American Society of Clinical Oncology Clinical Practice Guideline: Update on Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer

IDENTITY
Citation

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DEVELOPER
Developer Name
· American Society of Clinical Oncology

Conflict Of Interest Policy
Conflict Of Interest Disclosure

PURPOSE
Objective

INTENDED AUDIENCE
Intended Users
Care Setting

METHOD OF DEVELOPMENT
Rating Scheme
Evidence Quality Rating Scheme
Recommendation Strength Rating Scheme
Qualifying Statement
Patient And Public Involvement
## TARGET POPULATION

**Inclusion Criterion**
- postmenopausal women with hormone receptor–positive breast cancer

**Exclusion Criterion**

## KNOWLEDGE COMPONENTS

### DEFINITIONS

**RECOMMENDATION:** 1

<table>
<thead>
<tr>
<th>Conditional:</th>
<th>The Update Committee recommends, on the basis of data from randomized, controlled trials, that most postmenopausal women consider taking an AI during the course of adjuvant treatment to lower recurrence risk, either as primary therapy or after 2 to 3 years of tamoxifen—strategies that yield equivalent outcomes in prospective studies. Duration of AI therapy should not exceed 5 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision Variable:</td>
<td>postmenopausal</td>
</tr>
<tr>
<td>Value:</td>
<td>true</td>
</tr>
<tr>
<td>Decision Variable:</td>
<td>adjuvant treatment</td>
</tr>
<tr>
<td>Value:</td>
<td>true</td>
</tr>
<tr>
<td>Decision Variable:</td>
<td>tamoxifen use</td>
</tr>
<tr>
<td>Value:</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Action:</td>
<td>Consider taking an AI</td>
</tr>
<tr>
<td>Description:</td>
<td>Duration of AI therapy should not exceed 5 years</td>
</tr>
<tr>
<td>Reason:</td>
<td>In comparison to 5 years of tamoxifen alone, use of an AI in either primary, sequential, or extended treatment improves disease-free survival and reduces the risk of breast cancer events, including distant recurrence, locoregional recurrence, and contralateral breast cancer</td>
</tr>
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<td>Reason:</td>
<td>Breast cancer events such as locoregional recurrence, contralateral breast cancer, and early distant metastatic recurrence are clinically important to patients. For this reason, the Update Committee recommended consideration of AI therapy at some time during adjuvant endocrine therapy even though few trials demonstrated statistically significant differences in overall survival.</td>
</tr>
<tr>
<td>Logic:</td>
<td>If postmenopausal is [true] AND adjuvant treatment is [true]</td>
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**Decision Variable:** postmenopausal  
**Value:** true  
**Decision Variable:** adjuvant treatment  
**Value:** true  
**Decision Variable:** tamoxifen use  
**Value:** false  
**Action:** consider taking an AI  
**Description:** Duration of AI therapy should not exceed 5 years.  
**Reason:** In comparison to 5 years of tamoxifen alone, use of an AI in either primary, sequential, or extended treatment improves disease-free survival and reduces the risk of breast cancer events, including distant recurrence, locoregional recurrence, and contralateral breast cancer  
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**Logic:**  
If  
postmenopausal is [true]  
AND  
adjuvant treatment is [true]  
AND  
tamoxifen use is [false]  
Then  
consider taking an AI  

**Notes:** SCENARIO 4  

**RECOMMENDATION:** 2
**Conditional:** The Update Committee recommends that patients who are initially treated with an AI but discontinue treatment before 5 years of therapy consider taking tamoxifen for a total of 5 years of adjuvant endocrine therapy. {Rec_4:Cond_7}

**Decision Variable:** AI  
**Value:** true  
**Decision Variable:** tamoxifen  
**Value:** false  
**Action:** consider tamoxifen for a duration of (5 years minus AI duration) years  
**Reason:** The treatment regimen for patients in the sequencing trials spanned 5 years. No data support clinical benefits for durations of AIs longer than 2 or 3 years in a sequencing strategy.  
**Reason:** Data from randomized, controlled trials demonstrate that women who receive primary AI therapy should be treated for a total of 5 years.  
**Logic:**

```
If
   AI is [true]
   AND
      tamoxifen is [false]
Then
   consider tamoxifen for a duration of (5 years minus AI duration) years
```

**Conditional:** Therapy with an AI should not extend beyond 5 years in either the primary or extended adjuvant settings outside the clinical trials setting. {Rec_4:Cond_9}

**Decision Variable:** in the primary setting  
**Value:** true  
**Decision Variable:** in the extended adjuvant setting  
**Value:** true  
**Decision Variable:** in a AI clinical trial  
**Value:** false  
**Decision Variable:** AI use  
**Decision Variable:** tamoxifen use  
**Value:** 2-3 years  
**Action:** discontinue AI after 5 years total endocrine therapy  
**Reason:** Safety and efficacy data from the primary trials support up to 5 years of AI therapy as a primary adjuvant strategy, a duration used in two trials of extended therapy after 5 years of tamoxifen.  
**Logic:**
If
(in the primary setting is [true]
OR
in the extended adjuvant setting is [true] )
AND
in the clinical trials setting is [false]
AND
(AI use
OR
tamoxifen use is [2-3 years] )
Then
discontinue AI after 5 years total endocrine therapy

