

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

By Eric P. Winer, Clifford Hudis, Harold J. Burstein, Rowan T. Chlebowski, James N. Ingle, Stephen B. Edge, Eleftherios P. Mamounas, Julie Gralow, Lori J. Goldstein, Kathleen I. Pritchard, Susan Braun, Melody A. Cobleigh, Amy S. Langer, Judy Perotti, Trevor J. Powles, Timothy J. Whelan, and George P. Browman

Objective: To conduct an evidence-based technology assessment to determine whether the routine use of anastrozole or any of the aromatase inhibitors in the adjuvant breast cancer setting is appropriate for broad-based conventional use in clinical practice.

Potential Interventions: Anastrozole, letrozole, and exemestane.

Outcomes: Outcomes of interest include breast cancer incidence, breast cancer-specific survival, overall survival, and net health benefit.

Evidence: A comprehensive, formal literature review was conducted for relevant topics and is detailed in the text. Testimony was collected from invited experts and interested parties. The American Society of Clinical Oncology (ASCO)-prescribed technology assessment procedure was followed.

Benefits/Harms: The ASCO panel recognizes that a woman and her physician's decision regarding adjuvant hormonal therapy is complex and will depend on the importance and weight attributed to information regarding both cancer and non-cancer-related risks and benefits.

THERE HAS BEEN growing research and clinical interest in the use of third-generation aromatase inhibitors in the treatment of breast cancer. In December 2001, the results of the multinational, randomized Arimidex (anastrozole) or Tamoxifen Alone or in Combination (ATAC) study were presented at the San Antonio Breast Cancer Symposium. In the months since the ATAC results were presented, there has been considerable discussion within the oncology community, by both health care providers and patients, about how the results should be applied to clinical practice. The current dilemma for oncologists and their patients is whether the promising preliminary results from the ATAC trial justify the routine use of anastrozole or any of the aromatase inhibitors in the adjuvant setting. At the request of the American Society of Clinical Oncology (ASCO) President and Board of Directors in January 2002, the ASCO Health Services Research Committee convened a multidisciplinary panel of experts to conduct a technology assessment. The panel was asked to review the data on

Conclusion: The panel was influenced by the compelling, extensive, and long-term data available on tamoxifen. Overall, the panel considers the results of the Arimidex (anastrozole) or Tamoxifen Alone or in Combination (ATAC) trial and the extensive supporting data to be very promising but insufficient to change the standard practice at this time (May 2002). A 5-year course of adjuvant tamoxifen remains the standard therapy for women with hormone receptor-positive breast cancer. The panel recommends that physicians discuss the available information with patients, and, in making a decision, acknowledge that treatment approaches can change over time. Individual health care providers and their patients will need to come to their own conclusions, with careful consideration of all of the available data. (Specific questions addressed by the panel are summarized in Appendix 3.)

Validation: The conclusions of the panel were endorsed by the ASCO Health Services Research Committee and the ASCO Board of Directors.

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the adjuvant use of aromatase inhibitors and to make recommendations to health care providers and patients.

BACKGROUND: ADJUVANT HORMONAL THERAPY OF BREAST CANCER

Adjuvant hormonal therapy can prevent recurrences and improve survival in women with operable breast cancer whose tumors are positive for hormone receptors.¹ Tamoxifen received Food and Drug Administration approval for adjuvant therapy in postmenopausal women with positive nodes in 1986, and in pre- and postmenopausal women with

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Address reprint requests to American Society of Clinical Oncology, Health Services Research Department, 1900 Duke St, Suite 200, Alexandria, VA 22314; email: guidelines@asco.org.

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node-negative disease in 1990. As demonstrated in multiple randomized trials and an individual patient data meta-analysis, adjuvant tamoxifen reduces the risk of disease recurrence and improves overall survival.¹⁻³ Tamoxifen is beneficial in women of all age groups, and the benefits are similar regardless of whether a woman has received chemotherapy. Multiple randomized trials have addressed the optimal duration of tamoxifen therapy. The results of these trials have shown that a 5-year course of tamoxifen is superior to 1 or 2 years,^{1,4} although a 10-year course of treatment has not been shown to be better than 5 years.^{5,6} In women who have taken tamoxifen for 5 years, the benefits persist beyond the completion of therapy, including a lower risk of recurrence and a decreased likelihood of death for at least 5 years after discontinuing tamoxifen compared with women who never took tamoxifen. In absolute terms, a 5-year course of tamoxifen results in an improvement in survival at 10 years of 5.6% in patients with negative axillary nodes and 10.9% in those with positive nodes. Tamoxifen also has been shown to decrease a woman's risk of developing a contralateral breast cancer.¹

The benefits of tamoxifen must be considered in light of the side effects and risks of treatment. The most common side effects include hot flashes and vaginal discharge. Tamoxifen is associated with an increased risk of thromboembolic events, endometrial cancer,² and probably cerebrovascular disease, particularly in women over age 50.^{7,8} Some of the undesired effects from tamoxifen, such as the increased risk of endometrial cancer, were not apparent until tamoxifen had been in clinical use for many years. In general, the side effects associated with tamoxifen are limited and are far outweighed by the benefits. The National Institutes of Health Consensus Statement issued in late 2000 recommended that adjuvant tamoxifen be considered for all women with hormone receptor-positive breast cancer.⁹

The other established adjuvant hormonal therapy for premenopausal women with hormone receptor-positive tumors is ovarian ablation or suppression. A meta-analysis and selected individual studies suggest that the benefit from ovarian ablation or suppression is similar to that seen with chemotherapy.¹⁰⁻¹⁶ There is, however, less extensive experience with ovarian ablation or suppression than with chemotherapy. At this time, it remains unclear how ovarian ablation or suppression should be incorporated into the management strategies and treatment for premenopausal women with operable breast cancer.^{9,11}

AROMATASE INHIBITORS IN WOMEN WITH METASTATIC BREAST CANCER

A number of hormonal therapies are available to women with hormone receptor-positive, advanced breast cancer, in-

cluding selective estrogen receptor modulators, pure antiestrogens, progestins, estrogens, androgens, and aromatase inhibitors. Among these, aromatase inhibitors have played a role in the management of metastatic breast cancer for over two decades. For many years only aminoglutethimide, an agent with considerable toxicity, was available. Development of the third-generation aromatase inhibitors represented a significant advance in the treatment of metastatic breast cancer.

