



Adjuvant endocrine therapy for early breast cancer: a systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline

O.C. Freedman MD, G.G. Fletcher MSc,[†]
S. Gandhi MSc MD,[‡] M. Mates MD,[§] S.F. Dent MD,^{||}
M.E. Trudeau MD,* and A. Eisen MD**

ABSTRACT

Background

Cancer Care Ontario's Program in Evidence-Based Care (PEBC) recently created an evidence-based consensus guideline on the systemic treatment of early breast cancer. The evidence for the guideline was compiled using a systematic review to answer the question "What is the optimal systemic therapy for patients with early-stage, operable breast cancer, when patient and disease factors are considered?" The question was addressed in three parts: cytotoxic chemotherapy, endocrine treatment, and HER2 (human epidermal growth factor receptor 2)—targeted therapy.

Methods

For the systematic review, the literature in the MEDLINE and EMBASE databases was searched for the period January 2008 to May 2014. The Standards and Guidelines Evidence directory of cancer guidelines and the Web sites of major oncology guideline organizations were also searched. The basic search terms were "breast cancer" and "systemic therapy" (chemotherapy, endocrine therapy, targeted agents, ovarian suppression), and results were limited to randomized controlled trials (RCTs), guidelines, systematic reviews, and meta-analyses.

Results

Several hundred documents that met the inclusion criteria were retrieved. Meta-analyses from the Early Breast Cancer Trialists' Collaborative Group encompassed many of the RCTs found. Several additional studies that met the inclusion criteria were retained, as were other guidelines and systematic reviews.

Summary

The results of the systematic review constitute a comprehensive compilation of high-level evidence, which

was the basis for the 2014 PEBC guideline on systemic therapy for early breast cancer. The review of the evidence for systemic endocrine therapy (adjuvant tamoxifen, aromatase inhibitors, and ovarian ablation and suppression) is presented here; the evidence for chemotherapy and HER2-targeted treatment—and the final clinical practice recommendations—are presented separately in this supplement.

KEY WORDS

Early breast cancer, hormonal therapy, endocrine therapy, hormone receptor–positive breast cancer, tamoxifen, aromatase inhibitors, ovarian ablation, ovarian suppression

1. INTRODUCTION

The outcomes of patients with early breast cancer have improved with the use of adjuvant systemic treatments¹, which include chemotherapy, endocrine therapy, and targeted agents (trastuzumab) for eligible subgroups of patients. Several clinical practice guidelines have—based on primary evidence, consensus, or both—made recommendations for the selection of adjuvant systemic therapy. Nevertheless, practice remains variable in the Ontario health care setting². The Program in Evidence-Based Care (PEBC), together with the Breast Cancer Disease Site Group of Cancer Care Ontario (CCO), is charged with developing evidence-based practice guidelines pertaining to breast cancer care. Over many years, the PEBC has created clinical practice guidelines addressing various aspects of adjuvant systemic therapy for early breast cancer. Recently, the creation of an

The complete version of this guideline will be posted on the Cancer Care Ontario Web site at <https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebc/>.

Supplemental material available at <http://www.current-oncology.com>.

updated comprehensive guideline pertaining to all aspects of early breast cancer systemic therapy was identified as a priority. The resulting guideline is most applicable to the Canadian (and particularly Ontario) setting, but any high-resource health care context might find the guideline applicable to their circumstances. A systematic review of the evidence helped to inform the guideline recommendations. Thereafter, expert consensus was used to validate the compiled recommendations before the final guideline was created. The recommendations and a summary of the consensus process are published in this supplement as well as on the cco Web site³. In the present article, the evidence base for the adjuvant endocrine therapy recommendations is outlined. This document can be used as a standalone reference to the extensive data on this important area of breast cancer care. The evidence reviews for chemotherapy and biologic or targeted therapy (trastuzumab) are published elsewhere in this supplement.

For the purpose of the present work, early breast cancer was defined primarily as invasive cancers staged I–IIA (T1N0–1, T2N0). Studies describing breast cancers as operable or staged I–IIIA were also included (see the Methods section). Although several of the systemic therapies discussed here can be considered in the neoadjuvant setting, the review focused on trials having disease-free (DFS) or overall survival (OS) as endpoints; it thus excluded several neoadjuvant trials that used only pathologic complete response as the primary endpoint.

1.1 Hormonal Therapy for Hormone Receptor–Positive Tumours

The therapeutic manipulation of endogenous estrogen levels and the interaction of estrogen with its receptor is a cornerstone of adjuvant therapy in female patients with hormone receptor (HR)–positive breast cancer [meaning estrogen receptor (ER)–positive or progesterone receptor (PR)–positive, or both]. In premenopausal patients, the ovaries are the main site of hormone production, and therefore surgical removal, permanent inactivation by ovarian irradiation, or temporary ovarian suppression by administration of luteinizing hormone–releasing hormone (LHRH) agonists (also called gonadotropin–releasing hormone agonists) have been used in treatment. Tamoxifen is a selective estrogen receptor modulator that blocks the effect of estrogen in HR-positive cancers. It has been found to be effective in both pre- and postmenopausal patients. In postmenopausal women, aromatase inhibitors (AI) prevent the action of aromatase in the synthesis of estrogen, but are not effective in inhibiting the high levels of estrogen produced in the ovaries before menopause.

Considerable evidence has been accrued of a benefit for ovarian ablation or suppression (OA/S) or for tamoxifen in patients with HR-positive cancer

and for AI in postmenopausal patients. There is less agreement about the value of using OA/S in combination with AI or tamoxifen, or the role of OA/S after cytotoxic chemotherapy. Although OA/S should render premenopausal patients similar to postmenopausal patients, the use of AI in women with induced menopause, while proposed, is not standard practice. The recent SOFT (<http://clinicaltrials.gov/ct2/show/NCT00066690>) and TEXT (<http://clinicaltrials.gov/ct2/show/NCT00066703>) trials^{4–6} investigated OA/S combined with AI in premenopausal patients [see the OA (Surgical or Radiation) and Ovarian Suppression subsection later in this article].

Accurate assessment of HR status is critical for the use of adjuvant hormonal therapy in breast cancer (discussed in the Assessment of HR Status subsection, later in this article). Determination of menopausal status is an important factor in deciding on treatment. Some of the issues related to the determination of menopausal status and appropriate treatment are discussed in the Danish guideline *Menopausal Status and Adjuvant Hormonal Therapy for Breast Cancer*⁷.

2. METHODS

One systematic review was conducted for all systemic therapies, and therefore the search strategy and subsequent general results apply to chemotherapy, hormonal therapy, and targeted therapy combined.

2.1 Literature Search Strategy

The literature in the MEDLINE and EMBASE databases was searched for the period January 2008 to March 5, 2012; the search was later updated to May 12, 2014. To be selected, publications had to include terms related both to breast cancer and to systemic therapy (chemotherapy; endocrine therapy, including ovarian suppression; and targeted agents). The search was limited to randomized controlled trials (RCTs), guidelines, systematic reviews, and meta-analyses. Although systemic agents were, in most cases, indexed to terms such as “adjuvant therapy,” individual chemotherapy agents or regimens were also included. The full database search strategy is presented in Supplementary Appendix 1. Guidelines were also located in the Standards and Guidelines Evidence directory of cancer guidelines and at the Web sites of organizations known to produce oncology-related guidelines [National Institute for Health and Clinical Excellence (United Kingdom), Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (United States), National Health and Medical Research Council (Australia), New Zealand Guidelines Group]. Evidence was selected and reviewed by one member (GGF) of the PEBEC Early Breast Cancer Systemic Therapy Working Group; all authors provided input on the included results once initial screening was complete.

2.2 Study Selection Criteria—RCTs

Clinical trials were included if they evaluated at least 100 female patients with early-stage breast cancer randomized to at least 1 systemic agent and if they used survival (generally OS or DFS) as one of the primary or secondary outcomes. Studies had to describe the patients as having early or operable breast cancer, or had to allow the population characteristics to be ascertained from the methods or results. Trials evaluating patients with stages IIB and IIIA cancers were included only if stage IIA patients were also part of the population and if at least half the patients had stages I–IIB cancer. When only tumour size and nodal status were reported, stage was estimated according to the *AJCC Cancer Staging Manual*, 6th edition^{8,9} to decide whether the study met the inclusion criteria. Studies with mostly stage III or locally advanced tumours were excluded, as were studies that focused on stage IV (metastatic) breast cancer, noninvasive cancers (ductal carcinoma *in situ* or lobular carcinoma *in situ*), or treatment of cancer relapse. Trials primarily evaluating antiemetic drugs, erythropoiesis-stimulating agents, or autologous hematopoietic stem-cell transplantation were excluded. Studies of bisphosphonates to prevent metastasis or cancer recurrence were included; studies evaluating any bone-targeted agents to treat bone metastasis were excluded. Studies were eliminated if they were not relevant to the current practice setting in Ontario (for example, they evaluated older drugs no longer used), reported only exploratory analyses or correlations, or did not report survival endpoints.

2.3 Other Publication Selection and Assessment

Clinical practice guidelines were considered relevant if their recommendations were based on a systematic review of the literature or were described as evidence-based consensus. Systematic reviews and meta-analyses were also evaluated. Quality of the systematic reviews and meta-analyses was assessed using the AMSTAR tool¹⁰. For RCTs, study or trial design and quality characteristics were assessed; however, RCTs included in high-quality systematic reviews and meta-analyses were not separately appraised. Relevant RCTs cited in systematic reviews, guidelines, or meta-analyses were compared with those found in the MEDLINE and EMBASE database search results. Any studies that had not been captured in the search were retrieved if deemed important for further evaluation. Studies whose long-term follow-up data were pending and studies referenced in abstract form only were targeted for further literature review to retrieve any updated documents. Referenced trials from before 2008 were also retrieved when deemed appropriate. Abstracts presented at major conferences were initially searched as part of the grey literature;

however, most of the relevant studies were found to be included in the updated EMBASE database results, and conference proceedings were therefore not explicitly included.

