therapy+ with exemestane is at least as effective as initial therapy with anastrozole or sequential therapy with tamoxifen followed by exemestane in postmenopausal women with early-stage hormone receptor-positive breast cancer.[10001,10002]

In the first study (Tamoxifen Exemestane Adjuvant Multinational [TEAM]), 9779 postmenopausal women with early-stage hormone receptor-positive breast cancer were randomized to receive exemestane 25 mg daily for 5 years or sequential therapy with tamoxifen 20 mg daily for 2–3 years followed by exemestane 25 mg daily for a total treatment duration of 5 years.[10001] Most (98%) of the patients enrolled in the study had estrogen receptor-positive tumors.[10001] The primary end point of the study was disease-free survival.[10001] At a median follow-up of 5.1 years, no significant difference in estimated 5-year disease-free survival was observed between patients receiving sequential therapy and those receiving initial exemestane therapy (85 and 86%, respectively; hazard ratio of 0.97 with a 95% confidence interval of 0.88–1.08); in addition, no difference in 5-year overall survival was observed between the groups.[10001] Disease relapse or breast cancer-related death occurred in similar proportions of patients receiving sequential therapy (11%) or initial exemestane therapy (10%).[10001] In this study, fractures, osteoporosis, hyperlipidemia, hypertension, and cardiac failure occurred more frequently in patients receiving initial exemestane therapy, whereas venous thrombosis, vaginal bleeding, and endometrial disorders occurred more frequently in those receiving sequential therapy.[10001]

In the second study (MA.27), 7576 postmenopausal women with hormone receptor-positive primary invasive breast cancer were randomized to receive exemestane 25 mg daily or anastrozole 1 mg daily for 5 years, with or without celecoxib; however, random assignment to celecoxib was halted when data from another study suggested that celecoxib may increase cardiovascular risk.[10002] Patients were stratified according to lymph node status, receipt of prior adjuvant chemotherapy, use of concomitant trastuzumab therapy, and previous random assignment to celecoxib and concomitant prophylactic aspirin therapy. [10002] Most (99%) of the patients enrolled in the study had estrogen receptor-positive tumors.[10002] The primary end point of the study was event-free survival.[10002] At a median follow-up of 4.1 years, no significant difference in estimated 4-year event-free survival was observed between patients receiving exemestane and those receiving anastrozole (91 and 91.2%, respectively; hazard ratio of 1.02 with a 95% confidence interval of 0.87–1.18).[10002] In addition, no difference in overall survival was observed between the groups.[10002] Elevations in aminotransferase (ALT or AST) concentrations (3 versus 1%), elevations in serum bilirubin concentrations (2 versus 1%), and atrial fibrillation (2 versus 1%) occurred more frequently in patients receiving exemestane, whereas hyperlipidemia (18 versus 15%), hypertriglyceridemia (3 versus 2%), and osteoporosis (35 versus 31%) occurred more frequently in patients receiving anastrozole.[10002]

Clinical Role

Based on data from randomized controlled trials demonstrating prolonged disease-free survival in patients receiving aromatase inhibitor-based adjuvant regimens,[10,10001,10002] use of exemestane may be considered a reasonable choice (accepted, with possible conditions) for initial adjuvant therapy in postmenopausal women with early-stage hormone receptor-positive breast cancer; factors that should be considered when selecting an appropriate aromatase inhibitor include tolerability, patient preference, and preexisting conditions.

The American Society of Clinical Oncology (ASCO) states that most postmenopausal women with early-stage hormone receptor-positive breast cancer should consider receiving an aromatase inhibitor (e.g., exemestane) during the course of adjuvant therapy, either as primary (initial) therapy or following 2–3 years of tamoxifen therapy (sequential therapy), to complete a total of 5 years of adjuvant endocrine therapy.[10] Clinically meaningful differences among the currently available aromatase inhibitors (i.e., anastrozole, exemestane, letrozole) have not been demonstrated to date.[10,10002] Data also support switching to an aromatase inhibitor following 5 years of adjuvant tamoxifen therapy (extended therapy) (see the AHFS Final Determination of Medical Acceptance: Off-label Use of Exemestane for Extended Adjuvant Therapy of Early-stage Breast Cancer).[10] The optimal time for switching from tamoxifen to an aromatase inhibitor is not known.[10] The duration of aromatase inhibitor therapy should not exceed 5 years, since toxicity of long-term (e.g., beyond 5 years) use of aromatase inhibitors, including exemestane, has not been determined.[10] The optimal duration of adjuvant exemestane therapy is not known.[10] ASCO states that clinicians should consider adverse effects, patient preference, and preexisting conditions when selecting an adjuvant regimen; during the course of adjuvant therapy, patients who are intolerant of one aromatase inhibitor may be switched to a different aromatase inhibitor or to tamoxifen.[10]

