

American Society of Clinical Oncology Technology Assessment on the Use of Aromatase Inhibitors As Adjuvant Therapy for Postmenopausal Women With Hormone Receptor–Positive Breast Cancer: Status Report 2004

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A B S T R A C T

Purpose

To update the 2003 American Society of Clinical Oncology technology assessment on adjuvant use of aromatase inhibitors.

Recommendations

Based on results from multiple large randomized trials, adjuvant therapy for postmenopausal women with hormone receptor–positive breast cancer should include an aromatase inhibitor in order to lower the risk of tumor recurrence. Neither the optimal timing nor duration of aromatase inhibitor therapy is established. Aromatase inhibitors are appropriate as initial treatment for women with contraindications to tamoxifen. For all other postmenopausal women, treatment options include 5 years of aromatase inhibitors treatment or sequential therapy consisting of tamoxifen (for either 2 to 3 years or 5 years) followed by aromatase inhibitors for 2 to 3, or 5 years. Patients intolerant of aromatase inhibitors should receive tamoxifen. There are no data on the use of tamoxifen after an aromatase inhibitor in the adjuvant setting. Women with hormone receptor–negative tumors should not receive adjuvant endocrine therapy. The role of other biomarkers such as progesterone receptor and HER2 status in selecting optimal endocrine therapy remains controversial. Aromatase inhibitors are contraindicated in premenopausal women; there are limited data concerning their role in women with treatment-related amenorrhea. The side effect profiles of tamoxifen and aromatase inhibitors differ. The late consequences of aromatase inhibitor therapy, including osteoporosis, are not well characterized.

Conclusion

The Panel believes that optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an aromatase inhibitor as initial therapy or after treatment with tamoxifen. Women with breast cancer and their physicians must weigh the risks and benefits of all therapeutic options.

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INTRODUCTION

Adjuvant hormonal therapy results in substantial improvements in disease-free and

overall survival for women with operable breast cancer. For many years, treatment with tamoxifen has been the standard therapy for postmenopausal women with

hormone receptor–positive breast cancer.¹ In December 2001, the preliminary results from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial were presented at the San Antonio Breast Cancer Symposium.² With the availability of a new therapeutic approach, the American Society of Clinical Oncology (ASCO) convened a Technology Assessment Panel to provide guidance to physicians and patients concerning the use of the aromatase inhibitors in the adjuvant setting. The Panel published its initial report in 2002,³ and an update 1 year later.⁴

All Technology Assessments are reviewed on an annual basis. In early 2004, the Technology Assessment Panel met by teleconference to review newly released and published data concerning the use of the aromatase inhibitors in the adjuvant setting. In preparation for the teleconference, an updated MEDLINE search was performed; relevant manuscripts and conference presentations were reviewed; and pharmaceutical companies manufacturing a commercially available, third-generation aromatase inhibitor were contacted and asked to provide additional data. With the availability of new information,⁵⁻⁹ the Panel unanimously agreed to develop updated recommendations. The Panel focused on two separate but related topics: (1) evidence to support the substitution of an aromatase inhibitor for tamoxifen as initial adjuvant hormonal therapy in postmenopausal women, and (2) evidence to support switching postmenopausal women from tamoxifen to an aromatase inhibitor after 5 or fewer years of tamoxifen therapy.

It is important to emphasize that guidelines and technology assessments cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result.

Accordingly, ASCO considers adherence to this technology assessment to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, this technology assessment describes the use of procedures and therapies in clinical practice; it cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment are needed. In that guideline and technology assessment development involve a review and synthesis of the latest literature, a practice guideline or technology assessment also serves to identify important questions and settings for further research.

THIRD-GENERATION AROMATASE INHIBITORS

Anastrozole and letrozole are nonsteroidal aromatase inhibitors that result in a marked reduction in the concentra-

tion of circulating estrogen levels in postmenopausal women. Both agents have been evaluated extensively in women with metastatic breast cancer^{10,11} and are US Food and Drug Administration–approved in the United States for the first- and second-line treatment of hormone receptor–positive metastatic breast cancer. In the treatment of metastatic breast cancer, both anastrozole and letrozole have been shown to be equivalent or superior to tamoxifen in a variety of clinical parameters.^{12,13} Although letrozole has a more pronounced effect on reducing estrogen levels than does anastrozole,¹⁴ the clinical significance of this finding is uncertain. In a randomized unblinded trial comparing anastrozole and letrozole in patients with metastatic breast cancer, there was no significant difference between the two agents in time to progression (the predefined primary study end point).¹⁵ Letrozole was associated with a statistically higher overall response rate, but a statistically significant difference was not seen in patients known to have estrogen receptor (ER)–positive tumors. The two agents did not differ significantly in terms of clinical benefit rate or overall survival.

Exemestane is a steroidal aromatase inactivator. In the United States, it is approved for hormonal therapy for women with metastatic breast cancer after disease progression on or following therapy with an antiestrogen. Preclinical studies have suggested that it may have a different toxicity profile than the nonsteroidal agents¹⁶; however, these findings have yet to be confirmed in definitive clinical studies. A phase III randomized trial in the first-line metastatic setting has demonstrated superiority of exemestane over tamoxifen in terms of progression-free survival.⁸ A smaller, randomized trial comparing exemestane to anastrozole in women with metastatic breast cancer with visceral involvement revealed no significant difference in any clinical outcome.⁹

