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

Drug/Drug Combination: Exemestane

Off-label Use: Extended 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 a phase 3 randomized trial

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 Extended Adjuvant Therapy:

Efficacy of exemestane as extended adjuvant therapy in postmenopausal women with early-stage breast cancer who have received 5 years of adjuvant tamoxifen therapy has been evaluated in a double-blind, placebo-controlled, randomized phase 3 trial (National Surgical Adjuvant Breast and Bowel Project [NSABP] B-33) in postmenopausal women mostly with hormone receptor-positive breast cancer (97% hormone receptor-positive, 3% hormone receptor-unknown).[10005] In this trial, 1598 patients who had received adjuvant therapy with tamoxifen for approximately 5 years (range: approximately 4.75–5.6 years) were randomized to receive exemestane 25 mg daily or placebo for 5 years.[10005] Based on interim results from a similarly designed trial demonstrating benefit from extended adjuvant therapy with letrozole, recruitment of patients for the NSABP B-33 trial was halted early, the study was unblinded, and exemestane therapy was offered to all women who had been receiving placebo.[10005] After the study was unblinded, 44% of patients randomized to receive placebo crossed over to receive exemestane therapy and 72% of patients randomized to receive exemestane continued their assigned therapy.[10005]

At a median follow-up of 30 months, the estimated 4-year disease-free survival did not differ significantly between patients receiving exemestane and those receiving placebo (91 versus 89%, respectively, based on intent-to-treat analysis); in addition, no difference in overall survival was observed between the groups.[10005] A significant difference in estimated 4-year relapse-free survival was observed between patients randomized to receive exemestane and those randomized to receive placebo (96 versus 94%, respectively).[10005] Exemestane treatment was associated with numerically, but not significantly, fewer local or metastatic recurrences and with a significant reduction in the incidence of

new contralateral breast cancer, as compared with placebo.[10005] An exploratory subset analysis suggested that the effect of exemestane on disease-free survival was greater in patients with tumors larger than 2 cm or with node-positive disease.[10005] Although grade 3 adverse effects occurred more commonly in patients receiving exemestane, the incidence of grade 4 adverse effects was similar for patients receiving exemestane or placebo.[10005]

Clinical Role

Based on data from randomized controlled trials demonstrating prolonged disease-free survival in patients receiving aromatase inhibitors as extended adjuvant therapy,[10,10005] use of exemestane may be considered a reasonable choice (accepted, with possible conditions) for extended adjuvant therapy in postmenopausal women with early-stage hormone receptor-positive breast cancer who have received 5 years of adjuvant tamoxifen therapy; 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) recommends extended therapy with an aromatase inhibitor (e.g., exemestane) in postmenopausal women with early-stage hormone receptor-positive breast cancer who complete 5 years of adjuvant tamoxifen therapy.[10] (See Extended Adjuvant Therapy for Early-stage Breast Cancer in Uses: Breast Cancer, in Letrozole 10:00.) Clinically meaningful differences among the currently available aromatase inhibitors (i.e., anastrozole, exemestane, letrozole) have not been demonstrated to date.[10] Clinicians should consider adverse effects, patient preference, and preexisting conditions when selecting an adjuvant regimen.[10] ASCO states that women who receive extended adjuvant therapy should receive a total of 8–10 years of adjuvant endocrine therapy, including 5 years of tamoxifen therapy followed by 3–5 years of aromatase inhibitor therapy.[10] The optimal duration of exemestane as extended adjuvant therapy is not known, and the toxicity of long-term (e.g., beyond 5 years) use of aromatase inhibitors, including exemestane, in this setting has not been determined.[10] Ongoing clinical trials are evaluating whether longer durations of aromatase inhibitor therapy are more effective.[10]

Dosage as Extended Adjuvant Therapy:

When used for extended adjuvant treatment+ in postmenopausal women with early-stage breast cancer who have received 5 years of adjuvant tamoxifen therapy, exemestane has been administered at a dosage of 25 mg once daily.[10005] ASCO recommends that patients who receive an extended adjuvant regimen receive an aromatase inhibitor (e.g., exemestane) for 3–5 years beyond the initial 5 years of tamoxifen therapy, to complete a total of 8–10 years of adjuvant endocrine therapy.[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)

10005. Mamounas EP, Jeong JH, Wickerham DL, et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant

Breast And Bowel Project B-33 trial. *J Clin Oncol*. 2008; 26:1965-71.
(PubMed 18332472) (DOI 10.1200/JCO.2007.14.0228)

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 inhibitors as extended adjuvant therapy, use of exemestane may be considered a reasonable choice (accepted, with possible conditions) for extended adjuvant therapy in postmenopausal women with early-stage hormone receptor-positive breast cancer who have received 5 years of adjuvant tamoxifen therapy; 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: [Specific patient population] to be determined.

Reviewer #2: [Specific patient population] in node-positive locally advanced breast cancer.

Reviewer #4: Based on patient/physician choice of aromatase inhibitor and exemestane.

Comments on Draft Narrative Summary:

Reviewer #1: Important to recognize the data is disease-free survival and relapse-free survival and not [overall] survival.

Comments on Proposed Consensus Recommendation:
None submitted.

Participants:

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

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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