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## Evidence-based Series #1-18: Section 1

# The Role of Aromatase Inhibitors in Adjuvant Therapy for Postmenopausal Women with Hormone Receptor-positive Breast Cancer: Guideline Recommendations

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The full Evidence-based Series #1-18 is comprised of 3 sections  
and is available on the CCO website (<http://www.cancercare.on.ca>)

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Section 1: Guideline Recommendations

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## QUESTIONS

In postmenopausal women with early-stage, hormone receptor-positive breast cancer:

1. Compared with adjuvant tamoxifen alone for five years, do adjuvant aromatase inhibitors (anastrozole, letrozole, or exemestane) alone for five years improve clinically meaningful outcomes (disease-free or overall survival)?
2. Compared with adjuvant tamoxifen alone for five years, do adjuvant aromatase inhibitors in sequence with tamoxifen for a total of five years improve clinically meaningful outcomes?
3. Compared with placebo, do aromatase inhibitors after five years of adjuvant tamoxifen therapy improve clinically meaningful outcomes?
4. Compared with tamoxifen or placebo, what are the harms associated with aromatase inhibitors?
5. Compared with tamoxifen, does the efficacy of aromatase inhibitors depend on p185<sup>HER2/neu</sup> glycoprotein expression?

## TARGET POPULATION

These recommendations apply to postmenopausal women with early-stage, hormone receptor-positive breast cancer.

## RECOMMENDATIONS AND KEY EVIDENCE

### ***Recommended treatment options for postmenopausal women with hormone receptor-positive early breast cancer:***

Available trial evidence supports six adjuvant hormonal therapy options, summarized across four recommendations directly below, for the treatment of the target population. At present, there are no data available to compare between the various adjuvant aromatase inhibitor strategies. Rather, the use of adjuvant aromatase inhibitors has been compared to the standard of five years of adjuvant tamoxifen. Therefore, the decision about which therapy option to consider for patients beginning hormonal therapy should be made on an individual patient basis. Key evidence and qualifying statements in support of the recommendations will follow the recommendations and proceed in a similar order.

#### *Recommendations*

<p><b>1. Adjuvant tamoxifen (20 mg daily for five years) remains an acceptable option for the treatment of women with hormone receptor-positive, early-stage breast cancer.</b></p>
<p><b>2. Adjuvant anastrozole (1.0 mg daily for five years) or letrozole (2.5 mg daily for five years) is an acceptable alternative to five years of adjuvant tamoxifen therapy.</b></p>
<p><b>3. Adjuvant tamoxifen (20 mg for two to three years) followed by switching to either adjuvant exemestane (25 mg daily, to a total of five years of hormone therapy) or adjuvant anastrozole (1mg daily, to a total of five years) therapy is also an acceptable alternative to five years of tamoxifen.</b></p>
<p><b>4. Adjuvant letrozole (2.5 mg daily for five years) should be considered for women who have completed five years of adjuvant tamoxifen therapy.</b></p>

#### *Key Evidence*

<ul style="list-style-type: none"> <li>• The Arimidex (anastrozole) or Tamoxifen Alone or in Combination (ATAC) study (n=9,366) compared tamoxifen versus anastrozole versus tamoxifen plus anastrozole. At 68 months (5.7 years), disease-free survival was significantly improved in the anastrozole group versus the tamoxifen group (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.78 to 0.97; p=0.03). The absolute difference in four-year disease-free survival estimates was 2.4% (86.9% with anastrozole versus [vs.] 84.5% with tamoxifen). Additional benefit was seen for time to recurrence (TTR) and time to distant recurrence (TDR) with anastrozole. Overall survival was not significantly different.</li> <li>• The Breast International Group (BIG) 1-98 trial compared letrozole versus tamoxifen in 8,028 women. After a median follow-up of 51 months, patients treated with letrozole had significantly better disease-free survival (primary endpoint) versus those treated with tamoxifen (HR, 0.82; 95% CI, 0.71 to 0.95). There was also significant benefit for TTR and TDR with letrozole. Overall survival was not significantly different.</li> <li>• The Intergroup Exemestane Study (IES) (n=4,742) compared two to three years of tamoxifen followed by exemestane with two to three years of tamoxifen followed by further tamoxifen, each to a total of five years of adjuvant hormone therapy. At 55.7 months median follow-up, the exemestane arm showed significantly improved disease-free survival</li> </ul>
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(HR, 0.76; 95% CI, 0.6 to 0.88) but showed no significant benefit for overall survival. Time to contralateral breast cancer, TTR, and TDR were also significantly improved in women who switched to exemestane. Overall survival was significantly improved only during a subgroup analysis that excluded patients with estrogen receptor-negative disease (HR 0.83, 95% CI 0.69 to 1.00 in favour of switching to exemestane).