RANDOMIZED TRIALS OF THE THIRD-GENERATION AROMATASE INHIBITORS IN THE ADJUVANT AND PREOPERATIVE SETTINGS

Four phase III randomized, adjuvant trials have assessed the third-generation aromatase inhibitors in comparison with tamoxifen or to a placebo following 5 or fewer years of tamoxifen therapy (Table 1). The ATAC trial¹⁷ compared initial therapy with anastrozole, with initial therapy with tamoxifen. In the Italian trial (ITA)¹⁸ and the Intergroup Exemestane Study (IES),⁵ women who had received 2 to 3 years of tamoxifen were randomly assigned to either continue treatment with tamoxifen for a full 5 years or to receive an aromatase inhibitor (anastrozole in the ITA trial and exemestane in the IES trial). In the MA-17 trial,¹⁹ women who had completed approximately 5 years of tamoxifen were randomly assigned to receive either letrozole

Table 1.				
	Design	N	Median Follow-Up (months)	Key Findings
ATAC	Double-blind Tamoxifen vs Anastrozole vs Tamoxifen + Anastrozole in newly diagnosed patients	9,366	33.3	1) In hormone receptor-positive patient population, HR for recurrence (A vs T) is 0.82 (0.70-0.96; <i>P</i> = 0.014) 2) Total events-Anastrozole 413 Tamoxifen 472 3) Distant recurrence-Anastrozole 196 Tamoxifen 223
ITA	Open label Patients who had completed 2-3-year course of tamoxifen and were disease-free	426	24	1) In total population, HR for recurrence is 0.36 (0.17-0.75; <i>P</i> = .006) 2) Total events-Anastrozole 10 Tamoxifen 26
IES	Double-blind Tamoxifen vs Exemestane in patients who had completed 2-3-year course of tamoxifen and were disease-free	4,742	30.6	1) In total population, HR for recurrence (E vs T) is 0.68 (0.56-0.82; <i>P</i> = .00005) 2) Total events-Exemestane 183 Tamoxifen 266 3) Distant recurrence-Exemestane 114 Tamoxifen 174
MA-17	Double-blind Letrozole vs Placebo in patients who had completed 5-year course (4.5 years-6 years) of adjuvant trial and were disease-free	5,187	26.8	1) In total population, HR for recurrence (Letrozole vs Placebo) is 0.57 (0.43-0.75; <i>P</i> = .00008) 2) Total events-Letrozole 92 Placebo 155 3) Distant recurrence-Letrozole 57 Placebo 94

Abbreviations: ATAC, Arimidex, Tamoxifen, Alone or in Combination; ITA, Italian trial; IES, Intergroup Exemestane Study.

or a placebo. The ITA trial was substantially smaller than the other three studies, and a full report of the trial has yet to be published.

Several randomized preoperative trials comparing tamoxifen with an aromatase inhibitor as initial therapy have also been conducted. None of the trials has included more than 400 patients, and none was designed to assess the long-term benefits of the aromatase inhibitors. Nevertheless, these trials provide evidence supporting the clinical effectiveness of the aromatase inhibitors in postmenopausal women with newly diagnosed breast cancer.

The three large adjuvant studies (excluding the ITA) utilized double-blind, placebo-controlled designs. In the ATAC trial, more than 9,000 postmenopausal women were randomly assigned to receive anastrozole plus placebo, tamoxifen plus placebo, or anastrozole plus tamoxifen. With a median follow-up of 47 months, there was no difference in disease-free survival between the combination arm and the tamoxifen arm. In comparison to the tamoxifen arm, anastrozole resulted in a statistically significant reduction in breast cancer events and an improvement in disease-free survival.²⁰ The IES trial randomly assigned 4,742 women who had received 2 to 3 years of tamoxifen to continue tamoxifen for a total of 5 years or to receive exemestane to complete a 5-year course of hormonal therapy. After a median follow-up of 30.6 months, the trial demonstrated a significant reduction in events (recurrence, contralateral breast cancer, or death) in favor of the exemestane arm. The

MA-17 trial involved 5,187 postmenopausal women who had taken tamoxifen for approximately 5 years and who were disease free at study entry and randomly assigned them to receive either letrozole or a placebo for an additional 5 years. After a median follow-up of 2.4 years, the study was halted by the Data Safety Monitoring Board because of a significant reduction in breast cancer events on the letrozole arm.¹⁹ In an updated analysis, the study was reported to demonstrate an overall benefit in distant disease-free survival and a survival advantage in the subset of women on the trial who had node-positive disease.²¹ The only trial to demonstrate a statistically significant survival advantage to date is the MA-17 study. Of note, the survival advantage was only seen in women with node-positive disease. There is no clear demonstration of a difference in overall patient-rated quality of life as a result of treatment with an aromatase inhibitor in the adjuvant setting. Nevertheless, differences in disease-free survival in the adjuvant setting often lead to differences in overall survival with prolonged follow-up. While we await more mature results and findings from additional trials using the aromatase inhibitors in the adjuvant setting, many patients and physicians have elected to use the third-generation aromatase inhibitors either as initial therapy in the adjuvant setting or following a course of tamoxifen.

In an effort to provide guidance to patients and physicians, the Panel chose to address a series of questions concerning the use of the aromatase inhibitors as

adjuvant treatment for women with operable breast cancer. The Panel has chosen to refer to the aromatase inhibitors as a class of agents in the questions below, though it is unknown if the three available drugs are interchangeable in clinical practice. In general, the Panel favors using the aromatase inhibitor that has been studied in the setting most closely approximating any individual patient's clinical circumstance. As additional data from ongoing trials become available, the Panel may support greater or lesser flexibility in the choice of one aromatase inhibitor over another.

QUESTIONS ADDRESSED BY THE PANEL

Are There New Data to Prompt a Recommendation for an Aromatase Inhibitor As Initial Adjuvant Therapy in Unselected Postmenopausal Patients With Hormone Receptor–Positive Breast Cancer?

The ATAC data were first presented in December 2001. A year later, updated data showed that the initial advantage in disease-free survival of anastrozole over tamoxifen was maintained. An event-driven survival analysis is anticipated in the near future. At such time, additional information may also be available with regard to disease-free survival, toxicity, and quality of life.