3. RESULTS AND DISCUSSION

3.1 Literature Search Results

After removal of duplicate citations, the searches in MEDLINE and EMBASE located 14,444 publications (11,435 RCTs and 3009 systematic reviews, guidelines, or meta-analyses). Of the guidelines, systematic reviews, or meta-analysis, 287 were deemed to be of relevance; most were reviewed to locate RCTs not captured in the database search. In addition, those publications helped to inform patient selection criteria for the guideline recommendations. Approximately fifty trials (chemotherapy, hormonal therapy, or targeted therapy) found in MEDLINE or EMBASE had not been cited in the other guidelines and systematic reviews. Ultimately, 516 trial publications (from the database results and targeted searching) were extracted; 232 were pertinent to hormonal therapy.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) is an international collaboration that was formed in 1985 to evaluate studies of early (operable) breast cancer. Every 5 years, the group completes a meta-analysis using individual patient data (considered the highest level of evidence)¹¹ from all RCTs worldwide on aspects of early breast cancer therapy. Several of the EBCTCG meta-analyses^{12–16} are referenced in our series of systematic reviews. Given the rigorous methodology and comprehensiveness of the EBCTCG analyses, many of the individual RCTs used in those analyses were not retrieved for data extraction or quality appraisal; however, some limitations of the EBCTCG data are discussed.

Individual RCTs and the guidelines, reviews, and meta-analyses were sorted into studies of chemotherapy, endocrine therapy for HR-positive cancers, and targeted therapy for HER2 (human epidermal growth factor receptor 2)–positive cancers. Chemotherapy trials were further subdivided into major cytotoxic classes: anti-metabolites, including CMF [cyclophosphamide–methotrexate–5-fluorouracil], anthracyclines, taxanes, and other agents. The major endocrine therapies were tamoxifen, AIS, and ovarian suppression (by LHRH agonists) or ovarian ablation (OA, by surgery or radiation). For HER2-positive cancers, trastuzumab was the only biologic or targeted agent that was found to have sufficient evidence to be included in the final guideline recommendations. The results of the adjuvant endocrine studies are discussed in this systematic review; results pertaining to chemotherapy treatments and trastuzumab are published elsewhere in this supplement.

3.2 Tamoxifen Treatment

3.2.1 Tamoxifen for 2–5 Years

The recent EBCTCG meta-analysis¹⁴ included all trials worldwide on early breast cancer (excluding ductal carcinoma *in situ*) that compared adjuvant tamoxifen with no tamoxifen. Most studies used 5 years of tamoxifen. Supplementary Table 1 summarizes the 10-year recurrence rates¹⁴, and Supplementary Table 2 summarizes the corresponding survival rates¹⁴.

In patients with ER-negative cancer, tamoxifen did not improve the rate of recurrence or survival. Overall mortality rates were substantially reduced in all subgroups of patients with ER-positive cancer¹⁴, including patients grouped by age (<45 years), by tumour grade and size, by chemotherapy use and sequence with tamoxifen, and by nodal status. Estrogen receptor positivity at the level of 10 fmol/mg or more was enough to yield a positive tamoxifen effect. Given a known ER status, PR status was not significantly predictive of response.

For patients with ER-positive cancer, a greater effect on 10-year breast cancer mortality rates was observed with 5 years than with 1 or 2 years of tamoxifen. For patients with ER-positive cancer who received 5 years of tamoxifen, the 15-year recurrence rate was 33% (compared with 46.2% without tamoxifen), and the breast cancer mortality rate was 23.9% (compared with 33.1%). The benefit of tamoxifen was thus observed to persist after its use was discontinued. In fact, the 2011 EBCTCG update¹⁴ found that tamoxifen reduced recurrence rates in patients with ER-positive cancer by one half in years 0–4 and by one third in years 5–9; little effect was observed after year 10. Side effects of tamoxifen included increased risks for uterine cancer (in those more than 45 years of age) and thromboembolic disease (in those 55 years of age and older).

3.2.2 Tamoxifen for More Than 5 Years

The ATLAS¹⁷ and ATOM^{18,19} trials randomized 12,894 and 6953 female patients who had received approximately 5 years of tamoxifen to another 5 years or to no additional tamoxifen and found a benefit for extended tamoxifen. Those results contrast with the findings in earlier, smaller studies (National Surgical Adjuvant Breast and Bowel Project B-14 and Scottish trials), which found no benefit of extending tamoxifen for more than 5 years^{20–23}.

The ATLAS trial¹⁷ (12,894 female patients) found that extending the duration of tamoxifen to 10 years in ER-positive cases further reduced the risk of breast cancer recurrence (617 cases vs. 711 cases, –2.80% difference, $p = 0.002$), breast cancer mortality (331 deaths vs. 397 deaths, $p = 0.01$), and overall mortality (639 deaths vs. 722 deaths, –2.48% difference, $p = 0.01$). The recurrence prevention benefit was similar for subgroups determined by menopausal status at study entry (premenopausal hazard ratio: 0.81; $p = 0.15$;

postmenopausal hazard ratio: 0.85; $p = 0.05$). However, premenopausal patients constituted only approximately 9% of the study population, and statistical significance was not reached, likely because of the much smaller number of events in that subgroup.

For all ER groups combined (ER-positive, ER-negative, and unknown), small increased incidences of pulmonary embolus [41 cases vs. 21 cases; difference of 0.31%; relative risk (RR): 1.87; $p = 0.01$] and of endometrial cancer (116 cases vs. 63 cases; difference of 0.82%; RR: 1.74; $p = 0.0002$) were observed, although no significant difference in mortality resulted (10 deaths vs. 8 deaths, $p = 0.69$, and 17 deaths vs. 11 deaths, $p = 0.29$). A decrease in ischemic heart disease was noted (127 cases vs. 163 cases, –0.56% difference, $p = 0.02$), as was a lower rate of death from heart attack or other vascular causes, excluding stroke or pulmonary embolism (178 deaths vs. 205 deaths, –0.43% difference, $p = 0.10$).

The ATOM trial (published only as abstracts)^{18,19}, which included 2755 ER-positive and 4198 ER-untested (estimated to be 80% ER-positive) women, also found that the extension of tamoxifen to 10 years was associated with a reduced recurrence rate (580 events vs. 672 events with 5 years of tamoxifen, $p = 0.003$), breast cancer mortality rate (392 deaths vs. 443 deaths, $p = 0.05$), and overall mortality rate (849 deaths vs. 910 deaths, $p = 0.1$), with little effect on the non-breast cancer mortality rate [457 deaths vs. 467 deaths; RR: 0.94; 95% confidence interval (CI): 0.82 to 1.07]. Increases in the occurrence of endometrial cancer (102 cases vs. 45 cases; RR: 2.2; $p < 0.0001$) and death (37 vs. 20, 1.1% vs. 0.6%, $p = 0.02$) were noted. Combining the ATOM results with those from the ATLAS trial enhanced the statistical significance of the benefits for recurrence ($p < 0.0001$), breast cancer mortality ($p = 0.002$), and OS ($p = 0.005$) that were associated with extended tamoxifen.

The revised ASCO guideline (May 2014) on adjuvant endocrine therapy²⁴ recommends that tamoxifen be used for up to 10 years. The report on tamoxifen and uterine cancer²⁵ from the Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists also indicated that tamoxifen use could be extended to 10 years. Patients should be informed of the risk of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas and of the need to report any abnormal vaginal bleeding. Postmenopausal patients should be monitored.

3.2.3 Delayed Adjuvant Tamoxifen

The TAM-02 trial²⁶ randomized patients treated at least 2 years beforehand (mean: 59 months) with any one or a combination of surgery, radiotherapy, and adjuvant chemotherapy (but no hormone therapy) to 5 years of tamoxifen or no treatment. The 10-year results indicated that, in node-positive and in HR-positive (ER-positive or PR-positive, or both)

tumours, tamoxifen was associated with significant improvements in OS and DFS rates. Patients having a delay longer than 5 years experienced a significantly improved DFS rate.

An Italian study²⁷ randomized patients with at least 2 years' delay after surgery (median: 25 months) to receive either 2 years of tamoxifen or follow-up only. At a median follow-up of 89 months, 5-year results showed fewer cases of contralateral breast cancer (4 cases vs. 10 cases, $p = 0.11$) and of ER-positive secondary breast cancers (1 case vs. 10 cases, $p = 0.005$) in the tamoxifen group; however, locoregional and distant relapses or metastasis were similar overall, and more ER-negative contralateral breast cancer was seen. Approximately one third of the patients were ER-positive, and one third were ER-negative; ER status in the remaining one third was unknown. No significant differences between those subgroups were reported. The small size of that study and the variability of the data limit its usefulness.

Although not definitive, the foregoing studies, together with the MA.17 trial^{28–36}, suggest that hormonal treatment could be beneficial for some patients even after a delay of several years.

3.2.4 Tamoxifen Plus Other Agents

The systematic review identified studies that examined the effect of adding octreotide to adjuvant tamoxifen (NCIC MA.14³⁷, National Surgical Adjuvant Breast and Bowel Project B-29³⁸). No benefit of adding octreotide to tamoxifen therapy was observed. Another study³⁹ examined the effect of tamoxifen on the local recurrence rate in low-risk patients treated with or without radiotherapy after surgery, showing a reduction in that rate.

3.3 AIs

3.3.1 AIs Compared with Tamoxifen

This section summarizes the EBCTCG meta-analyses, four recent systematic reviews or guidelines, and sixty-eight publications of twenty-three trials from the literature search (including studies updated or published since the EBCTCG meta-analysis). Supplementary Tables 3 and 4 present results from the EBCTCG meta-analyses^{40,41}, and Supplementary Table 5 presents results from the literature search^{4–6,28–36,42–91}.

An update⁴¹ of the original EBCTCG meta-analysis⁴⁰ was presented at the 2014 ASCO annual meeting. It included 36,889 postmenopausal patients, compared with 18,871 in the 2010 publication, and might encompass some of the more recent studies summarized in Supplementary Table 5. However, it was still limited to postmenopausal patients and to a total of 5 years of endocrine therapy. Most of the studies presented in Supplementary Table 5 were included in the PEBC 1-18 evidence-based guideline and in ASCO guidelines (discussed later in the present article), but the studies retrieved during

the literature search provided fuller publications (instead of abstracts) and longer-term follow-up.

