AHFS Final Determination of Medical Acceptance:
Off-label Use of Endocrine Therapy in Combination with Ovarian Suppression for the Adjuvant Treatment of Early-stage Hormone Receptor-positive Breast Cancer in Premenopausal Women

Drug/Drug Combination: Endocrine therapy in combination with ovarian suppression

Off-label Use: Adjuvant treatment of early-stage hormone receptor-positive breast cancer in premenopausal women

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

- Clinical results from four 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:

Adjuvant Therapy for Early-stage Breast Cancer in Premenopausal Women

Endocrine therapy (i.e., anastrozole, exemestane, letrozole, tamoxifen) has been used in combination with ovarian suppression+ as adjuvant therapy in premenopausal women+ with early-stage hormone receptor-positive breast cancer.[10010, 10011, 10013, 10023, 10026]

Clinical Trials.

Efficacy and safety of endocrine therapy in combination with ovarian suppression as adjuvant therapy in premenopausal women with early-stage hormone receptor-positive breast cancer have been studied in several open-label, randomized, phase 3 studies. [10010, 10011, 10013, 10026]

In the Suppression of Ovarian Function Trial (SOFT), 3066 premenopausal women with early-stage hormone receptor-positive breast cancer were randomized to receive 5 years of treatment with tamoxifen 20 mg daily, tamoxifen 20 mg daily and ovarian suppression, or exemestane 25 mg daily and ovarian suppression.[10010] Ovarian suppression could be achieved with triptorelin 3.75 mg administered by IM injection every 28 days, bilateral oophorectomy, or bilateral ovarian irradiation.[10010]

Approximately one-half (53%) of patients enrolled in the study had received prior adjuvant chemotherapy.[10010] The primary analysis involved comparison of tamoxifen and ovarian suppression with tamoxifen alone.[10010] At a median follow-up of 8 years, disease-free survival and overall survival were prolonged, without a reduction in distant recurrences, in women receiving tamoxifen and ovarian suppression compared with those receiving tamoxifen alone; a disease-free survival benefit and a reduction in distant recurrences were observed, without an overall survival benefit, in women receiving exemestane and ovarian suppression compared with those receiving tamoxifen alone.[10012] (See Table 1.)

Table 1. Efficacy Results for Combined Endocrine and Ovarian Suppression Therapy at 8 Years' Follow-up in the SOFT Study[(r10012)]

Treatment and Efficacy Measure	Hazard Ratio (vs tamoxifen)	Absolute Improvement (vs tamoxifen)[a]
Tamoxifen and Ovarian Suppression		
Disease-free survival	0.76	4.2%
Overall survival	0.67	1.8%
Freedom from distant recurrence	0.86	. . .
Exemestane and Ovarian Suppression		
Disease-free survival	0.65	7%
Overall survival	0.85	. . .
Freedom from distant recurrence	0.73	2.8%

[a] Percentage point difference in occurrence rates for the indicated treatment versus tamoxifen for events occurring at significantly different rates.

Subgroup analysis in the SOFT study suggested that the relative clinical benefits of the 3 treatments generally were similar regardless of prior use of adjuvant chemotherapy; however, no difference in disease-free survival was observed with the addition of ovarian suppression to tamoxifen therapy in patients at lower risk of breast cancer recurrence (i.e., older age, node-negative disease, low-grade tumor, smaller tumor size) who had not required prior adjuvant chemotherapy.[10010, 10012, 10017] The absolute benefit of combined endocrine and ovarian suppression therapy was greater in higher-risk patients who had received adjuvant chemotherapy.[10012] The absolute difference in 8-year disease-free survival rates between women receiving exemestane and ovarian suppression and those receiving tamoxifen alone was greater in women at higher risk of breast cancer recurrence (i.e., younger age, larger or high-grade tumor, lymph node involvement[10010, 10012]) who had received prior adjuvant chemotherapy (9%) compared with those in the lower-risk cohort (5.2%).[10012] The absolute difference in 8-year disease-free survival rates between women receiving tamoxifen and ovarian suppression and those receiving tamoxifen alone also was greater in women in the higher-risk cohort (5.3%) compared with those in the lower-risk cohort (3.2%).[10012]