Neither MA-17 nor the IES trial addressed the use of an aromatase inhibitor as initial therapy after a diagnosis of breast cancer. These studies have provided additional information suggesting that the aromatase inhibitors, as a class, are effective and generally well tolerated. MA-17 has shown a 43% reduction in events for letrozole in comparison to placebo, and the IES study has shown a 32% reduction in events for exemestane in comparison with tamoxifen.

The totality of evidence, both from the standpoint of efficacy and short- to moderate-term toxicity, suggests that treatment with an aromatase inhibitor is a reasonable alternative to tamoxifen following primary surgery for any postmenopausal woman with a hormone receptor–positive breast cancer. An aromatase inhibitor is the treatment of choice as initial adjuvant therapy for any postmenopausal women with hormone receptor–positive invasive breast cancer with a contraindication to tamoxifen. For women who do not have a contraindication to tamoxifen, it remains unclear if initial treatment with an aromatase inhibitor is superior, equivalent, or inferior to a planned cross-over from tamoxifen to an aromatase inhibitor after a fixed point in time. Ongoing studies will answer this pressing clinical question.

The long-term side effects of the aromatase inhibitors are not known, and it is possible that the toxicity profile will change with the accumulation of additional data. Some toxicities, such as thromboembolic events and uterine abnormalities are reduced with the use of an aromatase inhib-

itor when compared with tamoxifen. There is, however, an increase in osteoporosis and/or in fractures in women receiving the aromatase inhibitors. These findings suggest that close monitoring for bone loss and consideration of proactive treatment will be an important adjunct to the use of any aromatase inhibitor.

Are There Specific Patient Populations That Should Receive Initial Therapy With an Aromatase Inhibitor in Lieu of Tamoxifen?

As noted in the previous section, a postmenopausal woman with a hormone receptor–positive invasive tumor should receive an aromatase inhibitor if there is a contraindication to tamoxifen. The Panel has previously recommended that postmenopausal women who develop invasive breast cancer while receiving a selective estrogen receptor modulator (SERM) for either breast cancer risk reduction or bone loss, should be treated with an aromatase inhibitor. There is the suggestion, from a subgroup analysis within the ATAC trial, that women with ER+, progesterone receptor–negative tumors may derive relatively greater benefit from initial therapy with an aromatase inhibitor.²² Although this subset analysis was retrospective, the number of events considered was relatively large. Some Panel members felt the results should be factored into the decision-making process, while other Panel members did not favor using this information in clinical decisions.

For postmenopausal women with breast cancer overexpressing HER-2, higher response rates have been reported for aromatase inhibitors as compared with tamoxifen in two randomized neoadjuvant trials.^{22,23} However, both studies included a very limited number of women with HER-2–positive tumors. The Panel recognizes that debate continues regarding the optimal hormonal management of patients with HER-2–positive tumors. Based on the available clinical evidence, the Panel would generally recommend that HER-2 status not be considered when making choices about adjuvant hormonal therapy. It must be noted, however, that some Panel members are more inclined to recommend initial therapy with an aromatase inhibitor in postmenopausal women with HER-2–positive tumors.

Do the Results of the MA-17 Trial Provide Sufficient Evidence to Recommend the Use of an Aromatase Inhibitor in Postmenopausal Women With Hormone Receptor–Positive Breast Cancer Who Have Completed a 5-Year Course of Tamoxifen?

The MA-17 trial studied a population of patients—postmenopausal women finishing 5 years of tamoxifen—for whom no standard therapy exists. It demonstrated a statistically significant (43%) reduction in breast cancer events with the use of letrozole. This difference translated into an estimated 5% absolute improvement in recurrence risk through a projected 4 years of therapy, which would

represent a clinically significant difference to most patients. Subset analyses suggested that patients with both node-negative and node-positive disease derive benefit from letrozole in this setting. However, because of the difference in residual risk of recurrence among high-risk and low-risk patients, the absolute difference is greater for node-positive than for node-negative cohorts. Indeed, the most recent analysis revealed a small but statistically significant ($P = .04$) survival benefit in patients with node-positive disease.

Ongoing adjuvant endocrine therapy, as with letrozole in MA-17, is associated with continuing symptoms of estrogen deprivation. Patients and their physicians must carefully weigh the side effects and benefits of treatment. Because of early reporting of results, all present analyses are based on a median treatment duration of approximately 2.5 years. While the study was planned to evaluate a 5-year course of therapy, the optimal duration of treatment is not known. An extension study of MA-17 has been approved and will randomly assign women who have received 5 years of letrozole to an additional 5 years of letrozole or to placebo.

Based on findings from MA-17, postmenopausal women finishing 5 years of tamoxifen for ER-positive, early-stage breast cancer should consider treatment with an aromatase inhibitor. At present, a minimum of 2.5 years of therapy can be recommended based on the median follow-up from MA-17. Since all patients on the placebo arm were offered the option of beginning letrozole, the study will not provide additional data concerning the optimal duration from the standpoint of efficacy, though additional toxicity data will be available in the future.

In making a decision about the use of an aromatase inhibitor after the completion of a five-year course of tamoxifen, clinicians and patients should consider the residual risk of recurrence and individual preferences. The survival advantage in the subset of women with node-positive disease is noteworthy and strengthens the argument for use of an aromatase inhibitor after tamoxifen in this patient population.

Do the Results of the IES and ITA Trials Provide Sufficient Evidence to Recommend the Use of an Aromatase Inhibitor in Postmenopausal Women With Hormone Receptor-Positive Breast Cancer Who Have Received Tamoxifen for 2 to 3 Years?