Clinical Practice Guidelines: Four approaches for AI use have been recommended⁹²:

- Tamoxifen (20 mg daily) for 5 years
- Anastrozole (1 mg daily) or letrozole (2.5 mg daily) for 5 years
- Tamoxifen (20 mg daily) for 2–3 years, then a switch to exemestane (25 mg daily) or to anastrozole (1 mg daily) for a total of 5 years of endocrine therapy
- Tamoxifen (20 mg daily) for 5 years, followed by letrozole (2.5 mg daily) for 5 years

No data comparing those strategies are available. The guideline⁹² recommends that female patients receiving AIs be monitored for changes in bone mineral density. Data about cardiac outcomes and changes in lipid profile have been mixed. The ASCO guideline^{24,93} summarizes relative adverse effects in greater detail and recommends that postmenopausal patients with HR-positive breast cancer consider incorporating an AI at some point during adjuvant therapy, either up front or sequentially after tamoxifen. The optimal timing and duration of endocrine therapy remains unresolved, although a key change in ASCO's 2014 revision to its guideline²⁴ was a recommendation to extend tamoxifen use up to 10 years rather than for 5 years. Tamoxifen for 0–5 years followed by an AI for up to 5 years is an alternative, provided postmenopausal status is confirmed before the AI is instituted.

Tamoxifen and AIs are generally well tolerated, but have specific adverse effects, including effects on bone, cardiovascular, and gynecologic health. Aromatase inhibitors are associated with greater loss of bone mineral density and fractures, which can be mitigated with the use of bisphosphonate therapy. Aromatase inhibitors can cause a musculoskeletal or arthralgia syndrome characterized by bone and joint symptoms, including pain, stiffness, or aches that is symmetric and not associated with other signs of rheumatologic disorders. Data suggest that AIs are associated with increased cardiovascular disease, possibly including ischemic cardiac disease, although differences are small. Some studies have found an effect on lipid metabolism, including an increased risk of hypercholesterolemia. It has been suggested that these unfavourable changes in lipid profile might, in the switching studies, be related more to the discontinuation of tamoxifen than to a significant effect of the AI alone. The risk of venous thromboembolic events is higher with tamoxifen, with a 1%–2% greater risk of deep-vein thrombosis. Tamoxifen is associated with an increased risk of uterine cancer (approximately 1% of patients), benign endometrial pathology (bleeding, polyps,

hyperplasia), hysterectomy, and vaginal discharge. Aromatase inhibitors seem to be less frequently associated with hot flashes. Results for vaginal dryness and loss of libido are inconsistent.

Meta-Analysis by the EBCTCG: The EBCTCG meta-analysis⁴⁰ included patients with ER-positive cancer who, in RCTs of AI compared with tamoxifen, received the AI as monotherapy (cohort 1) or after 2–3 years of tamoxifen (cohort 2) for a total of 5 years of therapy (that is, randomized to continue tamoxifen or to switch to an AI for an additional 2–3 years). Trials of AI after 5 years of tamoxifen were not included. The analysis encompassed all trials started by year 2000 and data to September 30, 2006. Data were not available from the Austrian Breast and Colorectal Cancer Study Group (ABCSG) 12 trial and from the switching arms of Breast International Group (BIG) 1-98 (International Breast Cancer Study Group 18-98).

Cohort 1 (tamoxifen vs. AI as monotherapy for 5 years) included 9856 patients from the ATAC and BIG 1-98 trials with a mean of 5.8 years' follow-up since the start of treatment. Results were calculated for AI therapy compared with tamoxifen and are presented in Supplementary Table 3. Recurrence rates were better with AIS than with tamoxifen, but no significant differences in mortality rates were observed.

Cohort 2 included 9015 patients from four trials (German Adjuvant Breast Cancer Group/Arimidex–Nolvadex, Intergroup Exemestane/BIG 02-97, Italian Tamoxifen Anastrozole, ABCSG 8) with a mean follow-up of 3.9 years calculated from the time of treatment divergence, who were reported at 3 and 6 years (approximately 5 and 8 years after the start of hormonal treatment). The AIS were associated with a significant benefit for rates of recurrence and survival (Supplementary Table 4).

No heterogeneity in proportional risk reduction with respect to age, nodal status, or grade was apparent. The overall conclusion was that, compared with tamoxifen, AIS result in lower recurrence rates. For an analysis of long-term survival, more follow-up information is required. Cause-specific mortality rates were not reported in the analysis. In both cohorts, use of an AI was associated with modest absolute improvements in breast cancer endpoints and with significant reductions in recurrence rates. The absolute gain was greater in patients with a poorer prognosis.

Comparisons A and B in a 2014 abstract⁴¹ appear to correspond to cohorts 1 and 2, and the results resemble the 8-year data in Supplementary Tables 3 and 4. An additional comparison (“comparison C”) contrasted 5 years of AI with tamoxifen followed by AI. A recurrence benefit for continuous AI was observed overall (RR: 0.90; 95% CI: 0.81 to 1.00) and in years 0–1 (RR: 0.75; 95% CI: 0.62 to 0.89), but not in year 2 and onward. Recurrence rates at 5 years were 9.6% and 10.7% ($p = 0.042$), and breast cancer deaths

were 6.2% and 6.8% ($p = 0.097$). For all groups combined, fewer endometrial cancers (0.2% vs. 0.6%; RR: 0.37; 95% CI: 0.27 to 0.51) but more fractures (8.1% vs. 5.9%; RR: 1.40; 95% CI: 1.27 to 1.53) were seen with AI than with tamoxifen.

Individual Studies and Comparison with Earlier Reviews and Meta-analyses: Supplementary Table 5 summarizes patient characteristics and outcomes for the individual studies of AIS compared with tamoxifen identified in the present review. Those studies include updates of most of the trials used in the EBCTCG meta-analysis and other guidelines summarized here.

The ABCSG 12, SOFT, and TEXT trials (Supplementary Table 5) evaluated a different patient group: namely, premenopausal patients receiving an AI and OA/S (goserelin in ABCSG 12, triptorelin in TEXT, triptorelin or ovarian surgery or irradiation in SOFT). The foregoing studies are also relevant to the OA (Surgical or Radiation) and Ovarian Suppression subsection and are discussed there in more detail.

In the ABCSG 12 trial, patients were randomized to 3 years of anastrozole or tamoxifen, with secondary randomization to receive or not receive zoledronic acid. Adverse events were less serious with anastrozole. Overall, the DFS rates in the anastrozole and tamoxifen groups did not differ, but patients in the tamoxifen group experienced a significantly better OS rate. However, zoledronic acid was found to improve the OS and DFS rates in both groups and in the subgroup of patients more than 40 years of age (but not in the subgroup of patients 40 years of age and younger). Tamoxifen and anastrozole both resulted in bone loss, the adverse effect being greater with anastrozole (prevented with concomitant zoledronic acid administration). Combined analysis of the SOFT and TEXT trials^{4–6} found an improved DFS rate for exemestane plus OA/S compared with tamoxifen plus OA/S.

An additional issue not addressed in the previous analyses is whether a benefit accrues from more than 5 years of treatment. In the largest study, MA.17, patients received 5 years of either letrozole or placebo after 5 years tamoxifen. Findings included an improved DFS rate overall, in the node-positive and N0 subgroups, and in two age subgroups (<60 years of age, and 60–69 years of age). Letrozole was associated with a significant OS benefit for patients with node-positive disease, but no effect was observed in patients with node-negative cancer. A meta-analysis³⁶ (published as an abstract) of four studies, including MA.17, found that AI therapy after 5 years of tamoxifen was associated with a 2.9% decrease in the recurrence rate and a 0.5% decrease in the breast cancer mortality rate.

Considering all the evidence from the available clinical practice guidelines, meta-analyses, and individual trials of tamoxifen and AIS in the adjuvant treatment of HR-positive breast cancer, AIS have been

associated with a modest but significant improvement in clinical outcomes. The optimal sequence and duration of AI therapy, with or without tamoxifen, is uncertain. How adjuvant regimens containing AIS compare with the strategy of tamoxifen for 10 years is also unknown.

3.3.2 Comparison of AIs

Supplementary Table 6 presents studies comparing AIS^{68,94–103}. The MA.27 trial⁹⁷ found no difference in survival outcomes, but some differences in adverse effect profile. The study concluded that exemestane is comparable to anastrozole. The FACE⁹⁹, DATA¹⁰², and SOLE¹⁰³ trials are ongoing and have not yet produced survival rate data. The TEAM Japan study⁶⁸ reported that tamoxifen had a favourable effect on lipid profiles and might be preferred over exemestane and anastrozole (both of which had no clinically significant effect on serum lipids) for patients at high risk of cardiovascular events such as hyperlipidemia. Two additional publications (abstracts only)^{100,101} emerging from BIG 1-98 and ATAC provide an indirect comparison of anastrozole and letrozole, suggesting that letrozole could be more effective than anastrozole in reducing early distant recurrence and mortality rates at 5 years. That finding is based on trends (not statistically significant) and requires confirmation in ongoing trials. Taken together, the trials suggest that all AIS available in Ontario are active in this setting.

3.3.3 AIs Plus Chemotherapy

The two-stage NEOS National Surgical Adjuvant Study BC06 started recruitment in 2008^{104,105}. This ongoing study will evaluate the need for adjuvant chemotherapy in addition to endocrine therapy for patients who respond to neoadjuvant letrozole.

3.4 OA (Surgical or Radiation) and Ovarian Suppression

Ovarian ablation is the oldest form of systemic therapy for breast cancer¹⁰⁶. The term is often used to refer to surgical oophorectomy or ovarian irradiation. In contrast, ovarian suppression refers to the suppression of ovarian function, typically with LHRH agonists. Chemotherapy can partly interrupt ovarian estrogen production (permanently or temporarily), as indicated by chemotherapy-induced amenorrhea in many younger patients; however, it can have both cytotoxic and endocrine effects¹⁰⁷. Ovarian suppression has been studied as a method of preserving fertility during chemotherapy; those studies are beyond the scope of the present review.

