Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer

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Literature review current through: **Oct 2023.**
This topic last updated: **Jul 28, 2023.**

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the leading cause of death from cancer in women worldwide. Breast cancer is a heterogeneous, phenotypically diverse disease composed of several biologic subtypes that have distinct behavior and response to therapy. Hormone receptor-positive (ie, estrogen [ER] and/or progesterone [PR] receptor-positive) breast cancers comprise the most common types of breast cancer, accounting for 75 percent of all cases.

This topic will review adjuvant endocrine therapy for non-metastatic, hormone receptor-positive breast cancer occurring in postmenopausal women. Other topics, including the adjuvant treatment of hormone receptor-positive breast cancer in premenopausal women and adjuvant treatment of hormone receptor-negative breast cancer, human epidermal growth factor receptor 2 (HER2)-positive breast cancer, male breast cancer, and triple-negative breast cancer, are covered separately. In addition, a discussion on the role of osteoclast inhibitors in the adjuvant treatment of breast cancer is covered separately.

- (See "Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer".)

- (See "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer".)
- (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer".)
- (See "Adjuvant systemic therapy for HER2-positive breast cancer".)
- (See "ER/PR negative, HER2-negative (triple-negative) breast cancer".)
- (See "Breast cancer in men".)
- (See "Overview of the approach to early breast cancer in older women".)
- (See "Use of osteoclast inhibitors in early breast cancer".)

DEFINITION OF MENOPAUSE

Because the endocrine options for treatment depend on whether or not a woman is in menopause, defining menopausal status is important. For women with breast cancer who were premenopausal at diagnosis, particularly those treated with adjuvant chemotherapy, amenorrhea is not a reliable indicator of menstrual status. We agree with the following definitions of menopause used by the National Comprehensive Cancer Network [1]:

- Women 60 years and older are postmenopausal.
- Women less than 60 years are postmenopausal if one of the following conditions is met:
  - They previously underwent a bilateral oophorectomy.
  - They have not had any menstrual periods for 12 months or more in the absence of tamoxifen, chemotherapy, or ovarian suppression, and the serum estradiol is in the postmenopausal range.
  - They are amenorrheic on tamoxifen, and follicle-stimulating hormone (FSH) and serum estradiol are in the postmenopausal range.

The approach to premenopausal women with chemotherapy-induced amenorrhea is discussed elsewhere. (See "Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer", section on 'Patients who became amenorrheic during chemotherapy'.)

INDICATIONS

For women with estrogen receptor- or progesterone receptor-positive breast cancer, we recommend adjuvant endocrine therapy. Pathologic criteria for assigning hormone receptor status are discussed in detail elsewhere. (See "Hormone receptors in breast cancer: Clinical utility and guideline recommendations to improve test accuracy", section on 'Interpretation of ER and PR tests'.)

Although the risk of recurrence and therefore the absolute likelihood of benefit is higher for those with larger or higher-risk tumors, we recommend this treatment for those with hormone receptor-positive breast cancers regardless of size. This approach is supported by the consistent improvements in rates of recurrence, second breast cancers, and survival that have been observed in clinical trials enrolling patients with hormone receptor-positive tumors of any size.

Importantly, nearly all postmenopausal women who are candidates for endocrine therapy should be offered treatment, regardless of age. While the odds of having associated medical comorbidities increase with age, and these may predispose older women to increased toxicities related to treatment, the benefits of adjuvant endocrine therapy on reducing the risks of recurrence and death from breast cancer have been consistently demonstrated. Therefore, patients at risk for treatment-related toxicities due to adjuvant endocrine therapy should be managed appropriately, with care coordinated between their oncology team and primary care clinician. However, careful discussion with those patients is warranted if they have multiple comorbidities that may increase their risk of major toxicities, such as pre-existing history of thrombosis or cerebrovascular disease or osteoporosis and fractures refractory to skeletal modifying agents, and especially if their prognosis is particularly good. (See "Overview of cancer survivorship care for primary care and oncology providers", section on 'Coordination of care'.)

APPROACH TO TREATMENT

The approach to treatment of postmenopausal women with breast cancer is discussed in the sections below.

The approach to women with breast cancer who are pre- or perimenopausal at diagnosis is discussed in detail elsewhere. (See "Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer".)

AIs as preferred therapy — For most women with postmenopausal breast cancer, we administer an aromatase inhibitor (AI) rather than tamoxifen. As a class, the AIs have consistently been shown to improve outcomes for postmenopausal women with hormone

receptor-positive breast cancer compared with tamoxifen, both during and after treatment. (See 'Versus tamoxifen' below.)

Therefore, an AI is the preferred adjuvant treatment of postmenopausal women, although tamoxifen is an acceptable alternative for women who are intolerant of AIs. (See 'Tamoxifen as alternative option' below.)

Drugs in this class, with usual dosing, include:

- Anastrozole (1 mg daily)
- Letrozole (2.5 mg daily)
- Exemestane (25 mg daily)

AIs suppress plasma estrogen levels by inhibiting or inactivating aromatase, the enzyme responsible for the peripheral conversion of androgens to estrogens (table 1) [2]. AIs are inactive in women with intact ovarian function, including those who experienced therapy-induced amenorrhea, and hence ovarian suppression/ablation must be used in premenopausal women receiving AIs. This issue is discussed elsewhere. (See "Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer", section on 'Patients who became amenorrheic during chemotherapy'.)

Efficacy

Versus tamoxifen — Support for the use of AIs in these settings comes from numerous randomized trials and meta-analyses. A 2015 intention-to-treat meta-analysis that utilized individual patient data from almost 32,000 postmenopausal women with estrogen receptor (ER)-positive breast cancer participating in clinical trials comparing AIs with tamoxifen evaluated breast cancer outcomes in the following cohorts [3]:

- **AI versus tamoxifen** – In trials where women (n = 9885) were randomly assigned to treatment with a five-year course of an AI or tamoxifen, treatment with an AI resulted in:
  - Reduced breast cancer recurrence, particularly during years 0 to 1 (relative risk [RR] 0.64, 95% CI 0.52-0.78) and years 2 to 4 (RR 0.80, 95% CI 0.68-0.93). There was no further impact on recurrence rates after the 5-year treatment period.
  - Lower 10-year breast cancer mortality (RR 0.85, 95% CI 0.75-0.96).
- **Tamoxifen alone versus a short course of tamoxifen followed by an AI** – In trials where women (n = 11,798) were randomly assigned to a continuous five-year course of tamoxifen

versus two or three years of tamoxifen followed by an AI for five years of total endocrine therapy, switch to an AI resulted in:

- Reduced breast cancer recurrence during years 2 to 4 (RR 0.56, 95% CI 0.46-0.67), with no further effect on recurrence beyond the treatment period.
- Fewer deaths from breast cancer (RR 0.84, 95% CI 0.72-0.96).