The IES and ITA trials compared 5 years of tamoxifen versus 2 to 3 years of tamoxifen followed by 2 to 3 years of an aromatase inhibitor among postmenopausal women with ER-positive early-stage breast cancer. Both studies showed that a change in treatment from tamoxifen to an aromatase inhibitor reduced the risk of breast cancer recurrence (risk reduction 32% in IES). In the IES trial, this improvement translated into a projected absolute difference in disease-free survival of 4.7% at 3 years. There has been no significant difference in survival reported to date. Subset analyses

suggest similar relative benefits among women with node-negative or node-positive primary breast cancer. The side effect profiles differed between aromatase inhibitor therapy versus continued tamoxifen therapy in predictable ways.

These trials did not compare starting an aromatase inhibitor at 2.5 years versus starting an aromatase inhibitor following 5 years of tamoxifen therapy as in MA-17. Thus, the optimal moment of transition from tamoxifen to an aromatase inhibitor is not known.

Based on the findings in the IES trial, with supporting evidence from the ITA trial, postmenopausal women concluding 2 to 3 years of tamoxifen therapy may consider cross-over to an aromatase inhibitor. At present, such patients should plan on a total of 5 years of adjuvant endocrine therapy; it is not known if a longer duration of treatment with an aromatase inhibitor would be of sustained clinical benefit. Patients intolerant of aromatase inhibitors or unwilling to switch from tamoxifen should continue to receive tamoxifen for a total duration of 5 years based on previous randomized trials that demonstrated the benefits of a 5-year course of tamoxifen versus a shorter course.

What Is the Optimal Duration of Therapy With an Aromatase Inhibitor in the Adjuvant Setting? Should an Aromatase Inhibitor Be Continued for Longer Than 5 Years Outside of a Clinical Trial? In Women Who Are Switched From Tamoxifen to an Aromatase Inhibitor After 2 to 3 Years, Should Treatment With the Aromatase Inhibitor Continue Beyond the 5-Year Point?

ATAC^{17,20} and MA-17¹⁹ are the trials with the longest reported duration of adjuvant aromatase inhibitor therapy, though most patients have yet to finish all planned 5 years of study therapy to allow a full assessment of its therapeutic index. The ITA and IES trials reported on the use of 2 to 3 years of anastrozole or exemestane, respectively, following tamoxifen, for a total of 5 years of adjuvant hormonal therapy. Neither the IES nor the ITA studies address continuing an aromatase inhibitor beyond year 5 in those who took tamoxifen in the first 2 to 3 years. Breast International Group (BIG 1-98; with letrozole) and the Austrian Breast Cancer Study Group 8 (ABCSG 8) and Arimidex-Nolvadex (ARNO) trials (with anastrozole) are ongoing studies that employ a sequential strategy for a total of 5 years of hormonal therapy. At this time, there is no evidence to suggest that a longer than 5-year course of an aromatase inhibitor is of benefit. Treatment with more than a 5-year course of an aromatase inhibitor should only be administered as part of a clinical trial. A second randomization is now planned in trials NSABP B-33 (exemestane) and MA-17 (letrozole) for those who will have taken an aromatase inhibitor in years 6 to 10 to continue the same aromatase inhibitor *versus* placebo for 5 more years (years 11 to 15).

Are There Any Studies That Support the Use of Tamoxifen After an Aromatase Inhibitor?

Preclinical models of breast cancer indicate that antagonistic effects of tamoxifen might prevail in an estrogen environment, and agonistic effects, in an estrogen-deprived environment. An adaptive hypersensitivity to estrogen is also observed in long-term estrogen-deprivation models.²⁴ These observations raise theoretical concerns about the effects of sequential use of tamoxifen following an aromatase inhibitor.

Existing clinical data do not support the use of tamoxifen after an aromatase inhibitor in the adjuvant setting. One of the arms of the BIG 1-98 trial addresses this question by treating patients with 2 years of letrozole followed by 3 years of tamoxifen. At this time, women who complete initial adjuvant therapy with an aromatase inhibitor should not be routinely crossed over to tamoxifen outside of a clinical trial. However, if a woman initially treated with an aromatase inhibitor develops toxicity that would require premature discontinuation of adjuvant endocrine therapy, it is reasonable to consider either substituting another aromatase inhibitor or switching to tamoxifen.

Women with metastatic disease treated in a double-blind study of tamoxifen *versus* letrozole as first-line therapy²⁵ were allowed an optional cross-over on progression in a double-blind fashion (197 to tamoxifen and 194 patients to letrozole). A median survival of 19 months from the time of cross-over was observed among those who switched from letrozole to tamoxifen, but response and time to progression were not specifically reported for second-line treatment in this trial.

In a combined analysis of two double-blind randomized trials comparing tamoxifen with anastrozole as first-line therapy for metastatic disease, a questionnaire retrospectively administered to investigators suggested that tamoxifen was effective after initial therapy with anastrozole.²⁶ In a small double-blind cross-over analysis of another multicenter randomized trial, median time to progression was similar for either sequence (6.7 months for tamoxifen after anastrozole and 5.7 months for anastrozole after tamoxifen).²⁷ Although limited, such results suggest antitumor activity for tamoxifen following an aromatase inhibitor.

It must be emphasized, however, that there are no clinical data at this time that would support the initiation of tamoxifen after a course of therapy with an aromatase inhibitor in the adjuvant setting.

Is There Any Role for the Aromatase Inhibitors in Women With Hormone Receptor–Negative Breast Cancer?

There is overwhelming evidence that adjuvant hormonal therapy is effective only in patients with positive ER and/or progesterone receptors. Aromatase inhibitors have not been evaluated in the adjuvant setting in women whose tumors lack hormone receptors. Hormone receptor studies should be performed on all primary invasive tumors to guide the use of adjuvant hormonal therapy, and women whose tumors are

known to be hormone receptor–negative should not receive an aromatase inhibitor as adjuvant therapy. The Panel noted that false-negative hormone receptor assays can occur and would encourage clinicians to repeat hormone receptor studies if the result is in question or is discordant with the clinical picture.