Aromatase is an enzyme complex required for estrogen synthesis through conversion of androgens (androstenedione and testosterone) to estrone and estradiol, respectively. After menopause, conversion of androgens in muscle, skin, fat, and breast by aromatase results in relatively low, but generally stable, circulating estrogen levels.¹⁷ Each of the third-generation aromatase inhibitors leads to nearly total blockade of peripheral aromatization and a marked decline in circulating estrogen levels.¹⁸ With administration of the third-generation aromatase inhibitors, circulating estrogen levels are suppressed to approximately 1% to 10% of pretreatment levels.¹⁹ The selectivity of the third-generation aromatase inhibitors allows for marked decrease in estrogen levels without the concomitant side effects seen with earlier generation agents. In premenopausal women, first- and second-generation aromatase inhibitors were not able to suppress estrogen levels because of high levels of androstenedione as well as reflex increases in gonadotropins leading to higher levels of ovarian aromatase.¹⁷ The third-generation aromatase inhibitors have not been adequately tested in this setting.

In the United States, the third-generation antiaromatase agents that are commercially available include two nonsteroidal preparations, anastrozole and letrozole, and a steroid agent, exemestane. Anastrozole and letrozole are often referred to as aromatase inhibitors, whereas exemestane is called an aromatase inactivator; all three will be collectively referred to as aromatase inhibitors in this document because the clinical significance of the difference between the steroidal and nonsteroidal structures and their mechanisms of action has not been elucidated. All three agents have been shown to be superior to megestrol acetate as second-line hormonal therapy, with better disease control and/or decreased toxicity.¹⁹⁻²⁴ More recently, large randomized trials have compared anastrozole and letrozole, respectively, to tamoxifen.²⁵⁻²⁷ In patients with metastatic breast cancer, both anastrozole and letrozole demonstrated equivalent or improved efficacy when compared with tamoxifen, with similar or decreased toxicity. These studies have led to the approval of both anastrozole and letrozole as first-line hormonal therapy for postmenopausal patients with metastatic breast cancer. A smaller, randomized, phase II trial comparing exemestane with tamoxifen in women with metastatic disease also suggested superiority for the aro-

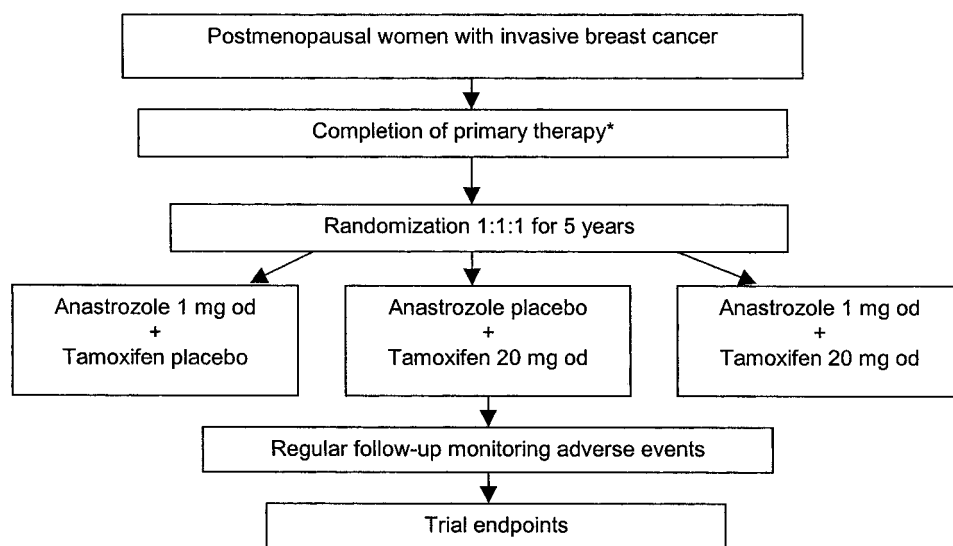


Fig 1. ATAC trial design. *Surgery ± radiotherapy ± chemotherapy. (Patients may start trial therapy while still receiving radiotherapy.)

matase inhibitor;²⁸ a larger phase III extension of that trial comparing exemestane and tamoxifen is underway. As a result of the trials detailed above, the third-generation aromatase inhibitors are established as either first- or second-line therapy for postmenopausal women with hormone receptor–positive, metastatic breast cancer.

Most trials of the third-generation aromatase inhibitors have been conducted in women with metastatic breast cancer, and the median duration of therapy in these trials is consistently less than 12 months.¹⁹⁻²⁸ There is no published experience describing the side effect profile associated with prolonged administration of the third-generation aromatase inhibitors. In particular, there are no data available concerning the tolerability of a 5-year course of these agents.

AROMATASE INHIBITORS IN THE ADJUVANT SETTING

Given the importance of hormonal therapy in the management of patients with early-stage breast cancer and the promising activity of the third-generation aromatase inhibitors in the advanced disease setting, a series of clinical trials was initiated evaluating these agents in the adjuvant setting (Appendix 1). Two small studies had previously used aminoglutethimide in the adjuvant setting, demonstrating the feasibility of aromatase inhibition in the adjuvant setting.²⁹⁻³¹ The current generation of adjuvant hormonal trials with aromatase inhibitors uses the following three distinct study designs in postmenopausal women: (1) randomized comparisons of tamoxifen versus a third-generation aromatase inhibitor; (2) randomized comparisons of a third-generation aromatase inhibitor versus placebo after the completion of 5 years of tamoxifen; and (3) randomized

comparisons of sequential therapy (tamoxifen followed by a third-generation aromatase inhibitor or a third-generation aromatase inhibitor followed by tamoxifen) administered for a total of 5 years versus single-agent therapy for 5 years. An additional question addressed in the ATAC trial is the efficacy of the concurrent use of a combination of tamoxifen and an aromatase inhibitor (anastrozole). The preliminary results from the first of these trials were reported at the 2001 San Antonio Breast Conference.