- **AI alone versus a short course of tamoxifen followed by an AI** – In trials where women (n = 12,799) were randomly assigned to five years of an AI versus two or three years of tamoxifen followed by an AI for five years of total endocrine therapy, treatment with an AI alone resulted in:
  - Lower recurrence rates during years 0 to 1, before the switch had occurred (RR 0.74, 95% CI 0.62-0.89).
  - Similar recurrence rates during years 2 to 4, when both groups were treated with an AI (RR 0.99, 95% CI 0.85-1.15), and beyond year 5.
  - A trend toward reduced breast cancer mortality, which did not reach statistical significance (RR 0.89, 95% CI 0.78-1.03).

  While not included in the meta-analysis, the approach of utilizing a short course of AI therapy followed by tamoxifen has also been studied and is an acceptable option:

- **AI alone versus short course of AI followed by tamoxifen** – The BIG 1-98 trial randomized over 8000 women to five years of tamoxifen or letrozole monotherapy, or sequential treatment with two years of one of these drugs followed by three years of the other [4]. While breast cancer outcomes were better for letrozole compared with tamoxifen monotherapy, there was no significant difference in either disease-free or overall survival (OS) between the sequential therapies and letrozole monotherapy. Moreover, efficacy of monotherapy with letrozole versus tamoxifen for contralateral breast cancer varied over time (0 to 5-, 5 to 10-, and >10-year hazard ratios [HRs] 0.62, 0.47, and 1.35, respectively) [5].

These data are consistent with the observation that the highest risk for recurrence is within the first few years after initial diagnosis, and that the more effective treatment strategy, aromatase inhibition, is preferable to tamoxifen during that time. However, once patients have remained disease free for a few years, switching to tamoxifen is similarly effective to continuation of AI treatment, and there may be a longer carry-over effect with tamoxifen than an AI in terms of protection against contralateral breast cancer.

Comparison between AIs — Evidence suggests similar clinical outcomes and tolerability between the aromatase inhibitors (AIs). As such, anastrozole, exemestane, and letrozole are all appropriate options for those warranting adjuvant treatment with an AI. Individual patients may tolerate one of these agents better than another, and it is reasonable to switch to an alternative AI if the initial AI is poorly tolerated and other strategies of managing side effects have been ineffective [6]. (See 'Side effects' below.)

In the FATA-GIM3 trial, over 1800 women were randomly assigned to oral anastrozole (1 mg per day), exemestane (25 mg per day), or letrozole (2.5 mg per day) for five years [7]. Five-year disease-free survival (DFS) was 90 percent with anastrozole (95% CI 87.9-91.7), 88 percent with exemestane (95% CI 85.8-89.9), and 89 percent with letrozole (95% CI 87.3-91.1). Gastrointestinal side effects were more common with exemestane than with letrozole, and hypercholesterolemia was more frequent with anastrozole and letrozole than with exemestane. All other side effects were similar between the agents. Treatment was interrupted due to toxicity in approximately 7 percent of patients on each of these treatment arms.

Trials have also been conducted to assess the following specific comparisons, again showing similar outcomes between agents:

- **Exemestane versus anastrozole** – In the NCIC-CTG MA.27 study, over 7500 women were randomly assigned to exemestane or anastrozole [8]. With a median follow-up of four years, there was no difference in the event-free survival or OS rate. Of note, 32 and 29 percent discontinued exemestane and anastrozole, respectively, during the study as a result of adverse events (AEs), concomitant illness, or study refusal. The implications of poor compliance on survival outcomes for women on endocrine therapy are an area of active investigation. (See 'Factors that limit efficacy' below.)

- **Letrozole versus anastrozole** – In the FACE trial, letrozole and anastrozole were found to have similar five-year DFS rates (85 versus 83 percent; HR 0.93, 95% CI 0.80-1.07) and comparable side effect profiles [9].

Side effects — While AIs are generally well tolerated, side effects may limit adherence in a number of women [10]. AIs may also reactivate ovarian function in premenopausal women, particularly in women with chemotherapy-induced amenorrhea. This issue is discussed elsewhere. (See "Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer", section on 'Risk of ovarian function reactivation on an AI'.)

In the short term, the side effects associated with AIs are not detrimental to quality of life [11,12]. However, up to one-third of women may not complete an assigned five-year course of treatment, according to one trial of adjuvant AIs [12], and the long-term effects of AIs (eg, bone

loss) have not been fully characterized at this time. While data are available regarding the long-term risks of tamoxifen, and in particular that the risk persists for the duration of treatment but not afterwards [13], such data are limited for aromatase inhibition. Long-term risks of premature menopause, including osteoporosis and cardiovascular risk, which have been observed in noncancer patients, may apply to these patients as well. (See "Evaluation and management of aromatase inhibitor-induced bone loss" and "Managing the side effects of tamoxifen and aromatase inhibitors" and "Overview of long-term complications of therapy in breast cancer survivors and patterns of relapse", section on 'Long-term adverse effects of primary therapy' and "Elective oophorectomy or ovarian conservation at the time of hysterectomy", section on 'Long-term health risks'.)

Musculoskeletal pains and stiffness — AIs are associated with musculoskeletal side effects including carpal tunnel syndrome as well as a constellation of symptoms including arthralgia, joint stiffness, and/or bone pain, which have been described as the AI-associated musculoskeletal syndrome (AIMSS) [14-18]. These symptoms may be severe in almost one-third of patients [16], and may be responsible for treatment discontinuation in 10 to 20 percent of patients [15-18]. Recognizing that there are few studies to inform the approach for patients with AIMSS, we suggest the following strategies, typically sequentially, although depending on patient preferences and severity of symptoms, this might not always be the case:

- **Exercise and NSAIDs** – The initial strategy for managing AIMSS includes exercise and nonsteroidal anti-inflammatory drugs (NSAIDs). In the HOPE trial, 121 postmenopausal women with AI-associated arthralgias were randomly assigned to an exercise regimen or to usual care [19]. The exercise regimen consisted of twice-weekly supervised resistance and strength training plus moderate aerobic exercise for 150 minutes per week. Patients undergoing the exercise regimen had reduction in their worst pain score (20 versus 1 percent average score reduction, respectively) and pain severity (21 versus 0 percent reduction) compared with usual care. They also experienced more weight loss and improvement in their exercise capacity. In addition, a dose-response relationship between exercise and symptom severity was identified. Compared with women who attended fewer than 80 percent of the exercise sessions, those who attended 80 percent or more experienced a greater reduction in their worst pain score (25 versus 14 percent, respectively).