Is It Reasonable to Use an Aromatase Inhibitor As Initial Hormonal Therapy in a Woman Who Is Premenopausal at Diagnosis and Who Appears to Have Gone Through Menopause With Chemotherapy?

Amenorrhea can occur following the administration of chemotherapy. The incidence of chemotherapy-related amenorrhea is dependent on the regimen utilized and the age of the patient.^{28,29} Cessation of menses, however, does not necessarily mean absence of ovarian function, as premenopausal estradiol levels may be found in women experiencing chemotherapy-related amenorrhea.³⁰ There is widespread agreement that aromatase inhibitors should not be employed as monotherapy in premenopausal women. This view stems from the lack of evidence for adequate estrogen suppression and potential for stimulation of the ovaries via increased gonadotropin release. The first- and second-generation aromatase inhibitors (aminoglutethimide and 4-hydroxyandrostenedione) were unable to adequately suppress plasma estrogen levels,³¹ and there are no published clinical data with the third-generation aromatase inhibitors. While aromatase inhibitors reduce estrogen levels in premenopausal women, there is a reflex increase in gonadotropin secretion. Letrozole at 2.5 mg per day (the usual dose employed in the treatment of breast cancer) given on days 3 to 7 following a menstrual cycle, has been shown to be effective in inducing ovulation, with one study that utilized this approach resulting in four pregnancies in the 22 patients who were treated.³² Thus, there are serious reasons for concern regarding the use of an aromatase inhibitor in women who are functionally premenopausal.

The ATAC trial allowed entry of women who were amenorrheic for fewer than 12 months if amenorrhea was a result of chemotherapy and if follicle-stimulating hormone level was in the postmenopausal range. The number of such patients on the trial was small. Thus, one is less confident of the generalizability of the ATAC results to this subset of patients. Furthermore, the premenopausal woman who has truly become postmenopausal has already had a substantial drop in estrogen levels, and it is not known whether the risk-benefit ratio of further lowering these levels would be of value.

Is It Reasonable to Use an Aromatase Inhibitor in Combination With a Luteinizing Hormone-Releasing Hormone Agonist or Oophorectomy in a Woman Who Is Premenopausal at Diagnosis?

There are no clinical trial data in premenopausal women from the adjuvant setting on which to judge the value of using an aromatase inhibitor in conjunction with ovarian function suppression (OFS). It has been demonstrated

that vorozole, a third-generation nonsteroidal aromatase inhibitor, provided substantial reductions in serum estradiol, estrone, and estrone-sulfate levels when given to women already receiving goserelin.³³ In the advanced disease setting, anastrozole plus goserelin has been shown to provide benefit in premenopausal women with disease progression on tamoxifen plus goserelin, in that 12 of 16 women (75%) achieved an objective response or stable disease at 6 months, with a median duration of remission of 17+ months.³⁴ Although limited, there are both endocrine and clinical data suggesting that aromatase inhibitors will be of value in premenopausal women being treated with OFS. Large, ongoing randomized clinical trials are addressing the value of aromatase inhibitors in such women. The ABCSG (Austrian Breast Cancer Study Group) Trial 12 plans to randomly assign 2,000 premenopausal women to receive 3 years of either tamoxifen or anastrozole, in combination with goserelin. Two trials evaluating the combination of OFS and an aromatase inhibitor are being coordinated by the International Breast Cancer Study Group (IBCSG), with involvement of the Breast International Group and the Breast Cancer Intergroup of North America. SOFT (Suppression of Ovarian Function Trial), IBCSG 24-02, has a target accrual of 3,000 premenopausal women who either do not receive chemotherapy or who remain premenopausal after chemotherapy and who are randomly assigned to 5 years of treatment with tamoxifen, OFS plus tamoxifen, or OFS plus exemestane. OFS can be accomplished by bilateral oophorectomy, radiation, or the gonadotropin-releasing hormone analog triptorelin. TEXT (Tamoxifen and Exemestane Trial), IBCSG 25-02, has a target accrual of 1,845 premenopausal women who are randomly assigned to 5 years of treatment with either triptorelin plus tamoxifen or triptorelin plus exemestane. These trials should provide evidence upon which to determine the value of aromatase inhibitors in premenopausal women treated with suppression of ovarian function. Until such evidence is available, aromatase inhibitors should not be used in premenopausal women outside of a clinical trial.

What Is Known About Bone and Musculoskeletal Toxicity Associated With the Aromatase Inhibitors?

Aromatase inhibitor use is associated with osteoporosis and fracture risk related to estrogen deprivation. In adjuvant trials, all three aromatase inhibitors have been associated with numerically more fractures than tamoxifen or placebo (letrozole 3.6% *v* placebo 2.9%, $P = .24$, Goss et al¹⁹; exemestane 3.1% *v* tamoxifen 2.3%, $P = .08$, Coombes et al⁵; anastrozole 7.1% *v* tamoxifen 4.4%, $P < .001$, Baum et al²⁰).

While the fracture incidence seems lower for aromatase inhibitor use after tamoxifen, the shorter follow-up of the exemestane and letrozole trials complicates the interpretation of the data. In the anastrozole trial, the annual fracture rate remained 60% higher than tamoxifen after 2 years.³⁵ None of the three trials incorporated a protocol-defined assessment of baseline fracture risk or ongoing bone density

monitoring.^{5,19,20} All three trials have ancillary studies evaluating serial bone densities in subsets of patients, which will provide important information.