THE ATAC TRIAL

The ATAC trial is a large, multinational, double-blind, placebo-controlled, randomized trial comparing standard adjuvant therapy of 5 years of tamoxifen versus 5 years of anastrozole versus 5 years of both agents given in combination in postmenopausal patients (Fig 1).³²

Accrual of 9,366 postmenopausal women with hormone receptor–positive or unknown tumors to the trial began in July 1996 and ended in March 2000. A total of 381 centers participated in the study in 21 different countries. The primary study end points were disease-free survival (defined as locoregional recurrence, distant recurrence, new primary breast cancer, or death from any cause) and safety/tolerability. Secondary end points included the incidence of second non–breast cancer primaries, time to distant recurrence, and overall survival. Of note, the end points of distant recurrence and overall survival are incorporated into the aggregated primary end point and, as such, have an impact on the statistical considerations and should be considered secondary analyses. A subset analysis of patients with known hormone receptor–positive tumors was part of the

Table 1. Table of First Events in ITT Population (Based on December 2001 presentation)

	No. of Patients		
	Anastrozole (n = 3,125)	Tamoxifen (n = 3,116)	Combination (n = 3,125)
First event	317	379	383
Recurrence			
Locoregional	67	83	81
Distant	156	181	202
Contralateral			
Invasive	9	30	23
DCIS	5	3	5
Deaths*	—	—	—

*Approximately 600 total deaths across the three arms, of which approximately 60% are because of breast cancer. A formal survival analysis has not been performed (J. Purvis, personal communication, April 2002).

initial planned analytic strategy. The predefined analyses were designed to assess if anastrozole was equivalent or superior to tamoxifen and to determine whether the combination of tamoxifen plus anastrozole was superior to tamoxifen. The first analysis was scheduled to occur when there had been a total of 1,056 events for the disease-free survival end point. Events were defined as locoregional or distant recurrence, contralateral invasive or noninvasive breast cancers, or death from any cause.

As expected in a large randomized trial, patient characteristics were well balanced across the three treatment arms. Mean age was 64 years, tumor size was 2 cm or less in approximately 63% of patients, and about one third of patients on each of the arms had positive lymph nodes. Approximately 23% of patients had tumors that were characterized as poorly differentiated; the remaining patients had well-differentiated, moderately differentiated, or unclassified tumors. Approximately 48% of patients had undergone a mastectomy, and 95% had an axillary lymph node dissection. Radiotherapy was administered to approximately 62% of patients, whereas adjuvant chemotherapy was administered to approximately 21%.

At the time of study analysis before the 2001 San Antonio Breast Conference, there were 1,079 events. Of these events, 766 occurred in the known hormone receptor-positive population. The median duration of therapy was 30.7 months, and the median follow-up was 33.3 months. There were 317 events on the anastrozole arm, 379 on the tamoxifen arm, and 383 on the combination arm (Table 1). A statistically significant improvement was detected in disease-free survival favoring anastrozole compared with tamoxifen (hazard ratio, 0.83; 95% confidence interval, 0.71 to 0.96; $P = .013$). There was no difference in disease-free survival between tamoxifen and the combination (hazard ratio, 1.02; 95% confidence interval, 0.88 to 1.18; $P = .77$).

Table 2. Adverse Events

	% of Patients		P
	Anastrozole	Tamoxifen	
Hot flashes	34.3	39.7	< .0001
Musculoskeletal disorders	27.8	21.3	< .0001
Fatigue/tiredness (asthenia)	15.6	15.1	.5415
Mood disturbances	15.5	15.2	.6900
Nausea and vomiting	10.5	10.2	.7005
Weight gain*	9.2	11.0	.0207
Fractures	5.9	3.7	< .0001
In spine, hip, wrist	2.2	1.5	.0299
Vaginal bleeding	4.5	8.2	< .0001
Vaginal discharge	2.8	11.4	< .0001
Endometrial cancer	0.1	0.5	.0267
Cataracts	3.5	3.7	.5427
Ischemic cardiovascular disease	2.5	1.9	.1391
Ischemic cerebrovascular events	1.0	2.1	.0006
Venous thromboembolic events	2.1	3.5	.0006
DVT events	1.0	1.7	.0183

Abbreviation: DVT, deep venous thrombosis.

*Ten percent gain in body weight from baseline to year 2 (non-pre-defined adverse event).

A formal survival analysis has yet to be performed and will be triggered by a predefined number of deaths in the study population (J. Purvis, personal communication, April 2002).

Adverse events associated with tamoxifen and anastrozole are listed in Table 2. Hot flashes, weight gain of $\geq 10\%$ at 2 years, vaginal bleeding, vaginal discharge, endometrial cancer, ischemic cerebrovascular events, and venous thromboembolic events were all significantly more common with tamoxifen than with anastrozole. Musculoskeletal disorders, fractures (all sites), and fractures in spine, hip, and wrist were all more common in women on anastrozole compared with tamoxifen. No data were provided concerning toxicity on the combination arm. As can be seen in Table 2, the absolute incidence of most life-threatening complications (ie, cancer, thromboembolic events) is quite low, and the absolute differences between the two arms are generally small.

TECHNOLOGY ASSESSMENT PROCESS

We define technology assessment as a process for determining whether a procedure is appropriate for broad-based conventional use in clinical practice. The process used in this technology assessment followed defined ASCO policies and procedures; these policies and procedures are similar to those published elsewhere.^{33,34} Pertinent information from the published literature was retrieved and reviewed for the creation of this assessment. Computerized literature searches of MEDLINE (National Library of Medicine, Bethesda, MD) were performed through January 2002.