A combined analysis of the SOFT study and the Tamoxifen and Exemestane Trial (TEXT) included data for 4690 premenopausal women with hormone receptor-positive operable breast cancer who were randomized to receive ovarian suppression and either exemestane 25 mg daily or

tamoxifen 20 mg daily for 5 years.[10011] Ovarian suppression could be achieved with triptorelin 3.75 mg administered by IM injection every 28 days, bilateral oophorectomy, or bilateral ovarian irradiation.[10011] In patients who received adjuvant chemotherapy in the TEXT study, triptorelin was initiated concomitantly with chemotherapy.[10011] Approximately one-half (57.4%) of patients in the combined analysis received adjuvant chemotherapy.[10011] A 5-year disease-free survival benefit and higher 5-year rates of freedom from breast cancer and freedom from distant recurrence were observed in women receiving exemestane and ovarian suppression compared with those receiving tamoxifen and ovarian suppression.[10011] Beneficial effects of combined exemestane and ovarian suppression therapy on disease-free survival and distant recurrences were maintained at 8 years.[10012] (See Table 2.) Musculoskeletal symptoms (89.9 versus 77.8%) and osteoporosis (42.2 versus 27.9%) occurred more frequently in exemestane-treated patients compared with tamoxifen-treated patients.[10012]

Table 2. Efficacy Results for Combined Endocrine and Ovarian Suppression Therapy in the Combined SOFT and TEXT Analysis[(r10011) (r10012)]

Efficacy Measure	Exemestane and Ovarian Suppression (%)	Tamoxifen and Ovarian Suppression (%)
Disease-free survival, 5 years	91.1	87.3
Overall survival, 5 years	95.9	96.9
Freedom from breast cancer, 5 years	92.8	88.8
Freedom from distant recurrence, 5 years	93.8	92
Disease-free survival, 8 years	86.8	82.8
Overall survival, 8 years	93.4	93.3
Freedom from distant recurrence, 8 years	91.8	89.7

In the HOBOE study, 1065 premenopausal women with early-stage hormone receptor-positive breast cancer were randomized to receive 5 years of treatment with tamoxifen 20 mg daily, letrozole 2.5 mg daily, or letrozole 2.5 mg daily in combination with zoledronic acid 4 mg IV every 6 months; all patients received ovarian suppression with triptorelin 3.75 mg by IM injection every 4 weeks for 5 years or until the age of 55 years.[10026] The majority (62.6%) of patients had received prior neoadjuvant or adjuvant chemotherapy.[10026] At a median follow-up of approximately 5.3 years, a substantial disease-free survival benefit was observed in women receiving letrozole in combination with zoledronic acid and ovarian suppression (hazard ratio of 0.52, which corresponded to an absolute improvement in disease-free survival of 7.9%) but not in those receiving letrozole and ovarian suppression (hazard ratio of 0.72 with a 95% confidence interval of 0.48−1.07), compared with women receiving tamoxifen and ovarian suppression.[10026] No difference in overall survival was observed among the 3 treatment groups.[10026] However, at the time of the analysis, only 81% of the number of events required for final analysis had occurred.[10026] Among patients receiving either letrozole or tamoxifen in combination with

ovarian suppression, hypercholesterolemia (30.4 versus 20.3%), arthralgia (44.5 versus 22%), bone pain (29 versus 15.3%), insomnia (8.1 versus 4.2%), sensory neuropathy (13 versus 7.7%), and vaginal dryness (20.8 versus 11.7%) occurred more frequently in those receiving letrozole, while endometrial abnormalities (3 versus 6.8%) occurred more frequently in those receiving tamoxifen.[10026]