- The Italian Tamoxifen Arimidex (anastrozole) (ITA) trial (n=426) compared tamoxifen (20 mg daily) for two or more years followed by further tamoxifen or anastrozole (1.0 mg daily) to a total of five years of adjuvant hormone therapy. At 64 months follow-up, disease-free survival (primary endpoint) was significantly improved in women who switched to anastrozole (HR, 0.57; 95% CI, 0.38 to 0.85). There was no significant difference in overall survival between therapy arms.
- The Austrian Breast and Colorectal Cancer Study Group (ABCSG)-8 and German Adjuvant Breast Cancer Group Arimidex/Nolvadex (ARNO)-95 trials had arms identical to the ITA trial described above. At 28-months median follow-up, a combined analysis showed significantly improved disease-free survival for women who switched to anastrozole (HR, 0.60; 95% CI, 0.44 to 0.81). Distant metastases-free survival was also significantly longer with anastrozole (HR, 0.61; 95% CI, 0.42 to 0.87). There was no significant difference in overall survival.
- A meta-analysis of the ABCSG-8, ARNO-95, and ITA trials found improvements in disease-free survival (HR, 0.59; 95% CI, 0.48 to 0.74;  $p < 0.0001$ ), distant recurrence-free survival (HR 0.61, 95% CI 0.45 to 0.83,  $p = 0.002$ ), and overall survival (HR, 0.71; 95% CI, 0.52 to 0.98;  $p = 0.04$ ) for women who switched to anastrozole.
- The MA.17 study (n=5,187) compared letrozole to placebo following 4.5 to six years of tamoxifen. In an interim analysis at 2.4 years, there was an improvement in disease-free survival favouring letrozole over placebo (HR, 0.57; 95% CI, 0.43 to 0.75;  $p = 0.00008$ ). The estimated four-year, disease-free survival rates were 93% with letrozole versus 87% with placebo (6% absolute difference). The final analysis at 2.5 years continues to show improved rates of recurrence (42% reduction in risk,  $p = 0.0004$ ). In the whole sample, overall survival was not significantly different at either analysis. In the final analysis, overall survival was significantly improved with letrozole in node-positive women (HR, 0.61; 95% CI, 0.38 to 0.98;  $p = 0.04$ ) and in those who received more than five years of tamoxifen (HR, 0.56; 95% CI, 0.33 to 0.97;  $p = 0.04$ ) but not in node-negative women (HR, 1.52; 95% CI, 0.76 to 3.06;  $p = 0.24$ ). Additional abstracts report on data at 4.5 years of median follow-up, at which time 73% of the placebo arm had crossed over to letrozole. Results indicate continued benefit in disease-free survival, but not overall survival, for all patients treated with letrozole including for those who had crossed over.

#### *Qualifying Statements*

- Tamoxifen remains an acceptable therapy option for several reasons. First, to date there has been no overall survival benefit detected for the use of anastrozole or letrozole alone over tamoxifen alone. Though a meta-analysis of trials indicated potential significant benefit in overall survival for switching to anastrozole in comparison to continued tamoxifen, consistent advantage in overall survival has not been observed, particularly for other aromatase inhibitors and in other treatment settings. Second, evidence indicates that patients treated with aromatase inhibitors experience a greater incidence of fractures and a greater loss of lumbar spine and hip bone mineral density (the latter specific to anastrozole; see Recommendation #5).
- Switching to aromatase inhibitors following less than two years of adjuvant tamoxifen therapy:

Women in the IES, ITA, and ABCSG-8/ARNO-95 trials received tamoxifen for at least two years, to three years maximum. Decisions regarding initiating aromatase inhibitors in

those women who have taken tamoxifen for less than two years will have to be individualized, and there is no evidence to support a decision process at this time.

- Use of aromatase inhibitors following five years of adjuvant tamoxifen:  
Patients in the MA.17 trial were treated within three months of stopping tamoxifen and had received tamoxifen for 4.5 to six years. Decisions regarding the initiation of letrozole therapy in women who have been off tamoxifen for more than three months will have to be individualized, based on the time since tamoxifen was discontinued, the prognosis of the patient, and the toxicity of treatment. Similarly, decisions regarding the initiation of letrozole in those who have taken tamoxifen for three to 4.5 years will have to be individualized.
- There is not enough evidence to evaluate the use of exemestane or anastrozole following five years of tamoxifen. The ABCSG-6a trial was developed as a continuation of the ABCSG-6 trial and compared three years of anastrozole or no further treatment following five years of adjuvant tamoxifen. At 60 months median follow-up, this trial, reported in abstract form, found significantly better disease-free survival in patients treated with anastrozole after five years of tamoxifen, with or without aminoglutethimide. No difference in overall survival was reported. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33 trial was amended to compare five years of exemestane or placebo following five years of adjuvant tamoxifen. After the release of the MA.17 results, accrual was halted, the trial was unblinded, and placebo patients were offered exemestane. At 30 months median follow-up, an abstract reported no significant difference in disease-free or overall survival.