Abstracts presented at ASCO annual meetings were also included. Key words/phrases included in the literature search were: breast neoplasms, breast cancer, mammary neoplasms, randomized trials, phase, meta-analysis, aromatase, exemestane, anastrozole, letrozole, megestrol acetate, antiaromatase, Arimidex, triazole, Femara, and Aromasin. Limits included English language and human studies. In addition, the ASCO Health Services Research Department staff contacted representatives of American, Canadian, and European cooperative groups concerning ongoing adjuvant trials with aromatase inhibitors. Each of the three pharmaceutical companies that manufactures one of the commercially available aromatase inhibitors was also contacted and given an opportunity to provide the expert panel with unpublished data and the design of ongoing or planned trials.

Panel Composition

The panel for this technology assessment was comprised of core members from the ASCO Health Services Research Committee and ad hoc members who provided needed content expertise in relevant disciplines (medical oncology, radiation oncology, and surgical oncology). Both academic and community physicians were represented from the United States, Canada, and Europe. Representatives from the nonmedical community (patient/advocacy groups) also participated in the deliberations of the panel at the invitation of ASCO. (A list of the panel members can be found in Appendix 2). On January 30, 2002, the panel met for a full day to review the available evidence. They chose to address 13 specific questions, as detailed below.

Disclosure of Conflict of Interest

All members of the Working Group complied with ASCO policy on conflict of interest, which requires disclosure of any interest (financial or otherwise) that might be construed as constituting an actual, potential, or apparent conflict. Members completed ASCO's disclosure form and were asked to reveal ties to companies developing products that might potentially be affected by promulgation of the technology assessment report. Information was requested regarding employment, consultant status, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees (Appendix 2).

QUESTIONS

The panel addressed the following questions to provide guidance to physicians and patients on the use of third-generation aromatase inhibitors in the adjuvant setting (see Appendix 3 for complete questions and answers):

1. What are the overall clinical implications of the findings from the ATAC trial for the adjuvant treatment of postmenopausal women with operable breast cancer?

Early results from the ATAC trial indicate that anastrozole produces a statistically significant improvement in disease-free survival compared with tamoxifen at a median follow-up of 33 months. Based on these preliminary findings and the experience with aromatase inhibitors from trials in the metastatic setting, some clinicians and patients may consider the substitution of anastrozole or other aromatase inhibitors for tamoxifen as adjuvant therapy. In interpreting the results of the ATAC trial, there are several important issues that should be considered:

- Tamoxifen is known to be effective in improving recurrence-free and overall survival when used as adjuvant hormonal therapy in patients with early-stage breast cancer and remains the standard therapy. Although tamoxifen is not devoid of side effects, there is extensive, long-term follow-up data on patients treated with tamoxifen and a clearer understanding of the risks associated with tamoxifen therapy.

- Except for musculoskeletal disorders and fractures, the short-term side effects with anastrozole seen in the ATAC trial seemed to be comparable with or fewer than those seen with tamoxifen; however, there are no data available concerning the toxicity of any of the aromatase inhibitors administered for extended periods (ie, 5 years or more). There are no data concerning the late effects (after discontinuation of therapy) of a prolonged course of an aromatase inhibitor. The long-term effects of profound estrogen deprivation as seen with the third-generation aromatase inhibitors are unknown. In particular, concern has been raised that the adverse bone effects seen in the ATAC trial could become more common and/or severe with further follow-up.

- Although the difference in disease-free survival between anastrozole and tamoxifen is statistically significant, the absolute difference in the percentage of patients who were disease-free at follow-up is 2.02% (89.86% v 87.84%). The absolute difference in distant and locoregional recurrence rates between the two arms is 1.33% (7.14% v 8.47%). The absolute difference in distant recurrence is 0.80% (5.00% v 5.80%).

- A 5-year course of treatment is required to see the full benefits of tamoxifen therapy.¹ With a median follow-up of only 33 months in the ATAC trial, the full benefits of treatment with tamoxifen have yet to be realized. Despite the encouraging preliminary results, it is conceivable that 5 years of anastrozole could be inferior to 5 years of tamoxifen. Although this argument can be used in interpreting the preliminary results of any trial, the valid concern is particularly important when the known benefits of one of the treatments require prolonged therapy (ie, 5 years). Given the

compelling survival advantage of a 5-year course of tamoxifen when compared with no adjuvant hormonal therapy, there is a genuine need for more mature data.

- There are no reported differences in survival between the two arms.

- The study continues to follow and to provide treatment to patients who are on the tamoxifen + placebo and anastrozole + placebo arms in a blinded fashion.

- The ATAC study design does not address the question of how long anastrozole should be continued for optimal therapeutic benefit.

- The ATAC trial does not study the sequence of tamoxifen for 2, 3, or 5 years followed by an aromatase inhibitor. This strategy is under active investigation in other trials.

- The data from the ATAC trial have not yet been subjected to rigorous peer review.

Panel consensus. The panel is of the unanimous opinion that the results of the ATAC trial should be considered preliminary and that a 5-year course of tamoxifen remains the standard adjuvant hormonal treatment for women with hormone receptor-positive breast cancer. The panel looks forward to updated data from the ATAC trial and other trials addressing questions about the third-generation aromatase inhibitors in the adjuvant setting. The panel encourages appropriate patients to consider participation in ongoing randomized trials.

2. Are all aromatase inhibitors equivalent? The third-generation aromatase inhibitors are highly selective in their ability to decrease aromatase activity. The three agents that are available in the United States, anastrozole, letrozole, and exemestane, differ in chemical structure, metabolic products, and perhaps the degree to which they suppress aromatase activity.³⁵ The clinical significance of these differences is not known, and the available literature does not suggest that these differences are large.