While all fractures are of concern, hip fractures represent a life-threatening event with serious medical sequelae.³⁶ In the ATAC trial, at last report, women receiving anastrozole had similar numbers of hip fractures (16 *v* 20) as women taking tamoxifen. Nonhip fractures, however, may be a harbinger of future hip fractures. Preclinical models and turnover studies suggest the steroidal aromatase inhibitor exemestane may have less adverse bone effect. A recent randomized trial in 147 women (128 evaluable for bone outcomes) suggested that the decline in bone mineral density was slightly greater with exemestane than placebo.³⁷

Aromatase inhibitor-associated bone loss may represent a preventable and treatable condition. Clinical trial evidence indicates that intravenous bisphosphonate,³⁸ as well as oral bisphosphonates clodronate^{39,40} and risedronate,⁴¹ are effective in maintaining bone density in breast cancer patients on hormonal therapy and with therapy-associated premature menopause.

In otherwise healthy women, a strong body of evidence supports early detection and therapy of osteoporosis.⁴² The ASCO bisphosphonate guideline⁴³ identifies postmenopausal breast cancer patients who receive aromatase inhibitors to be at high risk for osteoporosis and recommends that they have baseline bone mineral density evaluation. As in women without breast cancer, subsequent interventions are guided by the results of bone density testing. Details supporting this recommendation along with management strategies are outlined in the ASCO bisphosphonate and bone health guideline.⁴³ It is hoped that implementation of these recommendations will reduce fracture rates associated with adjuvant aromatase inhibitor use. Based on recent results and ongoing studies, adjuvant bisphosphonates may become a more standard component of the treatment of women with early-stage breast cancer.⁴⁴

In the ATAC trial, musculoskeletal disorders were reported in 28% of women on anastrozole and 22% of women on tamoxifen ($P < .0001$). Arthralgias were reported in 5.4% of women on exemestane compared with 3.6% of women on tamoxifen ($P = .01$) in IES.⁵ Finally, in MA-17, arthralgias (21% *v* 17%, $P < .001$) and myalgias (12% *v* 9%, $P = .02$) were more common with letrozole than placebo.⁶ Overall, these three large studies support the conclusion that there is a small but statistically significant increase in arthralgias and/or myalgias with aromatase inhibitors compared with either tamoxifen or placebo.

What Is Known About Vascular Complications and Endometrial Cancer in Women Treated on the Adjuvant Aromatase Inhibitors Trials?

Both anastrozole and exemestane were associated with significantly fewer endometrial cancers, as well as venous and arterial vascular events, when compared with tamoxifen.^{5,20} Thus, incidence of three life-threatening side effects

seen with tamoxifen—endometrial cancer, pulmonary emboli, and stroke—was significantly reduced with aromatase inhibitor use.

Although tamoxifen lowers cholesterol levels, its influence on cardiovascular disease is not established.⁴⁵ Current information is also insufficient to determine the effects of aromatase inhibitors on cardiovascular disease and coronary heart disease risk. Although not statistically significant, both anastrozole and letrozole were associated with numerically more cardiovascular disease events compared with tamoxifen.^{19,20} The effects of aromatase inhibitors on lipid profile and especially cardiac clinical outcomes warrant careful future monitoring.

What Is Known About Overall Quality Of Life and Sexual Functioning in Women on Aromatase Inhibitors?

In general, there have been no major differences in symptoms influencing quality of life comparing anastrozole with tamoxifen²⁰ or letrozole with placebo.¹⁹ Fallowfield et al have reported inferior sexual functioning in women randomly assigned to anastrozole compared with tamoxifen on the ATAC trial.⁴⁶ In the IES study, women taking tamoxifen reported less vaginal dryness but more vaginal discharge compared with those on exemestane.⁸

Aromatase inhibitor effects on cognition or dementia have not been reported. Concerns regarding adverse effects of aromatase were raised, largely based on absence of anticipated favorable effects of estrogen. Randomized trial results, however, now indicate exogenous estrogen (as menopausal hormone therapy) doubles rather than decreases dementia risk,^{47,48} perhaps mediated via the increase in arterial vascular effects.

Anastrozole, exemestane, and letrozole are all well tolerated, with small numbers of women discontinuing treatment in comparison to women on placebo or tamoxifen.^{5,19,20} The differing clinical situations and lack of standard criteria for collection of side effects hinder comparison of aromatase inhibitor effects on patient-perceived symptoms. For example, letrozole increased hot flashes compared with placebo, while exemestane and tamoxifen had similar hot flash frequency and anastrozole was associated with somewhat fewer hot flashes than tamoxifen. As well, use of either tamoxifen or an aromatase inhibitor will increase vasomotor symptoms, presenting a clinical management problem.^{49,50}

To What Extent Can Physicians Individualize Decisions About Adjuvant Hormonal Therapy? How Can Physicians Better Quantify the Risks of Relapse and/or Second Primary in Women Who Have Taken a Course of Tamoxifen for Either 2 to 3 or 5 Years?

The risk of relapse and/or second primary breast cancers observed in women who took tamoxifen alone in the three major trials was large enough on average to warrant an

attempt at improvement. For example, in the ATAC trial, with a median follow-up of 47 months, the disease-free survival for women on the tamoxifen-only arm was 84.5%. This degree of risk is typical for postmenopausal women with a mix of node-negative and node-positive hormone receptor-positive breast cancer. However, quantification of average risk of relapse is not the only feature by which to judge the utility of these agents for individual women. Because aromatase inhibitors are not free of costs and burdens to the patients and society, questions inevitably arise about whether they should be used for all postmenopausal women with receptor-positive tumors.

Tailoring decisions about adjuvant hormonal therapy requires an understanding of disease and patient characteristics associated with relapse and toxicity of each approach. Unfortunately, such information is not readily available from the three large randomized trials. Differences in absolute benefit that a woman may expect are important in the decision-making process. It is possible that the benefits of different approaches may vary widely across different patient populations. Future studies will need to address the differences in disease outcome and toxicity across patient and tumor subtypes.