The hormonal maneuver of OA/S benefits only female patients with HR-positive breast cancer. In addition, OA/S has endocrine effects only in premenopausal patients and thus should be considered a therapeutic strategy only in that age group. The use of OA/S has been studied both as the only form of

adjuvant therapy and in combination with every other systemic therapy (tamoxifen, AIS, chemotherapy). Despite the large body of evidence about OA/S in early-stage breast cancer, its current role as a treatment strategy remains unclear.

Several major meta-analyses and guidelines have addressed OA/S^{13,16,108–110}. The full guideline report³ provides a comprehensive list of the RCTs included in those works.

The data are complicated by the extremely large number of comparisons. Studies can use OA (by radiotherapy or surgery), ovarian suppression, or both. The comparisons can include no treatment, chemotherapy, or tamoxifen in either or both arms. The EBCTCG meta-analysis is the most complete comparison of OA or no OA and of OA plus chemotherapy or chemotherapy alone, and the relevant studies are not included in the other meta-analyses. Because the EBCTCG uses individual patient data, its meta-analyses are considered the most useful and comprehensive for the areas covered, although some limitations exist. The EBCTCG meta-analyses are discussed in the subsection that follows next. The other reviews or meta-analyses—as well as new studies from the literature search—are discussed in the subsequent subsections.

3.4.1 EBCTCG Meta-analyses

Supplementary Table 7 presents a summary of the EBCTCG meta-analysis published in 2005¹³. That analysis included 7725 female patients (<50 years of age with early breast cancer) from six trials of either OA ($n = 4317$) or ovarian suppression (LHRH inhibition, $n = 3408$) compared with no adjuvant OA/S. Age less than 50 years was used as a surrogate for menopausal status. Chemotherapy was allowed if equivalent in both the OA/S and control arms. The authors included ER-positive and ER-unknown cancers (63% of OA recipients and 26% of ovarian suppression recipients were ER-untested) and categorized the results according to age (<40 and 40–49 years). Overall, compared with no treatment or any other treatment without OA/S, OA and ovarian suppression were both associated with significantly improved rates of recurrence and survival. The overall recurrence rate at year 15 was 47.3% for the OA/S group compared with 51.6% for the control group ($p = 0.00001$). The corresponding breast cancer mortality rates at 15 years were 40.3% and 43.5% ($p = 0.004$).

Subgroup analyses found that, when both age groups were combined, the effect of OA/S was significant for patients not receiving chemotherapy. The effect appeared smaller in studies in which chemotherapy was also administered, and it was not significantly different from the effect in chemotherapy-only control groups, except in patients less than 40 years of age, who, if they received ovarian suppression, experienced a statistically significant improvement in recurrence rate (RR: 0.70; 95% CI: 0.39 to 0.996).

Because the overall effect was small, and events in the subgroups (especially mortality) were limited in number, caution should be used in interpreting the subgroup data. One concern about these data is that fewer than half the patients on OA were confirmed to be HR-positive.

The studies of ovarian suppression without chemotherapy compared goserelin with no goserelin. Although tamoxifen was administered in some studies, its use was not considered in the analysis. The EBCTCG meta-analysis does not answer the question of whether a LHRH adds to tamoxifen in patients treated with chemotherapy.

3.4.2 LHRH-Agonists in Early Breast Cancer Overview Group

The LHRH-Agonists in Early Breast Cancer Overview group conducted a meta-analysis of individual patient data in 2007¹⁰⁸. Supplementary Table 8 summarizes the results of that meta-analysis, which involved thirteen trials (sixteen, if the four ZIPP sites are considered separately) in which premenopausal patients ($n = 11,906$) received LHRH agonists (or, if multiple methods of suppression were used, more than half the patients received LHRH agonists).

Importantly, this analysis focused on the 9022 patients with HR-positive cancer, among whom 8278 (91.8%) were ER-positive. (It reported briefly on patients whose disease was HR-negative or ER/PR-unknown, but patients with unknown receptor status were not included in the meta-analysis.) Compared with the EBCTCG meta-analysis, it also included more studies using ovarian suppression and more patients, and it controlled for the use of tamoxifen. Of the included patients who received chemotherapy, 66% received a CMF-based regimen, and 32% received an anthracycline-based regimen. Data were analyzed in several subgroups depending on chemotherapy and tamoxifen use. Treatment with LHRH was most commonly administered for 2 years, but durations of 18 months and 3 or 5 years were also used. Although this meta-analysis is important, some of the comparisons are not relevant to modern practice.

In several comparisons, use of LHRH was associated with improved rates of recurrence and survival. The addition of LHRH plus tamoxifen to no systemic treatment, and the addition of LHRH plus tamoxifen to chemotherapy both led to significant improvement. The addition of LHRH to any systemic therapy (overall and for the subgroup ≤ 40 years of age, but not for the subgroup > 40 years of age) and the addition of LHRH to chemotherapy with or without tamoxifen also led to significant improvement. Addition of LHRH to tamoxifen was not associated with a significant improvement for the full age range of patients (change in the hazard ratio for recurrence: -14.5% ; $p = 0.20$). When recurrence was stratified by age, no effect was observed for patients more than 40 years of age (change in the hazard ratio: -1.5% ; $p = 0.91$), but for

patients 40 years of age and younger, the effect was much larger, although still not statistically significant (change in hazard ratio: -32% ; $p = 0.12$).

Compared with no systemic treatment, use of LHRH was almost significant for recurrence ($p = 0.08$) and for all deaths ($p = 0.11$); the unexpected lack of significance in those comparisons could be attributable to the small number of patients ($n = 338$). When results were analyzed by age (≤ 40 years or > 40 years), a large effect emerged in several comparisons. The addition of LHRH was associated with significantly improved recurrence rates for patients 40 years of age or younger, but not for patients more than 40 years of age [comparisons: LHRH plus chemotherapy vs. chemotherapy alone; LHRH plus chemotherapy with or without tamoxifen vs. chemotherapy with or without tamoxifen; and LHRH vs. any systemic therapy (note that the latter two comparisons are combinations of others)]. That finding is consistent with the EBCTCG analysis, which found that recurrence was significantly reduced when LHRH was administered in patients 40 years of age or younger. When results were analyzed in 5-year age groups, the effect was greatest in the groups less than 35 years of age (hazard ratio: 0.66) and 35–39 years of age (hazard ratio: 0.77), but not in the older groups. Although those results indicate a benefit of LHRH use in addition to chemotherapy for younger female patients (in the absence of tamoxifen use), and a possible benefit for the addition of LHRH to tamoxifen (in the absence of chemotherapy), they do not address the issue of LHRH added to combined tamoxifen and chemotherapy.

In the group that was mostly HR-negative (ER-negative or “poor,” plus PR-negative or “poor” or unknown), the addition of a LHRH agonist to other treatments did not generally affect the rates of death and recurrence. In contrast, use of a LHRH agonist instead of chemotherapy was associated with significantly increased rates of recurrence ($p = 0.001$) and mortality ($p = 0.08$), indicating that, for patients with HR-negative cancer, chemotherapy rather than ovarian suppression should be used.

3.4.3 PEBC Guideline 1-9

The PEBC 1-9 series systematic review and guideline¹⁰⁹ covers most of the literature (searched up to September 2009). The recommendations are based largely on the individual patient data meta-analyses published by the EBCTCG in 2005¹³ and by the LHRH-Agonists in Early Breast Cancer Overview group¹⁰⁸. All forms of OA or suppression are termed “ovarian ablation” in the guideline.

These were the PEBC’s recommendations:

- Ovarian ablation should not routinely be added to systemic therapy with chemotherapy, tamoxifen, or the combination of tamoxifen and chemotherapy.
- Ovarian ablation alone is not recommended as an alternative to any other form of systemic therapy,

except in the specific case of patients who are candidates for other forms of systemic therapy, but who for some reason will not receive any other systemic therapy (for example, patients who cannot tolerate other forms of systemic therapy, or patients who choose no other form of systemic therapy).

- When chemical suppression using LHRH agonists is the chosen method of OA, the opinion of the Breast Cancer Disease Site Group is that monthly injection is the recommended mode of administration (based on the fact that nearly all of the available trials have used monthly administration).
- There is no available evidence on which to base a recommendation about the specific form of OA (surgical oophorectomy, ovarian irradiation, or medical suppression) that should be preferred.

Some of the relevant trials have been updated since the 1-9 guideline was published.

3.4.4 Cochrane Collaboration

A review by the Cochrane Collaboration (Goel *et al.*¹¹⁰) included a literature search to February 2009. The review gives a complete description of the trials and their outcomes.

3.4.5 New Studies or Updates

ABCSG 12, SOFT, and TEXT Trials: The ABCSG 12^{42–45,47,111–114}, SOFT (International Breast Cancer Study Group 24-02, NCT00066690)^{4–6}, and TEXT (NCT00066703)^{4–6} trials found during the literature search are significant because they address the use of AIS together with ovarian suppression in premenopausal patients. Supplementary Table 5 summarizes the details and results of those trials.

The ABCSG 12 study compared goserelin plus tamoxifen with goserelin plus anastrozole in premenopausal patients with endocrine-responsive early breast cancer. In a second randomization, patients either received or did not receive zoledronic acid. Because all groups received goserelin, the contribution of ovarian suppression to other hormonal therapies could not be determined.

Because of fewer events than expected, the TEXT and SOFT trial results were combined to allow for earlier reporting of the OA/S plus exemestane versus OA/S plus tamoxifen results. Rates of DFS were better with exemestane plus OA/S than with tamoxifen plus OA/S (91% vs. 87%, $p < 0.001$). The OS rate was similar in both groups (96%); longer follow-up is required. These studies indicate higher rates of survival in premenopausal patients receiving exemestane plus OA/S.