In the metastatic setting, all three aromatase agents are effective in the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer. Both anastrozole and letrozole are approved for first- and second-line treatment of hormone receptor-positive breast cancer based on the results of large randomized studies. Exemestane is approved for second-line treatment, and a phase III trial comparing exemestane with tamoxifen is actively accruing patients. In addition, there are several studies ongoing that compare the aromatase inhibitors with one another and with other agents. Preliminary data are available from a trial comparing letrozole to anastrozole in 713 postmenopausal women with locally advanced or metastatic breast cancer, all of whom had received prior antiestrogen therapy. This study demonstrated no difference in clinical

benefit, time to progression, time to treatment failure, or duration of response, though there was an improvement in overall response rate for letrozole in comparison with anastrozole (19.1% v 12.3%, $P = .014$).³⁶

In the adjuvant setting, the only reported treatment data are with anastrozole. Adjuvant trials are underway with both letrozole and exemestane, as well as additional studies with anastrozole.

Panel consensus. At the present time, the only available data using the third-generation aromatase inhibitors in the adjuvant setting are with anastrozole. The three commercially available agents seem to be generally comparable in the metastatic setting. Although extrapolation from the ATAC trial to the use of other aromatase inhibitors is reasonable, direct data are lacking. Based on the extensive body of clinical trial data from the advanced disease setting, the effects of the three available aromatase inhibitors would be expected to be similar. At this time, however, the only evidence in the adjuvant setting involves anastrozole. Furthermore, the panel notes that closely related agents with similar mechanisms of action may have different toxicity profiles. For this reason, the panel considers anastrozole the preferred agent if an aromatase inhibitor is used in the adjuvant setting.

3. What is the role of aromatase inhibitors in women who have already started taking tamoxifen in the adjuvant setting? Data do not currently support the use of third-generation aromatase inhibitors in women who have had more than a minimal course of tamoxifen. A small trial comparing a 5-year course of tamoxifen with 3 years of tamoxifen followed by a 2-year course of aminoglutethamide demonstrated a statistically significant improvement in survival for the sequential arm.³¹ Ongoing clinical trials are comparing a 5-year course of tamoxifen with a 2- to 3-year course of tamoxifen followed by a 2- to 3-year course of a third-generation aromatase inhibitor. Although tamoxifen is generally well tolerated, some women are unable to tolerate it as a result of non-life-threatening symptoms (eg, hot flashes) or life-threatening complications (eg, thromboembolic events). In the ATAC trial, there were statistically significant differences favoring anastrozole for venous thromboembolic events, ischemic cerebrovascular events, vaginal bleeding, and endometrial cancer. These differences are consistent with the experience in trials comparing tamoxifen with an aromatase inhibitor in the metastatic setting.^{27,37} Hot flashes were significantly less common in women on the anastrozole arm in the ATAC trial. This difference is not, however, consistent with the experience in the metastatic setting in which hot flashes are somewhat more common in women on aromatase

inhibitors than in those on tamoxifen.^{27,37} Randomized trials have identified a variety of agents that can be useful in decreasing the frequency and severity of hot flashes in women on tamoxifen.³⁸

Panel consensus. There are currently no data to support substituting an aromatase inhibitor for tamoxifen as adjuvant therapy in a woman who has already started a course of tamoxifen. Outside of a clinical trial, women who are taking adjuvant tamoxifen and have not experienced significant side effects should continue tamoxifen therapy for a total of 5 years. Women experiencing intolerable side effects or who have developed a complication attributable to tamoxifen (ie, thromboembolic event, persistent vaginal bleeding) may consider switching to an aromatase inhibitor, though the benefit of such a strategy is unproven and the optimal duration of such therapy is not known.

4. Is there a role for an aromatase inhibitor in women who have completed a 5-year course of tamoxifen and are disease-free? There are no data concerning the use of aromatase inhibitors in women who have completed a 5-year course of tamoxifen. Trials evaluating the benefits of the third-generation aromatase inhibitors, in comparison with placebo, in patients who have completed a 5-year course of tamoxifen and are free of recurrent disease are ongoing.

Panel consensus. Patients who have completed a 5-year course of tamoxifen and are free of disease should not receive an aromatase inhibitor unless such therapy is part of a clinical trial.

5. If an aromatase inhibitor is used in the adjuvant setting, for how long should it be administered? Unlike the situation with tamoxifen, there are no trials that have addressed the issue of the duration of aromatase inhibition. In the ATAC trial, anastrozole is administered for 5 years. The results, however, were reported with a median duration on therapy of 31 months and median follow-up of 33 months. Because accrual did not begin until 1996, only a small proportion of the study population could have completed a 5-year course of treatment at the time the data were analyzed for the initial San Antonio presentation. Five years of treatment with tamoxifen is currently considered the optimal duration of therapy. It is not clear that this optimal treatment duration can be extrapolated to treatment with anastrozole or other aromatase inhibitors. The panel notes that studies evaluating the role of ovarian suppression in premenopausal women have shown benefit when this treatment is administered for 2, 3, or 5 years, with an optimal duration of therapy yet to be defined.

Panel consensus. Patients initiating aromatase inhibitor therapy in the adjuvant setting should be treated for at least 2 to 3 years based on the present experience

from the ATAC trial. At this time, neither the efficacy nor the toxicity of a longer duration of therapy has been established. Clinicians and patients should expect to review the question of aromatase inhibitor duration as more data become available over the next several years.

6. What is the role of aromatase inhibitors in women who are premenopausal at the time of initiation of adjuvant hormonal therapy? Single-agent therapy with aromatase inhibitors has no established role in premenopausal women with breast cancer. For reasons previously described, these agents are unlikely to sufficiently suppress estrogen levels to be of clinical benefit in women with functioning ovaries. In women with metastatic breast cancer, there are phase II trials demonstrating activity of combination regimens using luteinizing hormone-releasing hormone (LHRH) agonists in combination with aromatase inhibitors.^{39,40} Adjuvant trials are also planned to evaluate the role of LHRH agonists in combination with an aromatase inhibitor. The effectiveness and safety of such regimens as adjuvant therapy in premenopausal women with breast cancer is unknown.