CONCLUSION

There is now little question that the aromatase inhibitors play an important role in the adjuvant treatment of postmenopausal women with hormone receptor-positive breast cancer. Although only one trial (MA-17) demonstrated a survival advantage associated with the use of an aromatase inhibitor and this only in node-positive patients, the three large studies discussed in this Update show a clear and consistent improvement in disease-free survival among women who received an aromatase inhibitor compared with those who were randomized to a control arm and did not receive one of these agents. At this time, the Panel believes that optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer should include an aromatase inhibitor either as initial therapy or after treatment with tamoxifen. Of course, women with breast cancer and their physicians must weigh the risks and benefits of all therapeutic options. For some women, the risks and inconvenience of an aromatase inhibitor will outweigh the potential benefits.

There are many important and unresolved issues, many of which will be addressed by ongoing studies and additional follow-up. These issues include: (1) Are the aromatase inhibitors most effective if used as initial therapy or after exposure to tamoxifen? If tamoxifen is administered, how long should it be continued before the cross-over? (2) What are the long-term toxicities and risks associated with the aromatase inhibitors? Can these risks be modified

through the use of other medical interventions? (3) Are there specific patient populations who derive differing degrees of benefit from an aromatase inhibitor in comparison to tamoxifen or to no treatment? If so, can such patient populations be identified? (4) Are there specific patient populations who are at greater risk of toxicity from an aromatase inhibitor? (5) How long should an aromatase inhibitor be continued? (6) Are aromatase inhibitors effective agents in women who are premenopausal at the time of diagnosis? (7) Can the third-generation aromatase inhibitors be used interchangeably? Are there clinical differences in their toxicity profile (eg, bone health)?

The Panel looks forward to the availability of additional data in the years ahead. In the meantime, physicians and patients should carefully consider the advantages and disadvantages of different treatment strategies for the treatment of hormone receptor–positive breast cancer.

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REFERENCES

1. Anonymous: Tamoxifen for early breast cancer: An overview of the randomised trials—Early Breast Cancer Trialists' Collaborative Group. *Lancet* 351:1451-1467, 1998
2. Baum M, on behalf of the ATAC Trialists' Group: The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal women. *Breast Cancer Res Treat* 69, 2001 (abstr 8)
3. Winer EP, Hudis C, Burstein HJ, et al: American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: Status report 2002. *J Clin Oncol* 20:3317-3327, 2002
4. Winer EP, Hudis C, Burstein HJ, et al: American Society of Clinical Oncology technology assessment working group update: Use of aromatase inhibitors in the adjuvant setting. *J Clin Oncol* 21:2597-2599, 2003
5. Coombes RC, Hall E, Gibson LJ, et al: A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 350:1081-1092, 2004
6. Goss PE, Ingle JN, Martino S, et al: Updated analysis of the NCIC CTG MA. 17 randomized placebo controlled trial of letrozole after five years of tamoxifen in postmenopausal women with early stage breast cancer. *Proc Am Soc Clin Oncol* 23:87, 2004 (abstr 847)
7. Whelan TJ, Goss PE, Ingle JN, et al: Assessment of quality of life in MA. 17, a randomized placebo-controlled trial of letrozole in postmenopausal women following five years of tamoxifen. *Proc Am Soc Clin Oncol* 23:6, 2004 (abstr 517)
8. Paridaens R, Therasse P, Dirix L, et al: First line hormonal treatment for metastatic breast cancer with exemestane or tamoxifen in postmenopausal patients: A randomized phase III trial of the EORTC Breast Group. *Proc Am Soc Clin Oncol* 23:6, 2004 (abstr 515)
9. Cameron DA, Winer EP, Campos S, et al: A comparative study of exemestane versus anastrozole in postmenopausal breast cancer subjects with visceral disease. *Proc Am Soc Clin Oncol* 23:34, 2004 (abstr 628)
10. Buzdar A, Douma J, Davidson N, et al: Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J Clin Oncol* 19:3357-3366, 2001
11. Buzdar AU, Jones SE, Vogel CL, et al: A phase III trial comparing anastrozole (1 and 10 milligrams), a potent and selective aromatase inhibitor, with megestrol acetate in postmenopausal women with advanced breast carcinoma: Arimidex Study Group. *Cancer* 79:730-739, 1997
12. Bonnetterre J, Buzdar A, Nabholz JM, et al: Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer* 92:2247-2258, 2001
13. Nabholz JM, Buzdar A, Pollak M, et al: Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: Results of a North American multicenter randomized trial—Arimidex Study Group. *J Clin Oncol* 18:3758-3767, 2000
14. Geisler J, Haynes B, Anker G, et al: Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study. *J Clin Oncol* 20:751-757, 2002
15. Rose C, Vtoraya O, Pluzanska A, et al: Letrozole (Femara) vs. anastrozole (Arimidex): second-line treatment in postmenopausal women with advanced breast cancer. *Proc Am Soc Clin Oncol* 21:34, 2002 (abstr 131)
16. Goss PE, Strasser K: Aromatase inhibitors in the treatment and prevention of breast cancer. *J Clin Oncol* 19:881-894, 2001
17. Baum M, Budzar AU, Cuzick J, et al: Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomized trial. *Lancet* 359:2131-2139, 2002
18. Boccardo F, Rubagotti A, Amoroso D, et al: Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment. *Breast Cancer Res Treat* 82:, 2003 (abstr 3)
19. Goss PE, Ingle JN, Martino S, et al: A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 349:1793-1802, 2003
20. Baum M, Buzdar A, Cuzick J, et al: Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer* 98:1802-1810, 2003
21. Goss PE, Ingle JN, Martino S, et al: Updated analysis of the NCIC CTG MA. 17 randomized placebo (P) controlled trial of letrozole (L) after five years of tamoxifen in postmenopausal women with early stage breast cancer. *Proc Am Soc Clin Oncol* 23:87, 2004 (abstr 84)
22. Smith I, Dowsett M: Comparison of anastrozole vs. tamoxifen alone or in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial. *Breast Cancer Res Treat* 82, 2003 (abstr 1)
23. Ellis MJ, Coop A, Singh B, et al: Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial. *J Clin Oncol* 19:3808-3816, 2001
24. Santen RJ, Song RX, Zhang Z, et al: Adaptive hypersensitivity to estrogen: Mechanism for sequential responses to hormonal therapy in breast cancer. *Clin Cancer Res* 10:337S-345S, 2004
25. Mouridsen H, Gershanovich M, Sun Y, et al: Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: Results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 19:2596-2606, 2001
26. Thurlimann B, Robertson JF, Nabholz JM, et al: Efficacy of tamoxifen following anastrozole ("Arimidex") compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women. *Eur J Cancer* 39:2310-2317, 2003
27. Thurlimann B, Hess D, Koberle D, et al: Anastrozole ('Arimidex') versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: Results of the double-blind cross-over SAKK trial 21/95—a sub-study of the TARGET (Tamoxifen or 'Arimidex' Randomized Group Efficacy and Tolerability) trial. *Breast Cancer Res Treat* 85:247-254, 2004
28. Minton SE, Munster PN: Chemotherapy-induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer. *Cancer Control* 9:466-472, 2002
29. Goodwin PJ, Ennis M, Pritchard KI, et al: Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol* 17:2365-2370, 1999
30. Braverman AS, Sawhney A, Tendler A, et al: Premenopausal serum estradiol levels may persist after chemotherapy-induced amenorrhea in breast cancer. *Proc Am Soc Clin Oncol* 21:42, 2002 (abstr 164)
31. Dowsett M, Stein RC, Coombes RC: Aromatization inhibition alone or in combination with GnRH agonists for the treatment of premenopausal breast cancer patients. *J Steroid Biochem Mol Biol* 43:155-159, 1992
32. Mitwally MF, Casper RF: Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. *Fertil Steril* 75:305-309, 2001
33. Dowsett M, Doody D, Miall S, et al: Vorozole results in greater oestrogen suppression than formestane in postmenopausal women and when added to goserelin in premenopausal women with advanced breast cancer. *Breast Cancer Res Treat* 56:25-34, 1999
34. Cheung KL, Forward DP, Jackson L, et al: Combined use of goserelin (Zoladex) and anastrozole (Arimidex) as second-line endocrine therapy in premenopausal women with advanced breast cancer: A study of its clinical and endocrine effects. *Eur J Cancer* 37, 2001(suppl 1)
35. Howell A: Effect of anastrozole on bone mineral density: 2-year results of "arimidex" (anastrozole), tamoxifen, alone or in combination (ATAC) trial. *Breast Cancer Res Treat* 82, 2003 (abstr 129)
36. Kanis JA, Oden A, Johnell O, et al: The components of excess mortality after hip fracture. *Bone* 32:468-473, 2003
37. Lonning PE, Geisler J, Krag LE, et al: Effect of exemestane on bone: A randomized placebo controlled study in postmenopausal women with early breast cancer at low risk. *Proc Am Soc Clin Oncol* 23:7, 2004 (abstr 518)
38. Gnant M, Hausmaninger H, Samonigg D, et al: Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (+/- zoledronate) as adjuvant treatment for hormone receptor-positive premenopausal breast cancer: Results of a randomized multicenter trial. *Breast Cancer Res Treat* 76:531, 2002 (suppl)
39. Saarto T, Blomqvist C, Valimaki M, et al: Chemical castration induced by adjuvant