Results of the comparison with the tamoxifen-only arm in the SOFT trial^{115,116} were available only after completion of the present review and the corresponding guideline. Results are not included in Supplementary Table 5, and readers should consult the trial publications for additional details. A small

benefit was observed for the addition of ovarian suppression to tamoxifen (DFS: 86.6% vs. 84.7%; $p = 0.10$ before adjustment; $p = 0.03$ after adjustment for prognostic factors). No difference in DFS (93.4% vs. 93.3%) or OS (99.2% vs. 99.8%) was observed at 5 years in the subgroup of patients who had received no prior chemotherapy (likely because they had been assessed to be at low risk of recurrence). Most recurrences—and thus greater benefit—were found in patients who had received chemotherapy. For the latter patients, the addition of ovarian suppression to tamoxifen resulted in significantly better OS (94.5% vs. 90.9%; hazard ratio: 0.64; 95% CI: 0.42 to 0.96), with apparent improvements in DFS and recurrence (80.7% vs. 77.1% and 82.5% vs. 78.9% respectively) that were not statistically significant. Rates of freedom from distant recurrence at 5 years in patients receiving prior chemotherapy were 83.6% with tamoxifen, 84.8% with tamoxifen plus ovarian suppression (hazard ratio: 0.87; 95% CI: 0.64 to 1.17), and 87.8% with exemestane plus ovarian suppression (hazard ratio: 0.72; 95% CI: 0.52 to 0.98). The benefit of ovarian suppression plus exemestane was especially seen in the patient group less than 35 years of age (freedom from breast cancer: 67.7% with tamoxifen, 78.9% with tamoxifen plus ovarian suppression, and 83.4% with exemestane plus ovarian suppression). Compared with tamoxifen alone, tamoxifen or exemestane plus ovarian function suppression was associated with more toxicity and adverse effects (endocrine and sexual functioning symptoms). The profile of adverse effects was different for exemestane plus ovarian suppression (greater loss of sexual interest and arousal difficulties, vaginal dryness, bone pain) compared with tamoxifen plus ovarian suppression (more hot flashes and sweats).

The INT-0142/E-3193 study¹¹⁷, which compared tamoxifen with tamoxifen plus ovarian suppression, was also reported after our literature review. That study was terminated early because of slow accrual and is underpowered for a survival endpoint. However, results related to quality of life and sexual functioning showed more menopausal symptoms and sexual dysfunction and lower quality of life with the addition of ovarian suppression. Effects on quality of life have to be considered when choosing between tamoxifen, tamoxifen plus ovarian suppression, and exemestane plus ovarian suppression^{5,6,115–117}.

Masuda *et al.*¹¹⁸ (NCT00303524): Premenopausal Japanese patients with ER-positive early breast cancer were randomized to subcutaneous depot injection of goserelin 10.8 mg every 3 months ($n = 86$) or to 3.6 mg monthly ($n = 84$). Most patients experienced amenorrhea by week 8. Serum estradiol and follicle-stimulating hormone remained suppressed throughout the study. No patient had menses after week 16. No clinically important differences in safety and tolerability were found.

International Breast Cancer Study Group Trial 11-93^{119,120}: The study included premenopausal patients with endocrine-responsive (ER-positive or PR-positive) node-positive early breast cancer (T1a/b/c, T2 or 3, pN1M0). It compared 4 cycles of chemotherapy plus OA/s and 5 years tamoxifen with OA/s plus tamoxifen without chemotherapy. The trial closed after randomization of 174 patients and before target accrual was met ($n = 760$). At a median follow-up of 10 years, no differences in the rates of DFS and OS were observed in the two arms (DFS hazard ratio: 1.02; 95% CI: 0.57 to 1.83; $p = 0.94$; OS hazard ratio: 0.97; 95% CI: 0.44 to 2.16; $p = 0.94$). Because the study achieved less than 25% of its planned accrual, it could have been underpowered to draw firm conclusions.

The ZIPP Study^{121,122}: The ZIPP study included patients less than 50 years of age with invasive, operable breast cancer in one breast and no signs of metastasis. The study description and some results were included in the other systematic reviews and meta-analyses. Long-term follow-up for some subgroups at a median of 12 years¹²¹ is included in the PEBBC 1-9 evidence-based series. The four groups were control ($n = 476$), tamoxifen ($n = 879$), goserelin ($n = 469$), and tamoxifen plus goserelin ($n = 882$). The authors examined subgroup effects by age (<40 years and ≥ 40 years), nodal status, ER status, and prior adjuvant systemic chemotherapy [yes or no (43% received chemotherapy and 62% received radiotherapy)], stratified by trial centre (Cancer Research UK, Gruppo Interdisciplinare Valutazione Interventi in Oncologia, southeast Sweden, Stockholm). Some of the results are reproduced in Supplementary Table 9. Goserelin, tamoxifen, and goserelin plus tamoxifen were all similar in effectiveness and significantly better than no endocrine treatment (control). It should be noted that the groups were not equal, because most patients who received chemotherapy were node-positive, and most who did not receive chemotherapy were node-negative. The analysis showed no statistically significant benefit for giving both goserelin and tamoxifen compared with either agent alone.

Stockholm Substudy of ZIPP: Results for the Stockholm site of the ZIPP study (Sverrisdottir *et al.*, 2011¹²²) were reported for goserelin compared with no endocrine treatment, tamoxifen compared with no endocrine treatment, goserelin and tamoxifen compared with no endocrine treatment, and subgroups not receiving tamoxifen. Randomization was stratified into three groups based on nodal status and use of other adjuvant therapies: node-negative and no chemotherapy, 1–3 positive nodes and chemotherapy, 4 or more positive nodes and chemotherapy plus radiotherapy. (The other ZIPP centres did not use stratification.) Time to first recurrence was better for goserelin than for no endocrine treatment (hazard ratio: 0.68; 95% CI: 0.52 to 0.89; $p = 0.005$), for tamoxifen than for no endocrine treatment

(hazard ratio: 0.73; 95% CI: 0.56 to 0.95; $p = 0.018$), and for goserelin plus tamoxifen than for no endocrine treatment (hazard ratio: 0.76; 95% CI: 0.59 to 0.98). In the highly ER-positive group, goserelin was more effective than tamoxifen (hazard ratio for goserelin vs. no endocrine treatment: 0.52; 95% CI: 0.32 to 0.84; $p = 0.007$; hazard ratio for tamoxifen vs. no endocrine treatment: 0.68; 95% CI: 0.44 to 1.05; $p = 0.081$).

3.4.6 Summary of Conclusions for Each Comparison of OA/S to Other Treatments, from the Meta-analyses and Recent Data

Supplementary Table 10 summarizes the data used to support the conclusions that follow.

HR-Negative Disease: For female patients with HR-negative breast cancer, chemotherapy is superior to OA/s^{108,123}.

HR-Positive Disease: For female patients with HR-positive breast cancer, OA/s has been compared with chemotherapy, tamoxifen, and combinations of those therapies. Given the multiple treatment options, it is helpful to consider and summarize the results using this framework:

- **OA/S Alone Compared with No Systemic Therapy:** For female patients with HR-positive breast cancer, OA and ovarian suppression are both better than no systemic treatment^{13,108,121}. Thus, OA/s alone is a reasonable option in the specific case of patients who will not receive any other systemic therapy (for example, patients who cannot tolerate other forms of systemic therapy, or patients who choose no other form of systemic therapy).
- **OA/S Plus Chemotherapy Compared with Chemotherapy Alone:** The relevance of this comparison in modern practice is questionable, because the standard of care for HR-positive patients would generally also include tamoxifen. The available data suggest that adding ovarian suppression benefits patients 40 years of age and younger^{108,110,123}. In the EBCTCG meta-analysis, which included patients with HR-negative cancer, the addition of OA to chemotherapy did not add any benefit¹³. The meta-analysis by the LHRH-Agonists in Early Breast Cancer Overview group suggests that LHRH agonists are as effective as the chemotherapy regimens used, and that LHRH added to chemotherapy provides additional benefit in female patients 40 years of age and younger¹⁰⁸. In those female patients, chemotherapy is less likely to induce permanent amenorrhea.
- **OA/S Alone Compared with Chemotherapy Alone:** The relevant studies compared the OA/s strategy primarily with CMF chemotherapy, and thus the significance of the results with respect to contemporary practice is limited. No significant difference between OA/s and CMF chemotherapy was observed^{108–110}. The Cochrane

review¹¹⁰ found that amenorrhea was more common with LHRH than with CMF, but menses were more likely to resume at the end of LHRH than at 36 months after chemotherapy. The latter finding could be an important consideration in the treatment of young female patients with HR-positive breast cancer.

- *OA/S Alone Compared with Tamoxifen Alone:* The combined evidence suggests that there is no difference between OA/S alone and tamoxifen alone. An exception is the ZIPP Stockholm substudy¹²², which found a suppression benefit in highly ER-positive patients. For female patients who are not candidates for any other systemic therapy, OA/S alone is a reasonable option.
- *OA/S Plus Tamoxifen Compared with Tamoxifen Alone:* In the absence of chemotherapy, there is no evidence of overall benefit for OA/S plus tamoxifen compared with tamoxifen alone. However, some evidence suggests that certain subgroups might benefit from this strategy. For example, a trend toward greater benefit was noted for young female patients 40 years of age and younger (recurrence rate: $p = 0.12$ for age ≤ 40 years vs. $p = 0.91$ for age > 40 years)^{108,121,122}. The ongoing SOFT trial (Supplementary Table 5) will also address this question.
- *OA/S Plus Tamoxifen and Chemotherapy Compared with Tamoxifen and Chemotherapy:* Whether to add OA/S to combined tamoxifen and chemotherapy is the question most relevant to current practice. The results of a subset analysis from a single study suggest no benefit with the addition of OA/S¹²¹. Subgroup analysis of the ongoing SOFT trial (Supplementary Table 5) might provide an answer.
- *OA/S Plus Tamoxifen Compared with Chemotherapy Alone:* The meta-analysis by the LHRH-Agonists in Early Breast Cancer Overview group found no difference in outcome with these two strategies, although a trend toward a benefit with OA/S was noted for female patients 40 years of age or younger ($p = 0.22$) compared with those more than 40 years of age ($p = 0.72$)¹⁰⁸. As expected, the adverse effect profiles of the treatments differed: OA/S was associated with more hot flashes; chemotherapy was associated with more nausea, alopecia, stomatitis, and diarrhea. Goserelin or triptorelin plus tamoxifen resulted in amenorrhea in all patients¹⁰⁹.
- *OA/S Plus Tamoxifen Compared with No Systemic Therapy:* Compared with no systemic therapy, the combination of OA/S and tamoxifen was associated with decreased recurrence and improved survival rates. However, as discussed earlier, whether OA/S provides a benefit in addition to that associated with tamoxifen alone is unclear. Benefit may be greater for young patients (< 40 years of age).