Panel consensus. Aromatase inhibitors are contraindicated in premenopausal women with functioning ovaries. Such therapy has not been evaluated and is likely to be ineffective. The use of LHRH agonists plus an aromatase inhibitor or oophorectomy plus an aromatase inhibitor in the adjuvant setting has not been studied and is not recommended outside of a clinical trial.

7. What is the role of aromatase inhibitors in women who are premenopausal at diagnosis and who experience interruption of ovarian function from chemotherapy? The ATAC trial was conducted in women who were postmenopausal at the time of diagnosis, but many premenopausal women who receive adjuvant chemotherapy experience temporary or permanent cessation of ovarian function. The likelihood of disruption of ovarian function is related to the specific chemotherapy regimen and patient age.⁴¹ A substantial number of women who experience disruption of ovarian function will ultimately have a resumption of ovarian function after a number of months, or, in some cases, after a more prolonged interval. Resumption of ovarian function is more common in women who are younger than 40 to 45 at the time of chemotherapy administration and in those who receive certain regimens (ie, doxorubicin/cyclophosphamide for four cycles).^{42,43} The resumption of ovarian function in a woman on an aromatase inhibitor would, in all likelihood, render the therapy ineffective.

Panel consensus. The panel cautions against the use of adjuvant aromatase inhibitors in women who are premenopausal at the time of diagnosis and have experienced a disruption in ovarian function. The panel has

particular concerns about the use of aromatase inhibitors in women who have a substantial probability of resuming ovarian function.

8. What is the role of aromatase inhibitors in patients with ductal carcinoma-in-situ (DCIS)? There was a statistically significant decrease in contralateral cancers in women on anastrozole in comparison with tamoxifen on the ATAC trial, but there are presently no data concerning the benefits of an aromatase inhibitor in patients with DCIS. Ongoing trials are evaluating the role of third-generation aromatase inhibitors in patients with DCIS, and future studies are planned.

Panel consensus. Women with DCIS should not receive an aromatase inhibitor outside of the context of a clinical trial.

9. What is the role of aromatase inhibitors in women wishing to lower their risk of developing breast cancer? There are no clinical data concerning the role of aromatase inhibitors in women wishing to lower their risk of developing breast cancer. At this time, tamoxifen is the only agent that has been shown in clinical trials to reduce the risk of subsequent invasive breast cancer for women at increased risk who have not previously had breast cancer.^{44,45} In addition, tamoxifen is the only agent approved by the Food and Drug Administration to lower a woman's risk of developing breast cancer.⁸ The decrease in contralateral cancers seen on the anastrozole arm of the ATAC trial does not provide sufficient evidence to use an aromatase inhibitor to decrease breast cancer risk in an unaffected woman outside of a clinical trial. Ongoing studies are proposed for evaluating the safety and efficacy of third-generation aromatase inhibitors in the setting of risk reduction.

Panel consensus. Women with an increased risk of developing breast cancer should not receive an aromatase inhibitor to decrease risk outside of a clinical trial.

10. What is the role of aromatase inhibitors in women whose tumors have negative hormone receptors? There is overwhelming evidence that adjuvant hormonal therapy is effective only in patients with positive estrogen and/or progesterone receptors.¹ Aromatase inhibitors have not been evaluated in the adjuvant setting in women whose tumors lack hormone receptors.

Panel consensus. Women whose tumors are known to be hormone receptor–negative should not receive an aromatase inhibitor as adjuvant therapy.

11. What is the role of aromatase inhibitors in patients with certain biologic features, such as HER-2/neu positivity? Several retrospective studies have suggested that tamoxifen may be less beneficial in patients with HER-2–positive cancers.^{46–48} There are, however, conflicting reports

in the literature.^{49,50} Many of the studies have methodologic limitations because they are retrospective, involve small numbers of patients, and use inconsistent methods for defining HER-2 status. The National Institutes of Health Consensus Conference recommended that all women with hormone receptor–positive cancers receive treatment with adjuvant tamoxifen and cautioned against using HER-2/neu as a factor in making decisions about adjuvant therapy.⁹

A recent randomized trial compared preoperative tamoxifen with preoperative letrozole in postmenopausal women who were ineligible for breast conservation at diagnosis.⁵¹ Among 39 women with HER-2–positive tumors, the response rate to letrozole was 69%, compared with 17% with tamoxifen. In 36 women whose tumors were confirmed to be estrogen receptor–positive as well as HER-1- and/or HER-2–positive, the response rate to letrozole was 88%, compared with 21% with tamoxifen. Although these findings are of great interest, they are derived from a small patient cohort and with only 4 months of preoperative treatment. Ongoing studies are attempting to replicate these results.

Panel consensus. The panel recommends against the use of HER-2 status in making decisions about adjuvant hormonal therapy. The clinical data to support the use of HER-2 status in this setting are inadequate.

12. What is the role of aromatase inhibitors in patients with a relative or absolute contraindication to the initiation of adjuvant tamoxifen? Tamoxifen is associated with an increased risk of thromboembolic disease and cerebrovascular events. For this reason, many physicians are concerned about the use of tamoxifen in women with a history of a thrombotic event or cerebrovascular disease. The risks associated with tamoxifen therapy in these patients are uncertain. In the ATAC trial, anastrozole was associated with a lower risk of thromboembolic disease and ischemic cerebrovascular events. These data are consistent with findings from studies in the other settings.

Panel consensus. The panel considers it reasonable to initiate adjuvant hormonal therapy with an aromatase inhibitor in postmenopausal women who are thought to have a relative or absolute contraindication to adjuvant tamoxifen. Physicians and patients should carefully consider the significance of any relative contraindication in light of the proven benefits of adjuvant tamoxifen.