cyclophosphamide, methotrexate, and fluorouracil chemotherapy causes rapid bone loss that is reduced by clodronate: A randomized study in premenopausal breast cancer patients. *J Clin Oncol* 15:1341-1347, 1997

40. Saarto T, Vehmanen L, Elomaa I, et al: The effect of clodronate and antioestrogens on bone loss associated with oestrogen withdrawal in postmenopausal women with breast cancer. *Br J Cancer* 84:1047-1051, 2001

41. Delmas PD, Balena R, Confravreux E, et al: Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: A double-blind, placebo-controlled study. *J Clin Oncol* 15:955-962, 1997

42. Force USPST: Screening for osteoporosis in postmenopausal women: Recommendations and rationale. *Ann Intern Med* 137:526-528, 2002

43. Hillner BE, Ingle JN, Chlebowski RT, et al: American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 21:4042-4057, 2003

44. Powles TJ, Paterson E, McCloskey M, et al: Oral clodronate for adjuvant treatment of operable breast cancer: Results of a randomized, double-blind, placebo-controlled multicenter trial. *Proceedings from the American Society of Clinical Oncology* 23:9, 2004 (abstr 528)

45. Chlebowski RT, Col N, Winer EP, et al: American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition. *J Clin Oncol* 20:3328-3343, 2002

46. Fallowfield LJ, Cella DF, CRC Oncology Group: Assessing the quality of life of postmenopausal women randomized into the ATAC adju-

vant breast cancer trial. *Proc Am Soc Clin Oncol* 21:40, 2002 (abstr 159)

47. Shumaker SA, Legault C, Rapp SR, et al: Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's Health Initiative Memory Study—A randomized controlled trial. *JAMA* 289:2651-2662, 2003

48. Clinical alert: NIH asks participants in Women's Health Initiative estrogen-alone study to stop study pills, begin follow-up phase. http://www.nlm.nih.gov/databases/alerts/estrogen_alone.html

49. Burstein HJ, Winer EP: Primary care for survivors of breast cancer. *N Engl J Med* 343:1086-1094, 2000

50. Chlebowski RT, Kim JA, Col NF: Estrogen deficiency symptom management in breast cancer survivors in the changing context of menopausal hormone therapy. *Semin Oncol* 30:776-788, 2003

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