  Beyond exercise, the primary treatment for AIMSS often begins with the administration of NSAIDS because these agents are a mainstay of treatment for pain. (See "Pharmacologic management of chronic non-cancer pain in adults", section on 'Nonsteroidal antiinflammatory drugs'.)

- **Temporary discontinuation of AI, followed by initiation of a different AI** – For women in whom conservative measures including exercise and NSAIDs have been unsuccessful, we discontinue treatment for two to eight weeks and then begin a different AI. In one prospective study, almost 40 percent of patients were able to continue on the alternate AI [6].

- **Duloxetine** – Duloxetine is an appropriate option if symptoms persist, despite the above measures. In the SWOG S1202 trial, among 299 patients with stage I to III disease on AIs, those randomized to duloxetine (30 mg daily for 1 week, then 60 mg daily for 11 weeks, then 30 mg daily for 1 week) experienced improvement in joint pain through the 12 weeks of treatment relative to placebo, though results between the groups were similar at 24 weeks [20]. Duloxetine was relatively well tolerated; the most common AEs were grade 1 or 2 fatigue (32 percent), xerostomia (24 percent), nausea (30 percent), and headache (21 percent). Grade 3 or 4 toxicities affected 8.7 percent of patients, with the most common ones being insomnia (2.9 percent) and extremity pain (1.4 percent).

- **Acupuncture** – Acupuncture offers a nonpharmacologic method of treating AIMSS. Although benefits observed have not been large, we consider it to be an appropriate next-line option if the steps described above were attempted and unsuccessful, or for the patient who prefers to avoid duloxetine. In a randomized trial of 226 patients with joint pain on AIs randomly assigned to acupuncture, sham acupuncture, or waitlist control, those receiving acupuncture experienced close to a 1-point benefit in joint symptoms, on a scale of 1 to 10, over those receiving sham acupuncture or remaining on the waitlist [21]. Although the clinical significance of this small numerical improvement is unclear, some patients may desire a trial of this complementary form of therapy, particularly given its avoidance of systemic side effects.

- **Switch to tamoxifen, for those who are unable or unwilling to continue treatment with an AI.** (See 'Tamoxifen as alternative option' below.)

Understanding the etiology of AIMSS is complicated because rheumatologic symptoms are present in a significant number of women who go on to complain of AI-associated musculoskeletal (MSK) complaints. In one study, up to one-half of women who developed AIMSS had a pre-existing MSK disorder (eg, degenerative joint disease or morning stiffness) [18]. Risk factors for AIMSS have not been fully characterized, but decreased estrogen levels may play a role [17,18,22,23].

Sexual dysfunction — Because AIs block peripheral estrogen production, women are at an increased risk for vaginal symptoms and sexual dysfunction [24]. Women should be

counseled about these potential adverse effects as part of their education before starting treatment and on methods that may help alleviate them. The approach to breast cancer survivors who complain of sexual dysfunction is covered separately. (See "Genitourinary syndrome of menopause (vulvovaginal atrophy): Treatment", section on 'Patients with breast cancer' and "Genitourinary syndrome of menopause (vulvovaginal atrophy): Treatment", section on 'Initial therapy with moisturizers and lubricants' and "Overview of long-term complications of therapy in breast cancer survivors and patterns of relapse", section on 'Menopausal symptoms'.)

Management of hot flashes among women with a history of breast cancer is discussed elsewhere. (See "Menopausal hot flashes", section on 'Women with breast cancer'.)

Loss of bone density — Treatment with AIs results in bone loss due to estrogen deficiency. This is discussed in detail elsewhere. (See "Evaluation and management of aromatase inhibitor-induced bone loss".)

Other side effects — In one study, women on AIs reported higher rates of cognitive problems compared with women with breast cancer who did not take endocrine therapy; also, physical health scores one year after initiation of treatment were worse [25]. In another study, predictors of drug discontinuation at one year included fatigue, forgetfulness, and poor sleep hygiene [10]. AIs as well as tamoxifen have also been rarely associated with hair thinning, which is improved with topical minoxidil in the majority of cases [26].

Compared with tamoxifen, the AIs are associated with a higher risk of osteoporosis, fractures, cardiovascular disease, diabetes, and hypercholesterolemia [3,27-30]. By contrast, they are associated with a lower risk of venous thrombosis, and endometrial cancer [3], and a lower risk of fatty liver disease [31].

Tamoxifen as alternative option — Tamoxifen is a selective estrogen receptor modulator (SERM) that inhibits the growth of breast cancer cells by competitive antagonism of the ER. It is the endocrine agent of choice for the adjuvant treatment of premenopausal women with low- to average-risk cancers and for postmenopausal women who are not candidates for an AI for whatever reason. Discussion of the use of tamoxifen in premenopausal women, as well as mechanisms of resistance to tamoxifen, is found separately. (See "Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer", section on 'Low- to average-risk, hormone receptor-positive, HER2-negative cancers' and "Mechanisms of action of selective estrogen receptor modulators and down-regulators".)

While AIs are associated with consistent but modestly improved outcomes compared with tamoxifen, both agents reduce recurrences and new primary breast cancers, and some women

may tolerate the risks and toxicities of tamoxifen better than an AI. For women who wish to discontinue an AI, it would be reasonable to switch to tamoxifen.

Tamoxifen is administered as a 20-mg pill taken on a daily basis.

Efficacy of tamoxifen versus placebo — The data to support the use of adjuvant tamoxifen come from the 2011 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, which compared tamoxifen treatment for five years with no endocrine treatment and included both premenopausal and postmenopausal women [32]. With a median follow-up of 13 years, tamoxifen resulted in:

- A significant reduction in the risk of breast cancer recurrence at 15 years (relative risk [RR] 0.61, 95% CI 0.57-0.65).
- A significant reduction in the risk of breast cancer mortality at 15 years (RR 0.70, 95% CI 0.64-0.75).

Factors that limit efficacy

- **Compliance** – For women on endocrine therapy, less than optimal compliance (or nonadherence) to treatment may impact outcomes following the diagnosis of breast cancer. Although the limited data suggest that nonadherence increases the risk of death, it is not entirely clear if this is due to breast cancer-specific causes.

  As an example, in a cohort study involving over 3300 women, of whom 85 and 15 percent were prescribed adjuvant tamoxifen or an AI, respectively, low adherence (<80 percent) increased the risk of all-cause mortality (HR 1.20, 95% CI 1.03-1.40) [33]. However, there was no association between adherence levels and the risk of recurrence or breast cancer-specific mortality. In a separate study of 1177 premenopausal women on adjuvant tamoxifen, serum assessment of tamoxifen identified 16 percent of patients below the set adherence threshold (tamoxifen serum level <60 ng/mL, assessed one year after prescription) [34]. After a median follow-up of two years since tamoxifen serum assessment, patients who were biochemically nonadherent had shorter distant DFS (adjusted HR 2.3, 95% CI 1.1-5.1). Given the limited data, we continue to stress the importance of adhering to endocrine therapy as prescribed in order to maximize the impact of adjuvant treatment.