13. What is the role of aromatase inhibitors in patients who have developed hormone receptor–positive invasive breast cancer while taking either tamoxifen or raloxifene? Tamoxifen is increasingly being used to lower a woman's risk of developing breast cancer and as treatment for DCIS. Hormone receptor–positive invasive tumors that develop while a woman is taking tamoxifen are presumably insen-

sitive to tamoxifen. Although there are no data concerning the use of aromatase inhibitors in this specific situation, the aromatase inhibitors are effective in women with metastatic breast cancer who have developed disease progression on tamoxifen.¹⁹⁻²⁴ Raloxifene is also being used increasingly for the prevention and treatment of osteoporosis. Although raloxifene has been reported to lower a woman's risk of developing breast cancer,⁵² it is not currently approved for this indication.⁴⁴ The optimal adjuvant hormonal therapy for a woman who develops a hormone receptor–positive cancer while taking raloxifene is unknown. Preclinical data strongly suggest cross-resistance between tamoxifen and raloxifene.⁵³ Such data would suggest that tamoxifen may not be an effective adjuvant treatment for a patient whose tumor arises while on raloxifene.

Panel consensus. While recognizing the paucity of direct data, the panel considers it reasonable to use adjuvant hormonal treatment with an aromatase inhibitor in postmenopausal women with hormone receptor–positive cancers who had been taking tamoxifen or raloxifene at diagnosis and who are, therefore, considered clinically resistant to these antiestrogen agents.

REMARKS

This technology assessment seeks to guide patients and physicians on the use of aromatase inhibitors in the adjuvant setting. Individual health care providers and their patients will need to come to their own conclusions, with careful consideration of all of the available data. The panel recognizes that there is an inherent tension between the desire to provide patients with the most up-to-date treatment approaches while at the same time exerting appropriate caution that such new treatments are adequately evaluated. The panel was influenced by the compelling, extensive, and long-term data available on tamoxifen. Overall, the panel

considers the results of the ATAC trial and the extensive supporting data to be very promising but insufficient to change the standard practice at this time (May 2002). The panel recommends that physicians discuss the available information with patients, and, in making a decision, acknowledge that treatment approaches can change over time. Additional data will be available in the coming years concerning the role of aromatase inhibitors in the adjuvant setting. In particular, it will be important to see longer follow-up data, survival analyses, and the results from confirmatory studies, as well as those studies testing sequential use of aromatase inhibitors after tamoxifen. It is hoped that there will continue to be improvements in adjuvant hormonal therapy, leading to benefits for women with breast cancer in both overall survival and quality of life.

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APPENDICES 1, 2, and 3

The appendices listing selected adjuvant breast cancer trials, the ASCO aromatase inhibitors expert panel, and the summary of the panel's deliberations are available online at www.jco.org.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group: Tamoxifen for early breast cancer: An overview of the randomised trials. *Lancet* 351:1451-1467, 1998
2. Fisher B, Costantino J, Redmond C, et al: A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med* 320:479-484, 1989
3. Stewart HJ: The Scottish trial of adjuvant tamoxifen in node-negative breast cancer: Scottish Cancer Trials Breast Group. *J Natl Cancer Inst Monogr* 11:117-120, 1992
4. Ferno M, Stal O, Baldetorp B, et al: Results of two or five years of adjuvant tamoxifen correlated to steroid receptor and S-phase levels: South Sweden Breast Cancer Group, and South-East Sweden Breast Cancer Group. *Breast Cancer Res Treat* 59:69-76, 2000
5. Fisher B, Dignam J, Bryant J, et al: Five versus more than five years of tamoxifen for lymph node-negative breast cancer: Updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst* 93:684-690, 2001
6. Fisher B, Dignam J, Bryant J, et al: Five versus more than five years of tamoxifen therapy for breast cancer patients with negative

lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst* 88:1529-1542, 1996

7. Braithwaite RS, Law J, Chlebowski RT, et al: A meta-analysis of vascular and neoplastic events associated with tamoxifen. *Soc Med Decision Making* 22:198, 2000 (abstr)

8. Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 90:1371-1388, 1998

9. Anonymous: National Institutes of Health Consensus Development Conference statement: Adjuvant therapy for breast cancer. November 1-3, 2000. *J Natl Cancer Inst Monogr* 30:5-15, 2001

10. Early Breast Cancer Trialists' Collaborative Group: Ovarian ablation in early breast cancer: Overview of the randomised trials. *Lancet* 348:1189-1196, 1996

11. Davidson NE: Ovarian ablation as adjuvant therapy for breast cancer. *J Natl Cancer Inst Monogr* 30:67-71, 2001

12. Anonymous: Adjuvant ovarian ablation versus CMF chemotherapy in premenopausal women with pathological stage II breast carcinoma: The Scottish trial. Scottish Cancer Trials Breast Group and ICRF Breast Unit, Guy's Hospital, London. *Lancet* 341:1293-1298, 1993

13. Ejlertsen B, Dombrowsky P, Mouridsen HT, et al: Comparable effect of ovarian ablation and CMF chemotherapy in premenopausal hormone receptor positive breast cancer patients. *Proc Am Soc Clin Oncol* 18:66a, 1999 (abstr 248)

14. Jonat W, on behalf of the ZEBRA (Zoladex Early Breast Cancer Research Association) Trialists' Group: Zoladex vs CMF as adjuvant therapy in pre-/perimenopausal early (node positive) breast cancer: Preliminary efficacy—QOL and BMD results from the ZEBRA study. *Breast Cancer Res Treat* 64:29, 2000 (abstr 13)

15. Jakesz R, Hausmaninger H, Samonigg H, et al: Comparison of adjuvant therapy with tamoxifen and goserelin vs CMF in premenopausal stage I and II hormone-responsive breast cancer patients: Four-year results of Austrian Breast Cancer Study Group Trial 5. *Proc Am Soc Clin Oncol* 18:67a, 1999 (abstr 250)

16. Roche HH, Kerbrat P, Bonnetterre J, et al: Complete hormonal blockage versus chemotherapy in premenopausal early-stage breast cancer patients with positive hormone-receptor and 1-3 node-positive tumor, results of the FASG 06 trial. *Proc Am Soc Clin Oncol* 19:72a, 2000 (abstr 279)