In the E-3193/INT-0142 study, 345 premenopausal women with early-stage hormone receptor-positive breast cancer were randomized to receive tamoxifen 20 mg daily with or without ovarian suppression for 5 years.[10013] Ovarian suppression therapy could be achieved with goserelin 3.6 mg implanted subcutaneously every 4 weeks, leuprolide acetate 3.75 mg by IM injection every 4 weeks, bilateral oophorectomy, or bilateral ovarian irradiation.[10013] Patients enrolled in the study had baseline characteristics associated with lower risk of breast cancer recurrence (i.e., node-negative disease, tumor size of 3 cm or less, no prior adjuvant chemotherapy, median age 45 years).[10013, 10017] At a median follow-up of approximately 9.9 years, results of this study were consistent with those of the SOFT study, demonstrating no difference in disease-free or overall survival between lower-risk women receiving tamoxifen and ovarian suppression and those receiving tamoxifen alone; however, interpretation of the results is limited by failure to meet the accrual goal of 1600 patients for superiority testing.[10013, 10017] In this study, the addition of ovarian suppression to tamoxifen therapy was associated with increased menopausal symptoms, decreased sexual function, increased breast cancer-specific symptoms, and lower quality of life during the first 3 years of therapy.[10013]

Clinical Role.

Use of adjuvant exemestane or tamoxifen therapy in combination with ovarian suppression improved disease-free survival rates compared with tamoxifen alone in premenopausal women with early-stage hormone receptor-positive breast cancer in the SOFT study;[10012] however, more deaths occurred despite fewer distant recurrences in women receiving exemestane and ovarian suppression compared with those receiving tamoxifen and ovarian suppression.[10012, 10016] Factors contributing to the discordance between distant recurrence rates and overall survival in women receiving exemestane and ovarian suppression have not been elucidated; however, some clinicians suggest that incomplete and/or intermittent estrogen suppression with gonadotropin-releasing hormone (GnRH) agonists used to achieve ovarian suppression may be a potential mechanism.[10016, 10025, 10027] In the combined analysis of the SOFT and TEXT studies, clinical benefits (i.e., disease-free survival, freedom from distant recurrence) were observed in women receiving exemestane and ovarian suppression compared with

those receiving tamoxifen and ovarian suppression;[10012] however, in the HOBOE study, no difference in disease-free survival was observed between women receiving letrozole and ovarian suppression and those receiving tamoxifen and ovarian suppression.[10026]

The role of adding ovarian suppression to adjuvant endocrine therapy has not been fully elucidated; however, no discernible benefit from the addition of ovarian suppression to tamoxifen therapy has been observed in premenopausal women at lower risk of disease recurrence (i.e., older age, node-negative disease, low-grade tumor, smaller tumor size) in the SOFT and E-3193/INT-0142 studies, whereas a disease-free survival advantage was observed in a cohort of women at higher risk of disease recurrence (i.e., younger age, high-grade tumor, increased risk of lymph node involvement) receiving ovarian suppression in addition to exemestane or tamoxifen therapy in the SOFT study.[10012, 10017]

Based on current evidence,[10010,10011, 10012, 10013, 10023,10026] use of endocrine therapy (i.e., anastrozole, exemestane, letrozole, tamoxifen) in combination with ovarian suppression as adjuvant therapy may be considered a reasonable choice (accepted) in premenopausal women with early-stage hormone receptor-positive breast cancer at higher risk of disease recurrence (i.e., younger age, larger or high-grade tumor,increased risk of lymph node involvement) and those who received prior adjuvant chemotherapy.[10028] ASCO states that the duration of adjuvant GnRH agonist therapy should not exceed 5 years, since the toxicity of long-term (e.g., beyond 5 years) use of GnRH agonist-induced ovarian suppression has not been determined and comparative data for alternative treatment durations are lacking.[10017, 10018] Although inconsistent estrogen suppression may occur in premenopausal women receiving combined ovarian suppression and endocrine therapy, routine monitoring of serum estradiol concentrations is not recommended since there is insufficient evidence to support specific monitoring guidelines and validated estradiol assays are not widely available;[10016, 10017, 10020, 10025] however, ASCO recommends monitoring for physiologic changes that would suggest recovery of ovarian function.[10017] ASCO states that clinicians should consider recurrence risk, adverse effects, patient preference, quality of life, consequences for childbearing, and the potential for ambiguity regarding the status of ovarian function (e.g., in women with chemotherapy-induced amenorrhea, hysterectomy-induced amenorrhea, incomplete ovarian suppression, or noncompliance with ovarian suppression therapy) when considering the addition of ovarian suppression therapy to adjuvant endocrine therapy.[10017, 10018]