The use of a luteinizing hormone-releasing hormone (LHRH) agonist (e.g., triptorelin) in combination with exemestane as adjuvant therapy in *premenopausal* women with hormone receptor-positive breast cancer† is being investigated in a large randomized trial.[10003] The use of an aromatase

inhibitor as a single agent for adjuvant therapy is *not* appropriate in premenopausal women with breast cancer because these agents alone are not likely to provide sufficient suppression of ovarian function to be of clinical benefit.[10,10007] Similarly, the use of an aromatase inhibitor as monotherapy for adjuvant therapy for hormone receptor-positive breast cancer in premenopausal women experiencing a chemotherapy-induced disruption in ovarian function is not advised;[10,10007] a substantial number of such patients can expect resumption of ovarian function, and this would likely render therapy with an aromatase inhibitor ineffective.[10, 10004]

Dosage as Initial Adjuvant Therapy:

When used for initial adjuvant treatment† in postmenopausal women with early-stage hormone receptor-positive breast cancer, exemestane has been administered at a dosage of 25 mg once daily for 5 years.[10001,10002]

The American Society of Clinical Oncology (ASCO) states that an aromatase inhibitor (e.g., exemestane) may be administered to postmenopausal women with early-stage hormone receptor-positive breast cancer as initial adjuvant therapy and continued for a total of 5 years or may be administered following initial tamoxifen therapy as part of a sequential adjuvant regimen.[10] The optimal time to switch from tamoxifen to aromatase inhibitor therapy is not known; however, based on clinical trials conducted to date, ASCO recommends that patients who are disease-free may be switched to an aromatase inhibitor after 2–3 years of tamoxifen therapy to complete a 5-year sequential adjuvant regimen.[10] In patients who initially receive an aromatase inhibitor but discontinue therapy prior to 5 years, ASCO states that consideration should be given to administering tamoxifen to complete the 5-year adjuvant regimen.[10]

References:

10. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol.* 2010; 28:3784-96. (PubMed 20625130) (DOI 10.1200/JCO.2009.26.3756)

10001. van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. *Lancet.* 2011; 377:321-31. (PubMed 21247627) (DOI 10.1016/S0140-6736(10)62312-4)

10002. Goss PE, Ingle JN, Pritchard KI, et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27--a randomized controlled phase III trial. *J Clin Oncol.* 2013; 31:1398-404. (PubMed 23358971) (DOI 10.1200/JCO.2012.44.7805)

10003. Suppression of ovarian function and either tamoxifen or exemestane with or without chemotherapy in treating premenopausal women with resected breast cancer (PERCHE). From ClinicalTrials.gov Registry. Accessed 2013 Dec 12.

10004. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: status report 2002. *J Clin Oncol.* 2002; 20:3317-27. (PubMed 12149306)

10007. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol.* 2005; 23:619-29. (PubMed 15545664) (DOI 10.1200/JCO.2005.09.121)

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): 2 votes

Reasonable choice (Accepted, treatment option): 3 votes

Not fully established (Unclear risk/benefit or equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Proposed Consensus Recommendation:
Based on data from randomized controlled trials demonstrating prolonged disease-free survival in patients receiving aromatase inhibitor-based adjuvant regimens, use of exemestane may be considered a reasonable choice (accepted, with possible conditions) for initial adjuvant therapy in postmenopausal women with early-stage hormone receptor-positive breast cancer; factors that should be considered when selecting an appropriate aromatase inhibitor include tolerability, patient preference, and preexisting conditions.

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: In reference to the MA.27 trial, exemestane is an alternative (versus anastrozole) for treating women with early-stage breast cancer with baseline osteoporosis.

Reviewer #1: Study did not demonstrate superiority for exemestane but was not designed as a non-inferiority study. This is reasonable to use but not as rigorously shown to be as effective.

Reviewer #4: Patient and/or physician preference based on tolerability.

Reviewer #5: Although no specific subgroup shown to have more or less benefit with exemestane vs. other aromatase inhibitors or tamoxifen followed by an aromatase inhibitor, there are also no mortality data showing exemestane is clearly better than any other aromatase inhibitor containing adjuvant treatment strategy therefore it is a reasonable choice based on patient specific risk factors (e.g., VTE history, prior ADEs, etc.)

Reviewer #5: Could consider including Meta-Analysis of Breast Cancer Outcomes in Adjuvant Trials of Aromatase Inhibitors versus Tamoxifen. JCO; 28(3):509-518. (2010).

Comments on Draft Narrative Summary:

None submitted.

Comments on Proposed Consensus Recommendation:
None submitted.

Participants:

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AHFS Oncology Expert Committee Members (reviewing and voting): Massimo Cristofanilli, M.D., FACP; Raymond Hohl, M.D., Ph.D.; Beth Faiman, Ph.Dc., RN, ANP-BC, AOCN; Mandy Gatesman, Pharm.D., BCOP; Christine Gegeckas, RPh, BCOP

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.

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