17. Goss PE, Strasser K: Aromatase inhibitors in the treatment and prevention of breast cancer. *J Clin Oncol* 19:881-894, 2001

18. Geisler J: In vivo inhibition of aromatization by exemestane, a novel irreversible aromatase inhibitor, in postmenopausal breast cancer patients. *Clin Cancer Res* 4:2089-2093, 1998

19. Buzdar A: Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: Results of overview analysis of two phase III trials—Arimidex Study Group. *J Clin Oncol* 14:2000-2011, 1996

20. Buzdar AU: 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

21. Jonat W, Howell A, Blomqvist C, et al: A randomised trial comparing two doses of the new selective aromatase inhibitor anastrozole (Arimidex) with megestrol acetate in postmenopausal patients with advanced breast cancer. *Eur J Cancer* 32A:404-412, 1996

22. Dombrowsky P, Smith I, Falkson G, et al: Letrozole, a new oral aromatase inhibitor for advanced breast cancer: Double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 16:453-461, 1998

23. Buzdar A: 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

24. Kaufmann M, Bajetta E, Dirix LY, et al: Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: Results of a phase III randomized double-blind trial: The Exemestane Study Group. *J Clin Oncol* 18:1399-1411, 2000

25. Bonnetterre J: Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: Results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol* 18:3748-3757, 2000

26. Nabholz JM: 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. *Semin Oncol* 27:11-18, 2000

27. Mouridsen H: 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* 18:3758-3767, 2000

28. Dirix LY, Piccart MJ, Lohrisch C, et al: Efficacy of and tolerance to exemestane versus tamoxifen in 1st line hormone therapy of postmenopausal metastatic breast cancer patients: A European Organization for the Research and Treatment of Cancer (EORTC Breast Group) phase II trial with Pharmacia and Upjohn. *Proc Am Soc Clin Oncol* 20:29a, 2001 (abstr 114)

29. Powles TJ, Coombes RC, Smith IE, et al: A double blind randomised clinical trial of adjuvant aminoglutethimide versus placebo given to post menopausal patients with histologically confirmed stage II breast cancer. *Breast Cancer Res Treat* 7:S37-S40, 1986

30. Jones AL, Powles TJ, Law M, et al: Adjuvant aminoglutethimide for postmenopausal patients with primary breast cancer: Analysis at 8 years. *J Clin Oncol* 10:1547-1552, 1992

31. Boccardo F: Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: Results of an Italian cooperative study. *J Clin Oncol* 19:4209-4215, 2001

32. Baum M, on behalf of the ATAC Trialists' Group: The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in post-menopausal women. *Breast Cancer Res Treat* 69:210, 2001 (abstr 8)

33. American Society of Clinical Oncology: Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. *J Clin Oncol* 14:671-679, 1996

34. American Society of Clinical Oncology: Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. *J Clin Oncol* 14:2843-2877, 1996

35. 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

36. 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* 21:34a, 2002 (abstr 131)

37. Bonnetterre J: Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer* 92:2247-2258, 2001

38. Loprinzi CL, Zahasky KM, Sloan JA, et al: Tamoxifen-induced hot flashes. *Clin Breast Cancer* 1:52-56, 2000

39. Celio L, Martinetti A, Ferrari L, et al: Premenopausal breast cancer patients treated with a gonadotropin-releasing hormone analog alone or in combination with an aromatase inhibitor: A comparative endocrine study. *Anticancer Res* 19:2261-2268, 1999
40. Forward D, Cheung K, Jackson L, et al: Combined use of goserelin and anastrozole in premenopausal women with metastatic breast cancer. *Proc Am Soc Clin Oncol* 19:147a, 2000 (abstr 582)
41. Burstein HJ, Winer EP: Primary care for survivors of breast cancer. *N Engl J Med* 343:1086-1094, 2000
42. Burstein HJ, Winer EP: Reproductive issues, in Harris JR, Lippman MR, Morrow M, et al (eds): *Diseases of the Breast* (ed 2). New York, NY, Lippincott, 2000, pp 1051-1059
43. 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
44. Chlebowski RT, Collyar DE, Somerfield MR, et al: American Society of Clinical Oncology technology assessment on breast cancer risk reduction strategies: Tamoxifen and raloxifene. *J Clin Oncol* 17:1939-1955, 1999
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. Nordenskjöld B, Hatschek T, Källström A-C, et al: Results of prolonged adjuvant tamoxifen therapy of breast cancer correlated to steroid receptor, S-phase and ERBB2 levels. *Proc Am Soc Clin Oncol* 18:70a, 1999 (abstr 263)
47. Bianco AR, DeLaurentiis M, Carlomagno C, et al: HER2 overexpression predicts adjuvant tamoxifen (TAM) failure for early breast cancer (EBC): Complete data at 20 yr of the Naples GUN randomized trial. *Proc Am Soc Clin Oncol* 19:75a, 2000 (abstr 289)
48. Carlomagno C, Perrone F, Gallo C, et al: c-erb B2 overexpression decreases the benefit of adjuvant tamoxifen in early-stage breast cancer without axillary lymph node metastases. *J Clin Oncol* 14:2702-2708, 1996
49. Elledge RM, Green S, Ciocca D, et al: HER-2 expression and response to tamoxifen in estrogen receptor-positive breast cancer: A Southwest Oncology Group study. *Clin Cancer Res* 4:7-12, 1998
50. Berry DA, Muss HB, Thor AD, et al: HER-2/neu and p53 expression versus tamoxifen resistance in estrogen receptor-positive, node-positive breast cancer. *J Clin Oncol* 18:3471-3479, 2000
51. Ellis MJ: 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
52. Cummings SR, Duong T, Kenyon E, et al: Serum estradiol level and risk of breast cancer during treatment with raloxifene. *JAMA* 287:216-220, 2002
53. Jordan VC, Gapstur S, Morrow M: Selective estrogen receptor modulation and reduction in risk of breast cancer, osteoporosis, and coronary heart disease. *J Natl Cancer Inst* 93:1449-1457, 2001