- *OA/S Plus Tamoxifen and Chemotherapy Compared with Chemotherapy Alone:* The combination of OA/S, tamoxifen, and chemotherapy is better than chemotherapy in all patients^{108–110}. In the Eastern Cooperative Oncology Group E5188 trial¹²⁴, no consistent benefit was observed for adding tamoxifen to OA/S and chemotherapy. The trial did not have a chemotherapy plus tamoxifen arm; thus, the significance of its results is difficult to interpret.
- *OA/S Plus Tamoxifen Compared with OA/S Plus AIs:* The combined analysis of the TEXT and SOFT trials (Supplementary Table 5) indicates a DFS rate benefit for OA/S plus exemestane compared with OA/S plus tamoxifen in premenopausal patients. It is unclear how those approaches compare with the use of tamoxifen alone, because the results of the tamoxifen-only arm of SOFT have not yet been reported.
- *Other Considerations:* In one study, goserelin every 3 months (subcutaneous depot injection, 10.8 mg) was found to be equivalent to goserelin monthly (3.6 mg)¹¹⁸. Both goserelin doses were sustained-release formulations containing a lactide/glycolide copolymer, but in different ratios (95:5 vs. 1:1). In the trials summarized in the preceding subsections, the optimal duration of LHRH was not addressed.

3.5 Trials Examining the Benefit of Adding Chemotherapy to Endocrine Therapy

Several ongoing trials are examining whether molecular profiling of tumours can select HR-positive patients who might not require chemotherapy in addition to endocrine therapy. The TAILORX trial¹²⁵ is using Oncotype DX (Genomic Health, Redwood City, CA, U.S.A.) in N0 disease and is randomizing intermediate-risk patients to chemotherapy with hormonal therapy or to hormonal therapy alone. The ongoing SWOG S1007 trial (RXPONDER, commenced in 2011)¹²⁶ is evaluating best endocrine therapy against best endocrine therapy plus chemotherapy in N1 ER-positive HER2-negative patients with a low Oncotype DX recurrence score (≤ 25). Planned accrual is 4000 patients, who will be stratified by recurrence score (10–13 vs. 14–25), menopausal status, and axillary surgery (sentinel lymph node biopsy vs. full dissection).

The OPTIMA Prelim and OPTIMA studies¹²⁷ are ongoing trials evaluating whether chemotherapy plus endocrine therapy is better than endocrine therapy alone for patients with ER-positive HER2-negative cancer and involved nodes (pN1–2). In the preliminary trial, patients are being randomized to standard therapy (chemotherapy plus endocrine therapy) or to chemotherapy alone, with endocrine therapy added if their risk of recurrence is high based on results from Oncotype DX and other assays. The main trial will further assess the assays selected in the preliminary trial.

3.6 Endocrine Therapy Plus Everolimus

The UNIRAD study¹²⁸ and the SWOG/National Surgical Adjuvant Breast and Bowel Project s1207 study^{129,130} are ongoing trials that are investigating adjuvant endocrine therapy plus everolimus. The UNIRAD trial is randomizing patients (ER-positive, HER2-negative, pN+) who are disease-free after 3 years of adjuvant endocrine therapy to ongoing endocrine therapy with or without everolimus (10 mg daily) for a total of 5 years of adjuvant therapy. The trial started in 2013 and plans to enrol 1984 patients. The s1207 trial is randomizing patients [HR-positive, HER2-negative, high-risk (including either N0 T2+ and recurrence score > 25, N1 and recurrence score > 25, or N2+)] to standard endocrine therapy plus 1 year of everolimus (10 mg daily) or to standard endocrine therapy plus 1 year of placebo. Targeted accrual is 3500 patients over 3.5 years, with completion by about 2020.

3.7 Assessment of HR Status

Although accurate HR status is crucial in determining appropriate treatment, results have often been inaccurate and irreproducible. Thresholds for determining positivity also vary (for example, $\geq 1\%$, $\geq 10\%$, any). As a result, guideline recommendations for hormone receptor testing were prepared by the PEBC based on a joint systematic review by ASCO and the College of American Pathologists, and the PEBC^{131–133}.

The guideline indicates that core biopsies can be used to assess ER and PR status before neoadjuvant therapy, but cautions that, because findings might be derived from only a small sample of a larger tumour in which normal ducts and lobules are frequently not present, and in view of the heterogeneity in tumour HR expression, it is preferable to test the tumour in the surgical excision specimen when an adequate surgical specimen is available. The guideline also notes that comparisons of core biopsies with standard surgical specimens in eighteen studies found a median concordance of 95% for ER status (all studies: >83%) and 88.5% for PR status (all studies: >69%).

Some studies also indicated that ER and PR status can change during the course of treatment. Zhang *et al.*¹³⁴ published a meta-analysis of nine studies that compared HR status before and after neoadjuvant chemotherapy. In 14.6% of cases, ER status changed (8.9% ER-negative to -positive, 5.6% ER-positive to -negative); and in 24.8% of cases, PR status changed (7.3% PR-negative to -positive, 17.0% PR-positive to -negative). Possible limitations were the heterogeneity of antibody selection, cut-off values, and chemotherapy used in the included studies. The large variation in distribution of ER-positive to -negative and PR-positive to -negative in the studies also suggests that the patient populations studied were not equivalent. Most studies

used an immunohistochemical cut-off value of 10% or greater. It is not known whether using a cut-off value of 1% (as recommended in current CCO guidelines) would have resulted in less variation. The literature search for the current guideline on systemic therapy in early breast cancer did not find any studies that evaluated whether response to endocrine therapy correlates better with HR status before or after chemotherapy.

Van de Ven *et al.*¹³⁵ also conducted a systematic review of changes in ER, PR, and HER2 status after neoadjuvant therapy (with or without trastuzumab). Discordance was reported in four of eight studies in 8%–33% of patients. Studies that indicated stability in ER and PR were generally smaller. A switch to HER2-negative was reported in up to 43% of patients when neoadjuvant chemotherapy was combined with trastuzumab. After publication of those reviews, Lindstrom *et al.*¹³⁶ published another trial of patients with relapse and found that patients with breast cancer experienced altered HR and HER2 status throughout tumour progression, possibly influenced by adjuvant therapies. Assessment of markers at relapse might improve management.

4. SUMMARY

A comprehensive systematic review of the literature addressing the use of adjuvant systemic therapy for early breast cancer addressed the question “What is the optimal systemic therapy for early breast cancer when patient and disease characteristics are considered?” The present publication specifically addresses the use of adjuvant endocrine therapy. The recommendations and justification in the accompanying clinical practice guideline in this supplement are summarized in Table 1 and are based on the summary of the evidence for the use of adjuvant tamoxifen, AIS, and OA/S presented here.

5. REVIEW AND UPDATE

Practice guidelines and literature reviews developed by the PEBC are reviewed and updated regularly. For the full 1-21 evidence-based series and subsequent updates, please visit the CCO Web site at: <https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-eb/>.

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TABLE 1 Recommendations for adjuvant endocrine therapy

For the purpose of selecting adjuvant endocrine therapy, the most reliable definitions of menopause are

- bilateral oophorectomy, or
- at least 12 months of amenorrhea before initiation of chemotherapy or tamoxifen.

In female patients 60 years of age or younger who experience amenorrhea secondary to chemotherapy or tamoxifen, defining menopause is difficult; care must be taken when initiating an aromatase inhibitor (AI).

Adjuvant endocrine therapy should be considered in all patients with estrogen receptor (ER)-positive cancer [defined in guidelines from the American Society of Clinical Oncology and the College of American Pathologists as ER immunohistochemical (IHC) staining of 1% or greater], taking into consideration overall disease risk, patient preference, and potential adverse effects.

Consensus was not reached about whether to administer adjuvant endocrine therapy in patients with ER-negative but PR-positive tumours.

Tamoxifen for 5 years has been the standard of care, but tamoxifen for up to 10 years is a reasonable option for premenopausal patients with ER-positive tumours regardless of chemotherapy use.

Ovarian ablation or suppression (OA/S) is a reasonable treatment option for premenopausal patients with ER-positive tumours who refuse or who are not candidates for any other systemic therapy.

In premenopausal patients with ER-positive tumours (treated with or without chemotherapy), the addition of OA/S to tamoxifen is not the standard of care^a.

In premenopausal patients with ER-positive tumours, treated with or without chemotherapy, OA/S plus 5 years of an AI is not the standard of care^a.

The optimal^b adjuvant endocrine therapy for postmenopausal patients with ER-positive tumours should include an AI.

Tamoxifen for up to 10 years is an acceptable treatment for postmenopausal patients with ER-positive tumours treated with or without chemotherapy.

For postmenopausal patients with ER-positive breast cancer (treated with or without chemotherapy), the acceptable strategies for the use of AIs are

- upfront therapy for 5 years (instead of tamoxifen),
- switch to an AI after 2–3 years of tamoxifen (for a total of 5 years of endocrine therapy), or
- extended adjuvant therapy for 5 years after the completion of 5 years of tamoxifen.

In patients with ER-positive tumours who do not receive adjuvant endocrine therapy immediately after surgery or chemotherapy, delayed endocrine therapy is still clinically beneficial.

^a Subsequent to submission of this guideline for publication, additional results from the SOFT trial became available, indicating that, for women who remain premenopausal after chemotherapy (as demonstrated by estradiol levels), suppression of ovarian function in addition to tamoxifen reduces the risk of breast cancer recurrence, with a further reduction when exemestane rather than tamoxifen is used^{115,116}.

^b The risk–benefit ratio of using tamoxifen rather than AI must be taken into account, recognizing the different side effect profiles of those medications.

7. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: SG has received speaking honoraria from Novartis. AE has received a grant from Genomic Health for a pending research study and was a NCIC principal investigator for the olympia trial. SFD was a principal investigator for the APHINITY trial; has received speaking honoraria from Hoffman–La Roche, Amgen, and Novartis; travel support from Celgene and Roche; and unrestricted educational grants from Roche, Pfizer, GlaxoSmithKline, and Amgen. MET has overseen funds from Roche and Amgen for the Sunnybrook Odette Cancer Centre chemotherapy suite renovation,

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8. REFERENCES

1. Berry DA, Cronin KA, Plevritis SK, *et al.* on behalf of the Cancer Intervention and Surveillance Modeling Network (CISNET) collaborators. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med* 2005;353:1784–92.
2. Eisen A, Srikanthan A, Yeung L, Iyer R, Trudeau M. Provincial variation in utilization of adjuvant chemotherapy regimens in early stage breast cancer: data from the Cancer Care Ontario

- New Drug Funding Program (NDFP) [abstract P3-12-1]. *Cancer Res* 2013;73(suppl):.
3. Eisen A, Fletcher GG, Gandhi S, *et al.* *Optimal Systemic Therapy for Early Female Breast Cancer*. Evidence-based series 1-21. Toronto, ON: Cancer Care Ontario; 2014. [Available online at: <https://www.cancercare.on.ca/toolbox/qualityguide/lines/diseasesite/breast-eb5/>; cited August 19, 2014]
 4. Regan MM, Pagani O, Fleming GF, *et al.* on behalf of the International Breast Cancer Study and the GroupSOFT and TEXT investigators. Adjuvant treatment of premenopausal women with endocrine-responsive early breast cancer: design of the TEXT and SOFT trials. *Breast* 2013;22:1094–100.
 5. Bernhard J, Luo W, Ribi K, *et al.* Patient-reported endocrine symptoms, sexual functioning, and quality of life (QoL) in the IBCSG TEXT and SOFT trials: adjuvant treatment with exemestane (E) plus ovarian function suppression (OFS) versus tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC) [abstract 557]. *J Clin Oncol* 2014;32:. [Available online at: <http://meetinglibrary.asco.org/content/129713-144>; cited January 18, 2015]
 6. Pagani O, Regan MM, Walley BA, *et al.* on behalf of the TEXT and SOFT investigators and the International Breast Cancer Study Group. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014;371:107–18.
 7. De Vos FY, van Laarhoven HW, Laven JS, *et al.* Menopausal status and adjuvant hormonal therapy for breast cancer patients: a practical guideline. *Crit Rev Oncol Hematol* 2012;84:252–60.
 8. Singletary SE, Allred C, Ashley P, *et al.* Part VII. Breast. In: Greene FL, Page DL, Fleming ID, *et al.*, eds. *American Joint Committee on Cancer Staging Manual*. 6th ed. New York, NY: Springer-Verlag; 2002: 221–40.
 9. Singletary SE, Allred C, Ashley P, *et al.* Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol* 2002;20:3628–36.
 10. Shea BJ, Grimshaw JM, Wells GA, *et al.* Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:10. [Available online at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf>; cited December 7, 2013]
 11. Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin Trials* 2005;2:209–17.
 12. Peto R, Davies C, Godwin J, *et al.* on behalf of the Early Breast Cancer Trialists' Collaborative Group. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* 2012;379:432–44.
 13. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687–717.
 14. Davies C, Godwin J, Gray R, *et al.* on behalf of the Early Breast Cancer Trialists' Collaborative Group. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;378:771–84.
 15. Clarke M, Coates AS, Darby SC, *et al.* on behalf of the Early Breast Cancer Trialists' Collaborative Group. Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. *Lancet* 2008;371:29–40.
 16. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: overview of the randomised trials. *Lancet* 1996;348:1189–96.
 17. Davies C, Pan H, Godwin J, *et al.* on behalf of the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) collaborative group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805–16. [Erratum in: *Lancet* 2013;381:804]
 18. Gray RG, Rea D, Handley K, *et al.* ATOM: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer [abstract 05]. *J Clin Oncol* 2013;31:. [Available online at: <http://meetinglibrary.asco.org/content/112995-132>; cited December 20, 2014]
 19. Rea DW, Gray RG, Bowden SJ, *et al.* Overall and subgroup findings of the ATOM trial: a randomised comparison of continuing adjuvant tamoxifen to 10 years compared to stopping after 5 years in 6953 women with ER positive or ER untested early breast cancer [abstract 1860]. *Eur J Cancer* 2013;49:S402.
 20. Fisher B, Dignam J, Bryant J, Wolmark N. 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* 2001;93:684–90.
 21. Adjuvant tamoxifen in the management of operable breast cancer: the Scottish trial. Report from the Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC), Edinburgh. *Lancet* 1987;2:171–5.
 22. Stewart HJ, Prescott RJ, Forrest AP. Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years. *J Natl Cancer Inst* 2001;93:456–62.
 23. Dignam JJ, Bryant J, Wieand HS, Fisher B, Wolmark N. Early stopping of a clinical trial when there is evidence of no treatment benefit: protocol B-14 of the National Surgical Adjuvant Breast and Bowel Project. *Control Clin Trials* 1998;19:575–88.
 24. Burstein HJ, Temin S, Anderson H, *et al.* Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J Clin Oncol* 2014;32:2255–69.
 25. American College of Obstetricians and Gynecologists. Tamoxifen and uterine cancer. Committee Opinion No. 601. *Obstet Gynecol* 2014;123:1394–7.
 26. Delozier T, Switsers O, Genot JY, *et al.* Delayed adjuvant tamoxifen: ten-year results of a collaborative randomized controlled trial in early breast cancer (TAM-02 trial). *Ann Oncol* 2000;11:515–19.
 27. Veronesi A, Miolo G, Magri MD, *et al.* Late tamoxifen in patients previously operated for breast cancer without post-operative tamoxifen: 5-year results of a single institution randomised study. *BMC Cancer* 2010;10:205.
 28. 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* 2003;349:1793–802.

29. Goss PE, Ingle JN, Martino S, *et al.* Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;97:1262–71.
30. Ingle JN, Tu D, Pater JL, *et al.* Intent-to-treat analysis of the placebo-controlled trial of letrozole for extended adjuvant therapy in early breast cancer: NCIC CTG MA.17. *Ann Oncol* 2008;19:877–82.
31. Jin H, Tu D, Zhao N, Shepherd LE, Goss PE. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. *J Clin Oncol* 2012;30:718–21.
32. Goss PE, Ingle JN, Martino S, *et al.* on behalf of the National Cancer Institute of Canada Clinical Trials Group MA.17. Efficacy of letrozole extended adjuvant therapy according to estrogen receptor and progesterone receptor status of the primary tumor: National Cancer Institute of Canada Clinical Trials Group MA.17. *J Clin Oncol* 2007;25:2006–11.
33. Goss PE, Ingle JN, Martino S, *et al.* Impact of premenopausal status at breast cancer diagnosis in women entered on the placebo-controlled NCIC CTG MA17 trial of extended adjuvant letrozole. *Ann Oncol* 2013;24:355–61.
34. Muss HB, Tu D, Ingle JN, *et al.* Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG Intergroup trial MA.17. *J Clin Oncol* 2008;26:1956–64.
35. Goss PE, Ingle JN, Pater JL, *et al.* Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. *J Clin Oncol* 2008;26:1948–55. [Erratum in: *J Clin Oncol* 2008;26:3659]
36. Goss P, Mamounas E, Jakesz R, *et al.* Aromatase inhibitors (AI) versus not (placebo/observation) as late extended adjuvant therapy for postmenopausal women with early stage breast cancer (BC): overviews of randomized trials of AI after ~ 5 years of tamoxifen [abstract 4081]. *Cancer Res* 2009;69(suppl):.
37. Pritchard KI, Shepherd LE, Chapman JA, *et al.* Randomized trial of tamoxifen versus combined tamoxifen and octreotide LAR therapy in the adjuvant treatment of early-stage breast cancer in postmenopausal women: NCIC CTG MA.14. *J Clin Oncol* 2011;29:3869–76.
38. Chapman JAW, Costantino JP, Dong B, *et al.* Randomized trials of adjuvant tamoxifen versus tamoxifen and octreotide LAR in early-stage breast cancer: NCIC CTG MA.14 and NSABP B-29 [abstract 538]. *J Clin Oncol* 2012;30:. [Available online at: <http://meetinglibrary.asco.org/content/94683-114>; cited January 21, 2015]
39. Blamey RW, Bates T, Chetty U, *et al.* Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial. *Eur J Cancer* 2013;49:2294–302.
40. Dowsett M, Cuzick J, Ingle J, *et al.* Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* 2010;28:509–18.
41. Forbes JF, Dowsett M, Bradley R, *et al.* Patient-level meta-analysis of randomized trials of aromatase inhibitors (AI) versus tamoxifen (Tam) [abstract 529]. *J Clin Oncol* 2014;32:. [Available online at: <http://meetinglibrary.asco.org/content/132802-144>; cited January 21, 2015]
42. Gnant M, Mlineritsch B, Stoeger H, *et al.* on behalf of the Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol* 2011;12:631–41.
43. Alexander W. San Antonio Breast Cancer Symposium. *P T* 2011;36:156–8. [Available online at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3086108/>; cited January 21, 2014; report of presentation by Gnant M. Carry-over effect of adjuvant zoledronic acid after 48 and 62 months: the ABCSG-12 trial. Presented at the 2010 San Antonio Breast Cancer Symposium; San Antonio, TX, U.S.A.; December 8–12, 2010]
44. Bankhead C. SABCS: bone drug gives DFS boost in breast cancer [Web article]. In: MedPage Today. New York. NY: MedPage Today; 2011. [Available online at: <http://www.medpagetoday.com/MeetingCoverage/SABCS/30136>; cited September 7, 2012; report of presentation by Gnant M, Mlineritsch B, Luschin–Ebengreuth G, *et al.* Long-term follow-up in ABCSG-12: significantly improved overall survival with adjuvant zoledronic acid in premenopausal patients with endocrine-receptor-positive early breast cancer (abstract S1-2). Presented at the 2011 San Antonio Breast Cancer Symposium; San Antonio, TX, U.S.A.; December 6–10, 2011.]
45. Hadji P, Coleman R, Gnant M, Green J. The impact of menopause on bone, zoledronic acid, and implications for breast cancer growth and metastasis. *Ann Oncol* 2012;23:2782–90.
46. Gnant M. Zoledronic acid in the treatment of early-stage breast cancer: is there a final verdict? *Curr Oncol Rep* 2012;14:35–43.
47. Gnant M, Mlineritsch B, Luschin–Ebengreuth G, *et al.* on behalf of the Austrian Breast and Colorectal Cancer Study Group (ABCSG). Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density sub-study. *Lancet Oncol* 2008;9:840–9.
48. Rossi E, Morabito A, De Maio E, *et al.* Endocrine effects of adjuvant letrozole + triptorelin compared with tamoxifen + triptorelin in premenopausal patients with early breast cancer. *J Clin Oncol* 2008;26:264–70.
49. Rossi E, Morabito A, Di Rella F, *et al.* Endocrine effects of adjuvant letrozole compared with tamoxifen in hormone-responsive postmenopausal patients with early breast cancer: the HOBEO trial. *J Clin Oncol* 2009;27:3192–7.
50. Nuzzo F, Gallo C, Lastoria S, *et al.* Bone effect of adjuvant tamoxifen, letrozole or letrozole plus zoledronic acid in early-stage breast cancer: the randomized phase 3 HOBEO study. *Ann Oncol* 2012;23:2027–33.
51. Cuzick J, Sestak I, Baum M, *et al.* on behalf of the ATAC/LATTE investigators. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol* 2010;11:1135–41.
52. Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M on behalf of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008;9:45–53.