**Precautions**

*Recommendations*

**5. Women receiving aromatase inhibitors should be monitored for changes in bone mineral density.**

*Key Evidence*

- Compared with tamoxifen alone, evidence from the ATAC and BIG 1-98 trials indicate a higher incidence of fracture for aromatase inhibitors alone (11.0% vs. 7.7%,  $p < 0.0001$  for anastrozole alone; 8.6% vs. 5.8%,  $p < 0.001$  for letrozole alone), and greater decline in both lumbar spine mineral density (-8.1% [95% CI -10.1% to -6.1%,  $p < 0.0001$ ) and hip bone mineral density (-7.4% [95% CI -9.6% to -5.3%,  $p < 0.0001$ ) for patients treated with anastrozole alone. However, no patient in the ATAC trial with normal bone density at outset developed osteoporosis after five years of anastrozole.
- A Tamoxifen and Exemestane Adjuvant Multicenter (TEAM) International trial substudy also indicated that patients treated with exemestane alone experienced a mean decrease of -0.24 ( $p = 0.02$ ) and -0.25 ( $p = 0.005$ ) for spine and hip bone mineral density in comparison to tamoxifen alone.
- When switching to an aromatase inhibitor after two to three years of tamoxifen was compared to continued tamoxifen, evidence from the IES, and ABCSG-8/ARNO-95 trials indicate a higher incidence in fracture (7.0% vs. 4.9%,  $p = 0.003$  for exemestane; 2% vs. 1%,  $p = 0.015$  for anastrozole), osteoporosis (9.2% vs. 7.2%,  $p = 0.01$  for exemestane), and a greater decline in lumbar spine and hip bone mineral density (-1.4%, 95% CI -0.8% to -1.9%; and -2.7%, 95% CI -2.0% to -3.4%; respectively for exemestane at six months).
- Additional evidence from the MA.17 trial indicates a higher incidence of osteoporosis (8.1% vs. 6.0%,  $p = 0.003$ ) in women placed on letrozole following five years of tamoxifen compared to placebo.

*Qualifying Statements*

- Data on clinical cardiac outcomes and lipid profile changes are mixed. Adverse effects on lipids in some of the aromatase inhibitor trials may be due to the discontinuation of the protective effect of tamoxifen. Due to theoretical concerns and the lack of long-term data, clinical cardiac outcomes and lipid profile changes, as well as other harms associated with aromatase inhibitors, should be monitored.
- Evidence exists to suggest that aromatase inhibitors reduce the occurrence of venous thromboembolic and gynecologic events.
- Compared with placebo, letrozole may adversely affect quality of life and increase the occurrence of arthritis and/or arthralgia. Further evidence across various trials suggests that aromatase inhibitors increase the occurrence of arthralgia regardless of comparison group and mode of treatment.
- Aromatase inhibitors are contraindicated in premenopausal women.

***Predictors of Treatment Response***

*Recommendations*

**6. Due to the lack of evidence, no recommendation for the use of aromatase inhibitors based on HER2/*neu* status can be made at this time.**

*Qualifying Statements*

- No eligible trials on the efficacy of aromatase inhibitors according to HER2/*neu* status in the adjuvant setting were identified.
- A randomized trial comparing four months of neoadjuvant tamoxifen with letrozole in postmenopausal women with breast cancer ineligible for conservation surgery reported superior overall response rates in the letrozole group (60% vs. 41%;  $p=0.004$ ). In HER2/*neu*-overexpressing women, response rates were 88% and 21%, respectively ( $p=0.0004$ ). Conversely, in HER/*neu*-normal women, respective response rates were 54% and 42% ( $p=0.078$ ).
- In two trials where the primary outcome was the proliferation marker Ki67, HER2/*neu*-overexpressing women with operable breast cancer experienced greater reductions in Ki67 compared with HER2/*neu*-normal women; however, the difference was statistically significant in only one trial.

**RELATED GUIDELINES**

- Practice Guideline Report #1-5: *The Role of Aromatase Inhibitors in the Treatment of Postmenopausal Women with Metastatic Breast Cancer (4)* is related and may be of interest

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