- **Resistance** – A number of molecular factors may contribute to tamoxifen resistance in breast cancer, which are discussed elsewhere. (See "Mechanisms of action of selective

estrogen receptor modulators and down-regulators", section on 'Tamoxifen resistance in breast cancer'.)

- **Drug interactions** – Tamoxifen is converted to its active metabolites by cytochrome P450 2D6 (CYP2D6) and UDP-glucuronyltransferase-2B7 (UGT2B7). Drugs that inhibit CYP2D6, for example, certain selective serotonin reuptake inhibitors, may potentially alter the metabolism of tamoxifen. The clinical implications of this interaction remain uncertain. Details about specific interactions may be obtained by using the Lexicomp drug interactions tool included within UpToDate. This issue is discussed in detail elsewhere. (See "Mechanisms of action of selective estrogen receptor modulators and down-regulators", section on 'Patients taking SSRIs'.)

Side effects — In the meta-analysis discussed above, the major AEs associated with tamoxifen included an approximately two- to threefold increased relative risk of thromboembolic disease compared with placebo (ie, deep vein thrombosis and pulmonary emboli) as well as a nonstatistically significant increased risk of strokes [32]. In addition, tamoxifen increased the risk of uterine cancer, although the overall incidence of uterine cancer was low compared with placebo (4 versus 1 percent, respectively) and appeared to be limited to women over 55 years. Other side effects associated with the use of tamoxifen include fatty liver disease [31], hot flashes, vaginal discharge, sexual dysfunction, menstrual irregularities, and increased risk of diabetes [27]. Further discussion of the side effects and strategies for managing them is covered separately. (See "Managing the side effects of tamoxifen and aromatase inhibitors" and "Menopausal hot flashes", section on 'Women with breast cancer'.)

Incorporation of targeted therapies for select patients

CDK 4/6 inhibitors for select patients with high risk disease — For patients with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive breast cancer at high risk of recurrence, we suggest the addition of abemaciclib to adjuvant endocrine therapy. However, recognizing that the follow-up remains short, the effect on OS is yet unknown, and there are clear side effects of treatment (notably, diarrhea), it is also acceptable to omit this therapy.

Of note, there are no data on outcomes with cyclin-dependent kinase (CDK) 4/6 inhibitors in women with breast cancer susceptibility gene 1/2 (*BRCA1/2*) mutations, and for BRCA carriers with high-risk disease, adjuvant olaparib is the preferred approach in addition to endocrine therapy. (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer", section on 'BRCA carriers with high-risk disease'.)

- **Patient selection** – Abemaciclib is approved by the US Food and Drug Administration (FDA) as adjuvant therapy in patients with high-risk, node-positive, ER-positive, HER2-negative breast cancer [35]. We agree with guidelines from the National Comprehensive Cancer Network (NCCN) that define high-risk as either [36]:

  - ≥4 positive lymph nodes; or
  - 1 to 3 positive lymph nodes with one or more of the following: Grade 3 disease, tumor size ≥5 cm, **or** a Ki-67 score of ≥20 percent, based on the monarchE trial discussed below [37].

  Neither the NCCN definition nor the FDA require all patients to have a Ki-67 ≥20 percent, if other high-risk features are present [36]. We agree with this approach given substantial inter-observer/laboratory variability in Ki-67 values in the range of >5 to <30 percent [38]. It has also been noted that while those with Ki-67 ≥20 percent experience a greater absolute benefit with abemaciclib, the benefits in those with Ki-67<20 percent are still clinically meaningful [39].

  We acknowledge, however, that with fewer than five percent of overall survival outcomes having been collected, the effect on survival remains unclear [40].

- **Duration** – For patients taking adjuvant abemaciclib therapy, the duration is for two years, typically concurrently with the start of endocrine treatment.

- **Supporting data** – In the monarchE trial, over 5600 patients (just over one-half of whom were postmenopausal women) with hormone receptor-positive, HER2-negative, high-risk early breast cancer who had completed surgery were randomly assigned to abemaciclib plus endocrine therapy or endocrine therapy alone [37]. Patients may have received up to 12 weeks of endocrine therapy and must have been randomly assigned within 16 months of definitive breast cancer surgery. High risk was defined as having ≥4 positive nodes; or one to three positive nodes and at least one of the following: tumor size ≥5 cm, histologic grade 3, or central Ki-67 ≥20 percent. Patients in the abemaciclib/endocrine therapy group had improvement in invasive disease-free survival (IDFS) relative to the endocrine therapy alone group (three-year IDFS rates of 89 versus 83 percent, respectively; HR 0.70, 95% CI 0.59-0.82). Distant recurrence-free survival rates at three years were 90 versus 86 percent (HR 0.69, 95% CI 0.57-0.83), respectively [41]. Benefit was sustained at four years [42]. While improvements with the addition of abemaciclib did not reach statistical significance among postmenopausal women, they were statistically significant in the premenopausal subset. (See "Adjuvant endocrine therapy for premenopausal women with hormone

receptor-positive breast cancer", section on 'Addition of CDK 4/6 inhibitor to adjuvant endocrine therapy in high-risk disease'.)

The absolute IDFS benefit in the Ki-67 ≥20 percent group was 7.1 percent, versus 4.5 percent in the Ki-67 <20 percent group. The FDA approval is only in tumors that are Ki-67 ≥20 percent [41].

The most frequent AEs were diarrhea, neutropenia, and fatigue in the abemaciclib arm and arthralgia, hot flush, and fatigue in the control arm. A higher incidence of grade ≥3 AEs was observed with versus without abemaciclib (50 versus 16 percent, respectively).

Results from the NATALEE trial, presented in abstract form, suggest benefit of adjuvant ribociclib in patients with stage IIA to III disease. In this trial, over 5101 patients with stage IIA (with high-risk features) to III disease meeting eligibility criteria (table 2) were randomly assigned to a nonsteroidal AI (plus goserelin in men and premenopausal women), with or without ribociclib 400 mg daily for three weeks on/one week off for three years [43]. At a median follow-up of 34 months, the ribociclib group experienced improvement in IDFS (three-year rate of 90 versus 87 percent; HR 0.75, 95% CI 0.62-0.91). Distant DFS rates at three years were also improved (91 versus 89 percent; HR 0.74, 95% CI 0.61-0.91). Overall survival results are immature. Grade ≥3 toxicities were higher with ribociclib (eg, neutropenia, 44 versus 0.8 percent; liver related adverse events, 8.3 versus 1.5 percent). However, we await long term data and/or regulatory approval prior to using ribociclib in the adjuvant setting.