Notes: SCENARIO 4

RECOMMENDATION: 3

**Conditional:** The Update Committee recommends that women who are pre- or perimenopausal at the time of breast cancer diagnosis be treated with 5 years of tamoxifen. {Rec_1:Cond_1 }

- **Decision Variable:** not menopausal
  - **Description:** at the time of diagnosis
- **Decision Variable:** treatment-induced amenorrhea
- **Action:** treat with 5 years of tamoxifen as primary adjuvant endocrine therapy
  - **Description:** The Update Committee recommends that clinicians use caution in evaluating menopausal status of patients who were pre- or perimenopausal at diagnosis. Unequivocal determination of menopausal status may be challenging to prove. Even among women who have not experienced menses for more than 1 year, laboratory testing is inadequate because patients may recover ovarian function. This particularly applies to those patients who experience chemotherapy- or tamoxifen-induced amenorrhea.
  - **Reason:** AI therapy has been shown to be effective only in postmenopausal women and is contraindicated in patients with residual ovarian function. Patients accrued to ABCSG-12, the only trial to include premenopausal women, were all treated with gonadotropin-releasing hormone agonist therapy to achieve a postmenopausal state. Eligible patients had favorable prognosis and low-grade breast cancer, and none received adjuvant chemotherapy, though 5% did receive neoadjuvant chemotherapy. These patients are not necessarily representative of younger women with early-stage breast cancer. ABCSG-12 demonstrated equivalence with respect to time to recurrence, disease-free survival, and overall survival.
between tamoxifen and AI therapy in premenopausal women given ovarian suppression. Because of tamoxifen equivalence with AI therapy in that setting and the occasional failure to achieve menopausal status with ovarian suppression, the Update Committee strongly recommends tamoxifen as primary adjuvant endocrine therapy for all pre- or perimenopausal women and women with treatment-induced amenorrhea.

**Logic:**

If

- not menopausal
- OR
treatment-induced amenorrhea

Then

treat with 5 years of tamoxifen as primary adjuvant endocrine therapy

**Notes:** SCENARIO 3

**RECOMMENDATION: 4**

**Conditional:** The Update Committee suggests that clinicians consider recommending that patients change treatment if adverse effects are intolerable or if patients are persistently noncompliant with therapy. {Rec_6:Cond_12}

**Decision Variable:** adverse effects are intolerable  
**Decision Variable:** persistently noncompliant with therapy

**Action:** clinicians may recommend that patients change treatment

**Logic:**

If

- adverse effects are intolerable
- OR
- persistently noncompliant with therapy

Then

clinicians may recommend that patients change treatment

**Conditional:** The Update Committee recommends that clinicians consider adverse effect profiles, patient preferences, and pre-existing conditions when recommending an adjuvant endocrine strategy for postmenopausal women. {Rec_6:Cond_16}

**Decision Variable:** recommending adjuvant endocrine therapy

**Action:** consider adverse effects

**Action:** consider patient preferences

**Action:** consider pre-existing conditions
Logic:

If recommending adjuvant endocrine therapy
Then consider adverse effects
AND consider patient preferences
AND consider pre-existing conditions

**Conditional:** Clinicians should discuss adverse effect profiles when presenting available treatment options. {Rec_6:Cond_17 }

**Decision Variable:** Recommending adjuvant endocrine therapy  
**Action:** counsel about adverse effect profiles of tamoxifen and AI

Logic:

If Recommending adjuvant endocrine therapy
Then counsel about adverse effect profiles of tamoxifen and AI

**Notes:** SCENARIO 4

**RECOMMENDATION:** 5

**Conditional:** In the clinical opinion of the Update Committee (rather than direct evidence from randomized trials), postmenopausal patients intolerant of one AI but who are still candidates for adjuvant endocrine therapy may be advised to consider tamoxifen or a different AI. {Rec_7:Cond_13 }

**Decision Variable:** postmenopausal  
**Decision Variable:** intolerant of one AI  
**Decision Variable:** still candidate for adjuvant endocrine therapy  

**Action:** may be advised to consider tamoxifen  
**Action:** may be advised to consider a different AI

**Reason:** In the absence of direct comparisons, the Update Committee interprets available data as suggesting that benefits of AI therapy represent a “class effect.” Meaningful clinical differences between the commercially available third-generation AIs have not been demonstrated to date.

**Reason:** Previous results were limited to reports for principal use of a single AI in each of the clinical settings of primary, sequential, or extended adjuvant therapy. There are still no data from head-to-head comparisons of AIs. However, there are
data from randomized trials for each of the commercially available third-generation AIs for all of the adjuvant treatment strategies (primary, sequential, and extended). The Update Committee interprets the existing data comparing the AIs with tamoxifen as qualitatively similar with respect to efficacy and tolerability. Toxicity reports have not suggested obvious clinical advantages of one AI over another with respect to compliance, constitutional or menopausal symptoms, bone health, cardiovascular disease, or quality of life. Anecdotal experience suggests that patients may tolerate one AI better than another, but patterns are neither predictable nor consistent. Two trials—MA.27 and Femara versus Anastrozole Clinical Evaluation (FACE)—are directly comparing one AI against another as primary adjuvant therapy. However, data are not yet available from either trial.

**Logic:**

If
- postmenopausal
- intolerant of one AI
- still candidate for adjuvant endocrine therapy

Then
- may be advised to consider tamoxifen
- may be advised to consider a different AI

**Notes:** SCENARIO 4

**ALGORITHM:**

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