Dosage:

When endocrine therapy has been used in combination with ovarian suppression+ as adjuvant therapy in premenopausal women+ with early-stage hormone receptor-positive breast cancer, tamoxifen

20 mg once daily, anastrozole 1 mg once daily, exemestane 25 mg once daily, or letrozole 2.5 mg once daily for a duration of 5 years has been used.[10010, 10011, 10012, 10013, 10026] In clinical studies, ovarian suppression was achieved with goserelin 3.6 mg implanted subcutaneously every 4 weeks, leuprolide acetate 3.75 mg by IM injection every 4 weeks, triptorelin 3.75 mg by IM injection every 4 weeks, or surgical or radiation ablation. [10010, 10011, 10012, 10013, 10023, 10026]

References:

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10012. Francis PA, Pagani O, Fleming GF, et al. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. *N Engl J Med*. 2018; 379:122-137.

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10026. Perrone F, De Laurentiis M, De Placido S, et al. Adjuvant zoledronic acid and letrozole plus ovarian function suppression in premenopausal breast cancer: HOBOE phase 3 randomised trial. *Eur J Cancer*. 2019; 118:178-186.

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 current evidence,[10010,10011,10013,10026] use of endocrine therapy (i.e., anastrozole, exemestane, letrozole, tamoxifen) in combination with ovarian suppression as adjuvant therapy may be considered a reasonable choice (accepted) in premenopausal women with early-stage hormone receptor-positive breast cancer at higher risk of disease recurrence (i.e., younger age, larger or high-grade tumor, increased risk of lymph node involvement) and those who received prior adjuvant chemotherapy.[10028]

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] Those with high risk of recurrence (younger age, larger or high-grade tumor, lymph node involvement, previous adjuvant chemotherapy).

Reviewer #1: I would emphasize the importance of the utility in high risk versus low risk of recurrence as that appears to be a common theme.

Reviewer #3: I am a bit challenged by the wording "endocrine therapy", even though there is a definition outlining the drugs (and doses) included. I would have preferred two statements that address (1) aromatase inhibition and ovarian suppression and (2) SERM and ovarian suppression for clarity. I do believe that it would be clearer to suggest reasonable choice for one group and recommended for the other.

Reviewer #4: Survival advantage is not for younger age, node (-) disease, low grade tumor and no adjuvant chemotherapy.

Reviewer #4: The subgroup of older age, node (+) disease, high grade tumor and adjuvant chemotherapy benefits. There is an increased risk for musculoskeletal and osteoporosis in the ovarian suppressed groups.

Reviewer #5: [Specific patient population] Early stage.

Reviewer #5: Especially titrated against risk of recurrence. For certain individuals at very low risk, the benefit is less convincing.

Comments on Draft Narrative Summary:

Reviewer #1: Summary appears complete and well written, no changes recommended.

Reviewer #2: The summary includes appropriate trials with complete evaluation.

Reviewer #3: I think it would be helpful to address AI + OS separately from SERM +OS. I would not use the term "ASCO states" in document. Recommend referring to specific ASCO documents and refer to the recommendation from the documents. Suggest addressing the toxicities from different combinations as outlined in papers and table, as this is a clinically important aspect of decision making.

Reviewer #4: The summary is well-balanced and complete.

Comments on Proposed Consensus Recommendation:
None.

Participants:

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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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