By contrast, in PALLAS, the addition of two years of palbociclib to adjuvant endocrine therapy in patients with stage II or III hormone receptor-positive/HER2-negative breast cancer failed to improve IDFS, and the trial was closed early for futility [44,45]. Possible reasons for the difference in outcomes between PALLAS and other trials of CDK 4/6 inhibitors include different agents used, different patient eligibility criteria, as well as a high number of patients in PALLAS who did not complete assigned treatment. In the PENELOPE-B trial, the addition of one year of palbociclib to adjuvant endocrine therapy did not improve IDFS among those with hormone receptor-positive/HER2-negative breast cancer with residual disease after neoadjuvant chemotherapy [46].

Olaparib for select high risk, BRCA-mutated cancers — Olaparib has regulatory approval by the FDA for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated, HER2-negative, high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy [47]. This approach and the supporting data are discussed in detail elsewhere. (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer", section on 'BRCA carriers with high-risk disease'.)

DURATION OF ENDOCRINE TREATMENT

Women treated with adjuvant endocrine therapy are treated for a minimum duration of five years, with extended therapy offered to some with higher-risk features.

Rationale for extended treatment in some patients — Observational data suggest that the risk of distant recurrence after five years of adjuvant endocrine treatment continues steadily for at least the subsequent 20 years [48,49], which provides rationale to consider extended endocrine treatment in some patients. (See 'Selection of patients for extended therapy' below.)

In a meta-analysis of 88 trials that included 62,923 women with estrogen receptor (ER)-positive breast cancer who were disease free after 5 years of scheduled endocrine therapy, the risk of recurrence correlated strongly with the original lymph node status, tumor size, and grade [49]. Those with many positive nodes were at an annual risk of distant recurrence of nearly 3 percent per year; for those with one to three positive nodes, the annual risk was approximately 2 percent; for those with negative nodes but T2 or greater lesions, the risk was approximately 1 percent per year; and women with node-negative and smaller tumors experienced an annual risk of approximately 0.5 to 1.0 percent.

In a population-based study using the Danish Breast Cancer Group database, very similar findings were observed among approximately 20,000 patients who were survivors 10 years after diagnosis. In this study, the cumulative incidence of late recurrence was 8.5 percent 15 years after primary diagnosis, 12.5 percent 20 years afterwards, 15.2 percent 25 years afterwards, and 16.6 percent 32 years afterwards [48], and the risk/year remained relatively constant. However, the overall risk in the Danish study was slightly lower than that reported by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), perhaps because the EBCTCG study included only patients who went on clinical trials, whereas the Danish study included all patients diagnosed with breast cancer in that country. Furthermore, the Danish study began analysis in women who had reached 10 years without recurrence, whereas the EBCTCG study began its analysis at five years. Finally, the Danish investigators accounted for competing causes of death, which was not done in the EBCTCG. Regardless, as in the EBCTCG, high lymph node burden, large tumor size, and ER positivity were the most important factors associated with risk of late recurrence, and are consistent with the concern that patients with ER-positive breast cancer remain at risk for late distant recurrence as long as they are alive.

Selection of patients for extended therapy — Although women with hormone receptor-positive breast cancer are treated for a minimum of five years with adjuvant endocrine therapy, some data suggest that longer durations of endocrine therapy improve disease-free survival

(DFS), if not overall survival (OS). Extended adjuvant endocrine therapy beyond five years is an option for all patients with a prior history of invasive, ER-positive breast cancer, but some patients may be more likely to derive benefit than others. For women with larger tumors or node-positive disease, we suggest extended endocrine treatment. For women with smaller, node-negative tumors, the benefits are less clear and, for some, may not outweigh the risk of toxicities. A patient-by-patient decision must be made that includes risk of both ongoing symptomatic side effects and life-taking, -threatening, or -changing toxicities, such as thrombosis and endometrial cancer (both with tamoxifen), or fracture (with aromatase inhibitors [AIs]).

Retrospective evaluations of several adjuvant endocrine trials incorporating multiparameter gene and protein expression assays have suggested that such assays may identify patients who have such a favorable prognosis that extended endocrine therapy may be unlikely to provide sufficient benefit [50-52] to outweigh the side effects and possible long-term risks. Indeed, there is at least one peer-reviewed published study suggesting that each of the available assays (OncotypeDX, Endopredict, ProSigna, and the Breast Cancer Index [BCI]) identify a group of patients with such a favorable prognosis. However, each of these studies were conducted as a "prospective retrospective" investigation, using specimens from patients who participated in previously performed clinical trials, and are subject to the various biases and confounding issues built into such strategies [53]. Therefore, further study is necessary before routine clinical use of such tools in determining who should receive extended endocrine treatment.

As an example of one such study, the TransATAC trial evaluated the ability of several of these genomic signatures to identify patients at risk for late recurrence [50]. In this study, all assays were effective at identifying node-negative patients at low risk for late recurrence, although models integrating clinical information with genomic data (ie, PAM50 and Endopredict) were more effective at identifying node-positive disease at low risk for late recurrence than assays relying on genomics only (ie, Oncotype DX Recurrence Score or Breast Cancer Index). Further discussion on multiparameter assays is found elsewhere. (See "Prognostic and predictive factors in early, non-metastatic breast cancer", section on 'Receptor status' and "Deciding when to use adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer".)

Indeed, inclusion of more detailed clinicopathologic features, such as tumor size, grade, and age, a protein, immunohistochemical multiparameter assay designated IHC4 has been proposed. This "Clinical Treatment Score post-5 years (CTS5)" might be used to guide the use of extended therapy [54,55].

Perhaps the BCI (H/I), a modification of the original BCI assay, is the most intensively studied of these assays. Using specimens collected from patients who participated in six different trials,

investigators have reported that low compared with high BCI scores are associated with a lower risk of distant recurrence and no apparent improvement in DFS or OS for extended endocrine therapy, whereas those with high BCI (H/I) scores have a higher risk of recurrence and are also more likely to respond to extended endocrine therapy. Guidelines panels of both the National Cancer Center Network and the American Society of Clinical Oncology have given positive, although lukewarm, recommendations that the use of BCI may be used to inform decisions about extended endocrine therapy with tamoxifen, an AI, or the sequence of tamoxifen followed by an AI. We do not routinely use BCI to make decisions about extended endocrine therapy, especially in patients who originally had a high anatomic stage based on number of lymph nodes (>3) and size (>5 cm) of tumor and/or if they had high grade cancers. We do use it to on occasion to help women with relatively low anatomic stage at diagnosis who are uncertain whether they would prefer to continue or discontinue extended endocrine therapy.

Outcomes with extended endocrine treatment — Trials regarding extended endocrine treatment have been limited by patient crossover and inadequate power to detect small differences that may exist in certain subgroups.

The data regarding extended endocrine therapy are discussed below, according to the following subgroups:

- **Women treated with tamoxifen** – After five years of tamoxifen, either continuing tamoxifen or switching to an AI for an additional five years is effective in reducing the odds of distant recurrence as well as new primary breast cancers [13,56-60], with some evidence suggesting improved breast cancer-free survival and OS [13,57]. While AIs have never been compared with tamoxifen directly in the setting of extended endocrine therapy, cross-trial comparisons suggest that they may be slightly more effective. These differences are comparable to what has been observed in the early adjuvant setting as well.

    - **Extended tamoxifen after five years of tamoxifen** – In the ATLAS and aTTom trials, patients initially treated with tamoxifen for roughly five years were then randomly assigned to stop or continue tamoxifen for another five years. In ATLAS, which accrued nearly 7000 women, approximately 90 percent of whom were postmenopausal, the longer treatment was associated with reduction in the risk of recurrence (18 versus 20.8 percent, respectively; relative risk [RR] 0.84, 95% CI 0.76-0.94) and in breast cancer mortality (9.7 versus 11.5 percent, respectively) [13]. There were also decreases in the incidence of contralateral breast cancer. Preliminary results of the aTTom trial also demonstrated decreased recurrences and a reduction in breast cancer mortality (392 versus 443 deaths) with 10 versus 5 years of tamoxifen [60]. In these studies, the

increased risk of thrombosis and endometrial cancer persisted at the same rate throughout the period of time of tamoxifen administration, although consistent with previous reports, tamoxifen reduced the rate of ischemic heart disease [13,60].

- **Extended AI treatment after tamoxifen** – In MA.17, 5000 postmenopausal patients who had completed a five-year course of tamoxifen were randomly assigned to a five-year course of letrozole or placebo [56-58]. Letrozole was associated with an improvement in DFS compared with placebo (hazard ratio [HR] 0.52, 95% CI 0.45-0.61) and an improvement in OS (HR 0.61, 95% CI 0.52-0.71). Similarly, in National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33, exemestane as extended endocrine treatment after five years of tamoxifen resulted in improvement in recurrence-free survival [59].

  In a separate trial, postmenopausal women who remained recurrence free after a two- to three-year course of tamoxifen experienced modestly improved 12-year DFS outcomes with a subsequent five years of letrozole versus letrozole for two to three years (67 versus 62 percent; HR 0.78, 95% CI 0.65-0.93) [61].

- **Women treated with an AI** – Some, but not all, data suggest that for women completing five years of endocrine therapy that included an AI, an additional five years of AI improves recurrence-free survival; however, OS is not improved [62-65].

  For women who complete a five-year course of AI after any duration of prior tamoxifen, the MA.17R trial demonstrated that an additional five years of letrozole improved DFS but not OS [62]. Among approximately 1900 postmenopausal women who had completed 4.5 to 6 years of therapy with an AI (with a median duration of prior tamoxifen of five years), letrozole for an additional five years improved five-year DFS relative to those who received placebo (95 versus 91 percent). Nearly one-half of the events were new primary cancers. In this regard, the annual rate of contralateral breast cancer was reduced with letrozole (0.21 versus 0.49 percent; HR 0.42, 95% CI 0.22-0.81).

  A subsequent trial also confirmed DFS benefits with extending anastrozole treatment for an additional five years in postmenopausal patients who were disease free after either five years of anastrozole alone or two to three years of tamoxifen followed by two to three years of anastrozole (five year rate of DFS 91 versus 86 percent; HR 0.61, 95% CI 0.46-0.82) [66].

  Despite the improved DFS outcomes observed in these trials, results from NSABP-B42, the DATA trial, and the IDEAL trial have not confirmed this benefit [63,65,67]. The difference in results between these trials may be due to a difference in how they defined recurrence-

free survival; for example, MA.17R included only recurrences of the original breast cancer or a new breast cancer, and NSABP-B42 also included new nonbreast primary cancer and death from any cause. In both studies, the breast cancer-free interval was similarly defined and showed a small but statistically significant improvement with extended endocrine therapy. No trial has demonstrated an OS benefit to extended treatment among those who had already received a five-year course of an AI.

Extending AI therapy affects bone health. In MA.17R, bone-related toxic effects were more frequent among those receiving letrozole, including bone pain (18 versus 14 percent), fractures (14 versus 9 percent), and new-onset osteoporosis (11 versus 6 percent). Most patient-reported quality of life outcome measures were similar between the two groups [62]. A separate overview of trials comparing the published toxicities of extended versus shorter AI therapy demonstrated a higher rate of osteoporotic fractures and a trend toward increased cardiovascular events in the group that received longer AI therapy [68].

- **Durations of extended endocrine therapy** – For women with smaller, node-negative tumors (ie, stage I disease), it is not clear that there is a sufficiently high risk of late recurrence to justify the side effects and risks of extended endocrine therapy. If extended endocrine therapy is chosen in patients with low-risk cancers, an additional two years of treatment is appropriate (for a total of seven years of treatment). The benefits of a total of 10 versus 7 years of endocrine therapy are small, if any, in women with low-risk cancers, and the risks of adverse events persist. For patients with high-risk disease, a total duration between 7 and 10 years is appropriate, with preference for the higher end of this range, if treatment is well tolerated. Those who have been treated with tamoxifen only may have a higher likelihood of benefit.

  Trials have evaluated extended endocrine regimens administered for less than five additional consecutive years and suggested their equivalence with five additional years. As examples:

  - Among women who had received four to six years of adjuvant endocrine therapy, the SOLE trial compared an additional five years of continuous letrozole versus an intermittent schedule in which the AI was given for nine months followed by a three-month break each year [69,70]. There was no difference in DFS between the two schedules, with better tolerance of the intermittent schedule, supporting potential safety of temporary treatment breaks in patients who might require such interruption.

  - In ABCSG-16, women who had received five years of adjuvant endocrine therapy were randomly assigned to an additional two versus five years of anastrozole as extended

adjuvant treatment [71]. One- half of the patients had already been on AI during the first five years of treatment, and the study cohort was very low risk (two-thirds with stage I disease, and nearly all with stage I or II disease). Those in the two- year versus the five-year group experienced equivalent DFS (HR 0.99, 95% CI 0.85-1.15). Distant recurrences occurred in about 5 percent in each group. Bone fractures occurred in 4.7 versus 6.3 percent, respectively (HR 1.35, 95% CI 1.00-1.84).

TIMING OF ENDOCRINE THERAPY

For women with hormone receptor-positive breast cancer who are not recommended to receive other adjuvant therapy (eg, chemotherapy and/or radiotherapy), endocrine therapy is usually initiated four to six weeks after surgery.

- For patients receiving adjuvant chemotherapy, the initiation of endocrine therapy is commonly begun **after** chemotherapy has completed (ie, sequentially) rather than during chemotherapy (ie, concurrently), in order to minimize toxicities and possible antagonism between chemotherapy and endocrine therapy (which has been suggested with tamoxifen). However, the timing of endocrine therapy in relation to chemotherapy administration does not consistently appear to influence outcomes [32,72,73].

  As an example, in a North American Intergroup trial (SWOG 8814), 637 postmenopausal women with node-positive, hormone receptor-positive breast cancer were treated with chemotherapy and randomly assigned to treatment with tamoxifen initiated during or following completion of chemotherapy [72]. At 13 years of follow-up, sequential treatment resulted in a trend toward improvement in disease-free survival (DFS) compared with concurrent treatment (hazard ratio [HR] 0.84, 95% CI 0.70-1.01), but no improvement in overall survival (OS; HR 0.90, 95% CI 0.73-1.10). In addition, results of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis that compared concurrent with sequential treatment found similar reductions in the rate of recurrence when tamoxifen was used sequentially versus concurrently (relative risk [RR] 0.62 and RR 0.71, respectively) [32].

- For women receiving adjuvant radiation therapy (RT) for breast cancer, some experts at UpToDate initiate endocrine therapy concurrently with RT, while other experts initiate endocrine therapy sequentially, following the completion of RT. Multiple studies show that the timing of endocrine therapy in relation to RT does not impact survival [74-76]. Although older studies suggest that concurrent treatment increases the risks of treatment complications (including pulmonary and/or breast fibrosis) [77,78], other studies do not

[75,79]. (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer".)

Restarting adjuvant therapy — Despite the importance of continuing with adjuvant endocrine therapy, a significant percentage of women will discontinue treatment. For these women, restarting adjuvant therapy appears to be associated with improved DFS. This approach is supported by the following observations:

- In the MA.17 trial, patients who had been receiving placebo were offered the opportunity to receive or to be randomized to letrozole after the blind was broken. In spite of the varying intervals during which these patients had received no letrozole, both those randomized to letrozole and those who chose to take it had improved DFS [62].

- In a Swedish registry study of 3071 women diagnosed between 2005 and 2008 and given adjuvant endocrine therapy, 1464 (48 percent) discontinued treatment for at least 3 months [80]. Among those discontinuing treatment, 953 (65 percent) restarted adjuvant endocrine treatment, and 511 (35 percent) did not restart. DFS was significantly improved in the subset of women who restarted adjuvant therapy (eight-year DFS, 89.8 versus 82.0 percent; HR 0.61, 95% CI 0.43-0.87).

- As discussed above in the SOLE trial, women who reached five years on adjuvant aromatase inhibition without a recurrence were randomly assigned to continuous extended aromatase inhibitor (AI) therapy versus AI for nine months of the year [69]. There was no difference in event-free survival or OS, but the women in the alternating arm reported superior quality of life. (See 'Selection of patients for extended therapy' above.)

ADDITIONAL CONSIDERATIONS FOR HER2-POSITIVE DISEASE

Most patients with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-positive early breast cancer are treated with adjuvant chemotherapy plus trastuzumab followed by maintenance trastuzumab to complete one year of treatment. For these patients, we and others initiate endocrine therapy once chemotherapy has been completed (during maintenance trastuzumab) rather than delaying the start of endocrine therapy until all treatment with trastuzumab has been completed. This was the standard treatment paradigm in the seminal clinical trials that evaluated adjuvant trastuzumab. (See "Adjuvant systemic therapy for HER2-positive breast cancer".)

Efficacy of endocrine therapy in patients with hormone receptor-positive disease that is HER2 positive versus HER2 negative is discussed elsewhere. (See "HER2 and predicting response to

therapy in breast cancer" and "HER2 and predicting response to therapy in breast cancer", section on 'HER2 status and predicting treatment response'.)

No prospective trials have evaluated the efficacy of endocrine therapy plus trastuzumab without the incorporation of chemotherapy [81]. Therefore, adjuvant chemotherapy plus trastuzumab followed by endocrine therapy (plus maintenance trastuzumab) should be administered to these women. The use of endocrine therapy plus trastuzumab (without chemotherapy) remains investigational and should be done only as part of a clinical trial.

SPECIAL POPULATIONS

Obese women — We do not adjust our recommendations for adjuvant endocrine therapy solely on the basis of body mass index (BMI). However, some data obtained in studies predominantly involving postmenopausal women suggest that a higher BMI is associated with worse breast cancer outcomes despite treatment with chemotherapy and/or endocrine therapy [80-83], although not all studies have found this to be the case [82].

As an example, in a post-hoc analysis of the ATAC trial that included over 4900 postmenopausal women, women with a BMI >35 kg/m^2 at baseline were at a greater risk for recurrence compared with women with a BMI <23 kg/m^2 (21 versus 14 percent, respectively; hazard ratio [HR] 1.39, 95% CI 1.06-1.82) [83].

In a separate analysis of the BIG 1-98 trial, among 4700 postmenopausal women randomly assigned to treatment with tamoxifen or letrozole, obesity was associated with nonsignificant trends toward an increased risk of recurrence (30 versus 25 percent; HR 1.09, 95% CI 0.94-1.27) and all-cause mortality (21 versus 15 percent; HR 1.19, 95% CI 0.99-1.44), compared with women with a BMI <25 kg/m^2 [84]. These results were independent of endocrine therapy administered.

These data suggest that obesity may impact overall prognosis and the optimal choice of endocrine therapy. However, prospective trials are required before these data are used for clinical decisions. In addition, whether dietary and lifestyle interventions have an effect on survival outcomes in women with breast cancer requires further study. (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer", section on 'Obese women' and "The roles of diet, physical activity, and body weight in cancer survivors".)

Patients with cardiac risk factors — For patients with cardiac risk factors who are candidates for endocrine therapy, aromatase inhibitors (AIs) appear to be associated with a long-term increased risk of cardiovascular disease compared with tamoxifen [85]. Therefore, the risks and benefits of treatment should be individualized in this population. (See "Clinical manifestations,

diagnosis, and treatment of anthracycline-induced cardiotoxicity" and "Risk and prevention of anthracycline cardiotoxicity".)

Patients with mucinous or tubular/cribriform histologies — Because prospective data are limited for mucinous and tubular/cribriform histologies, our treatment approach for these entities is the same as for more common histologies. However, patients with mucinous or tubular/cribriform histotypes have a better prognosis and therefore may derive a smaller absolute risk reduction from endocrine therapy compared with patients with other breast cancer histologies, though they would still benefit a similar chemoprotective effect against a second breast cancer.

In an exploratory subset analysis of the BIG 1-98 trial, including 183 women with mucinous or tubular/cribriform histologies, tamoxifen was associated with nonsignificant trends towards improved disease-free survival and overall survival compared with letrozole [86]. Further study in larger numbers of patients is required to confirm these results.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Breast cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Treatment of early-stage, hormone-responsive breast cancer in postmenopausal women (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Introduction** – Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females. Estrogen receptor (ER)- and/or progesterone receptor (PR)-positive breast cancers comprise the most common type of breast cancer, accounting for 75 percent of all breast cancers. (See 'Introduction' above.)

- **Indication for endocrine therapy** – For most patients with hormone receptor-positive breast cancer, we recommend adjuvant endocrine therapy (**Grade 1A**). (See 'Indications' above.)

- **Choice of endocrine therapy** – For postmenopausal women with non-metastatic, hormone receptor-positive breast cancer, we suggest an aromatase inhibitor (AI) rather than tamoxifen as adjuvant endocrine treatment (**Grade 2A**). While AIs are associated with improved outcomes compared with tamoxifen, both agents reduce recurrences and new primary breast cancers, and some women may tolerate the risks and toxicities of tamoxifen better than an AI. For women who wish to discontinue an AI, it would be reasonable to switch to tamoxifen. (See 'AIs as preferred therapy' above.)

- **Incorporation of abemaciclib for high-risk disease** – For patients with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive breast cancer at high risk of recurrence, we suggest the addition of adjuvant abemaciclib to endocrine therapy (**Grade 2C**), but note that it is also acceptable not to administer this additional treatment, given the toxicity (notably, diarrhea) and only short-term supporting data. High-risk criteria are discussed above. (See 'Incorporation of targeted therapies for select patients' above.)

  Of note, there are no data on outcomes in women with breast cancer susceptibility gene 1/*2 (BRCA1/2*) mutations, and for such patients, olaparib is the preferred approach in addition to endocrine therapy. (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer", section on 'BRCA carriers with high-risk disease'.)

- **Duration of endocrine treatment** – For women receiving adjuvant endocrine therapy, we recommend at least a five-year course of treatment (**Grade 1A**). If there has been no disease recurrence at that point, consideration should be given regarding extended endocrine therapy, weighing risk of recurrence against side effects and risks for serious adverse events (AEs; eg, thrombosis and endometrial cancer with tamoxifen; or fracture with AIs).

- For women with higher-risk disease (eg, stage II or stage III disease), we suggest extended endocrine treatment (**Grade 2B**), although we recognize that some patients with poor tolerance may choose not to pursue extended treatment. For patients with high-risk disease, a total duration between 7 and 10 years is appropriate, with preference for the higher end of this range, if treatment is well tolerated. Those who have been treated with tamoxifen only may have a higher likelihood of benefit.

- For women with smaller, node-negative tumors (ie, stage I disease), it is not clear that there is a sufficiently high risk of late recurrence to justify the side effects and risks of extended endocrine therapy.

  - Women who wish to avoid side effects may reasonably stop endocrine therapy after five years.

  - Women who are tolerating endocrine treatment well and wish to decrease their likelihood of new breast cancers or recurrences may reasonably choose extended endocrine therapy. If extended endocrine therapy is chosen in patients with low-risk cancers, an additional two years of treatment is appropriate (for a total of seven years of treatment). The benefits of a total of 10 versus 7 years of endocrine therapy are small, if any, in women with low-risk cancers, and the risks of AEs persist. (See 'Duration of endocrine treatment' above.)

- **Timing of endocrine treatment** – For patients receiving adjuvant chemotherapy, we initiate endocrine therapy **after** chemotherapy has completed (ie, sequentially) rather than concurrently with chemotherapy, in order to minimize toxicities. For women receiving adjuvant radiation therapy (RT) for breast cancer, endocrine therapy may be initiated concurrently with RT or sequentially, following the completion of RT. (See 'Timing of endocrine therapy' above.)

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GRAPHICS

Aromatase inhibitors

Generation	Steroidal (type 1)	Nonsteroidal (type 2)
First (nonselective)	-	Aminoglutethimide
Second (selective)	Formestane	Fadrozole
Third (superselective)	Exemestane (Aromasin)	Anastrozole (Arimidex)
		Letrozole (Femara)

Graphic 61155 Version 1.0

Eligibility for the NATALEE trial

Adult patients with hormone receptor-positive/HER2-negative early breast cancer
Prior endocrine therapy allowed up to 12 months
Any of the following:
Anatomic stage IIA ▪ N0 with: • Grade 2 and evidence of high risk: ○ Ki-67 of at least 20% ○ Oncotype DX Breast Recurrence Score of at least 26, OR ○ High risk via genomic risk profiling • Grade 3 ▪ N1 **Anatomic stage IIB** ▪ N0 or N1 **Anatomic stage III** ▪ N0, N1, N2, or N3

HER2: human epidermal growth factor 2.

Graphic 141966 Version 1.0

Contributor Disclosures

Kathleen I Pritchard, MD, FRCPC Grant/Research/Clinical Trial Support: Amgen [Breast cancer]; Eisai [Breast cancer]; Novartis [Breast cancer]; Pfizer [Breast cancer]; Roche [Breast cancer]. Consultant/Advisory Boards: Amgen [Breast cancer]; Eisai [Breast cancer]; Genomic Health [Breast cancer]; Myriad Genetic Laboratories [Breast cancer]; Novartis [Breast cancer]; Pfizer [Breast cancer]; Roche [Breast cancer]. All of the relevant financial relationships listed have been mitigated. **Daniel F Hayes, MD** Equity Ownership/Stock Options: Inbiomotion [Breast cancer]. Patent Holder: Immunicon Corporation [Inventor]; University of Michigan [Inventor]; University of Michigan [Inventor]. Grant/Research/Clinical Trial Support: AstraZeneca [Breast cancer]; Menarini Silicon Biosystems, LLC [Breast cancer]; Pfizer [Breast cancer]. Consultant/Advisory Boards: Artiman Ventures [Breast cancer]; BioVeca [Breast cancer]; Cepheid [Breast cancer]; EPIC Sciences, Inc [Breast cancer]; Freenome, Inc [Colorectal cancer]; Guardant [Oncology]; Lexent Bio [Breast cancer]; L-Nutra [Breast cancer]; Macrogenics [Breast cancer]; OncoCyte [Biomarkers]; Predictus BioSciences [Breast cancer]; Tempus [Oncology]; Turnstone Biologics [Breast cancer]; Xilis [GI cancer]. Other Financial Interest: Menarini Silicon Biosystems [Royalties from licensing of patent – Breast cancer]. All of the relevant financial relationships listed have been mitigated. **Sadhna R Vora, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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