53. Duffy S, Jackson TL, Lansdown M, *et al.* on behalf of the ATAC Trialists' Group. The ATAC adjuvant breast-cancer trial: six-year results of the endometrial subprotocol. *J Obstet Gynaecol* 2010;30:596–604.
54. Regan MM, Neven P, Giobbie-Hurder A, *et al.* on behalf of the BIG 1-98 Collaborative Group and the International Breast Cancer Study Group. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncol* 2011;12:1101–8.
55. Colleoni M, Giobbie-Hurder A, Regan MM, *et al.* Analyses adjusting for selective crossover show improved overall survival with adjuvant letrozole compared with tamoxifen in the BIG 1-98 study. *J Clin Oncol* 2011;29:1117–24.
56. Crivellari D, Sun Z, Coates AS, *et al.* Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: the BIG 1-98 trial. *J Clin Oncol* 2008;26:1972–9.
57. Viale G, Regan MM, Dell'Orto P, *et al.* on behalf of the BIG 1-98 Collaborative and International Breast Cancer Study groups. Which patients benefit most from adjuvant aromatase inhibitors? Results using a composite measure of prognostic risk in the BIG 1-98 randomized trial. *Ann Oncol* 2011;22:2201–7.
58. Metzger O, Giobbie-Hurder A, Mallon E, *et al.* Relative effectiveness of letrozole compared with tamoxifen for patients with lobular carcinoma in the BIG 1-98 trial [abstract S1-1]. *Cancer Res* 2012;72:.
59. Filho OM, Giobbie-Hurder A, Mallon EA, *et al.* Relative effectiveness of letrozole alone or in sequence with tamoxifen for patients diagnosed with invasive lobular carcinoma [abstract 529]. *J Clin Oncol* 2013;31: [Available online at: <http://meetinglibrary.asco.org/content/112365-132>; cited January 28, 2015]
60. Pfeiler G, Stoger H, Dubsky P, *et al.* Efficacy of tamoxifen + aminoglutethimide in normal weight and overweight postmenopausal patients with hormone receptor-positive breast cancer: an analysis of 1509 patients of the ABCSG-06 trial. *Br J Cancer* 2013;108:1408–14.
61. Schmid M, Jakesz R, Samonigg H, *et al.* Randomized trial of tamoxifen versus tamoxifen plus aminoglutethimide as adjuvant treatment in postmenopausal breast cancer patients with hormone receptor-positive disease: Austrian Breast and Colorectal Cancer Study Group Trial 6. *J Clin Oncol* 2003;21:984–90.
62. Dubsky PC, Jakesz R, Mlineritsch B, *et al.* Tamoxifen and anastrozole as a sequencing strategy: a randomized controlled trial in postmenopausal patients with endocrine-responsive early breast cancer from the Austrian Breast and Colorectal Cancer Study Group. *J Clin Oncol* 2012;30:722–8.
63. Dubsky PC, Jakesz R, Greil R, *et al.* Two years of tamoxifen followed by 3 years of anastrozole versus 5 years of tamoxifen alone in postmenopausal women with hormone-responsive early breast cancer: efficacy results from 3,714 patients from the Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 8 [abstract 524]. *J Clin Oncol* 2010;28: [Available online at: <http://meetinglibrary.asco.org/content/50528-74>; cited January 22, 2015]
64. Bago-Horvath Z, Rudas M, Dubsky P, *et al.* on behalf of the Austrian Breast and Colorectal Cancer Study Group. Adjuvant sequencing of tamoxifen and anastrozole is superior to tamoxifen alone in postmenopausal women with low proliferating breast cancer. *Clin Cancer Res* 2011;17:7828–34.
65. van de Velde CJH, Rea D, Seynaeve C, *et al.* Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. *Lancet* 2011;377:321–31.
66. Bartlett JM, Brookes CL, Robson T, *et al.* Estrogen receptor and progesterone receptor as predictive biomarkers of response to endocrine therapy: a prospectively powered pathology study in the Tamoxifen and Exemestane Adjuvant Multinational trial. *J Clin Oncol* 2011;29:1531–8.
67. van de Water W, Fontein DB, van Nes JG, *et al.* Influence of semi-quantitative oestrogen receptor expression on adjuvant endocrine therapy efficacy in ductal and lobular breast cancer—a TEAM study analysis. *Eur J Cancer* 2013;49:297–304.
68. Hozumi Y, Suemasu K, Takei H, *et al.* The effect of exemestane, anastrozole, and tamoxifen on lipid profiles in Japanese postmenopausal early breast cancer patients: final results of National Surgical Adjuvant Study BC 04, the TEAM Japan substudy. *Ann Oncol* 2011;22:1777–82.
69. van Nes JG, Fontein DB, Hille ET, *et al.* Quality of life in relation to tamoxifen or exemestane treatment in postmenopausal breast cancer patients: a Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial side study. *Breast Cancer Res Treat* 2012;134:267–76.
70. Takei H, Ohsumi S, Shimozuma K, *et al.* Health-related quality of life, psychological distress, and adverse events in postmenopausal women with breast cancer who receive tamoxifen, exemestane, or anastrozole as adjuvant endocrine therapy: National Surgical Adjuvant Study of Breast Cancer 04 (N-SAS BC 04). *Breast Cancer Res Treat* 2012;133:227–36.
71. Aihara T, Suemasu K, Takei H, *et al.* Effects of exemestane, anastrozole and tamoxifen on bone mineral density and bone turnover markers in postmenopausal early breast cancer patients: results of N-SAS BC 04, the TEAM Japan substudy. *Oncology* 2010;79:376–81.
72. Hadji P, Asmar L, van Nes JG, *et al.* The effect of exemestane and tamoxifen on bone health within the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial: a meta-analysis of the US, German, Netherlands, and Belgium sub-studies. *J Cancer Res Clin Oncol* 2011;137:1015–25.
73. Kieback DG, Harbeck N, Bauer W, *et al.* Endometrial effects of exemestane compared to tamoxifen within the Tamoxifen Exemestane Adjuvant Multicenter (TEAM) trial: results of a prospective gynecological ultrasound substudy. *Gynecol Oncol* 2010;119:500–5.
74. Andersen J, Kamby C, Ejlersen B, *et al.* Tamoxifen for one year versus two years versus 6 months of tamoxifen and 6 months of megestrol acetate: a randomized comparison in postmenopausal patients with high-risk breast cancer (DBCG 89C). *Acta Oncol* 2008;47:718–24.
75. Boccardo F, Rubagotti A, Guglielmini P, *et al.* Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian Tamoxifen Anastrozole (ITA) trial. *Ann Oncol* 2006;17(suppl 7):vii10–4.
76. Boccardo F, Rubagotti A, Puntoni M, *et al.* Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole trial. *J Clin Oncol* 2005;23:5138–47.

77. Boccardo F, Guglielmini P, Bordonaro R, *et al.* Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: long term results of the Italian Tamoxifen Anastrozole trial. *Eur J Cancer* 2013;49:1546–54.
78. Kaufmann M, Jonat W, Hilfrich J, *et al.* Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 study. *J Clin Oncol* 2007;25:2664–70.
79. Bliss JM, Kilburn LS, Coleman RE, *et al.* Disease-related outcomes with long-term follow-up: an updated analysis of the intergroup exemestane study. *J Clin Oncol* 2012;30:709–17.
80. Jassem J on behalf of the International Exemestane Study Group. Intergroup Exemestane Study mature analysis: overall survival data. *Anticancer Drugs* 2008;19(suppl 1):S3–7.
81. Mieog JS, Morden JP, Bliss JM, Coombes RC, van de Velde CJH on behalf of the Committee IESS. Carpal tunnel syndrome and musculoskeletal symptoms in postmenopausal women with early breast cancer treated with exemestane or tamoxifen after 2–3 years of tamoxifen: a retrospective analysis of the Intergroup Exemestane Study. *Lancet Oncol* 2012;13:420–32.
82. Coleman RE, Banks LM, Girgis SI, *et al.* Reversal of skeletal effects of endocrine treatments in the Intergroup Exemestane Study. *Breast Cancer Res Treat* 2010;124:153–61.
83. Bertelli G, Hall E, Ireland E, *et al.* Long-term endometrial effects in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES)—a randomised controlled trial of exemestane versus continued tamoxifen after 2–3 years tamoxifen. *Ann Oncol* 2010;21:498–505.
84. Fallowfield LJ, Kilburn LS, Langridge C, *et al.* Long-term assessment of quality of life in the Intergroup Exemestane Study: 5 years post-randomisation. *Br J Cancer* 2012;106:1062–7.
85. Aihara T, Takatsuka Y, Ohsumi S, *et al.* Phase III randomized adjuvant study of tamoxifen alone versus sequential tamoxifen and anastrozole in Japanese postmenopausal women with hormone-responsive breast cancer: N-SAS BC03 study. *Breast Cancer Res Treat* 2010;121:379–87.
86. Ohsumi S, Shimozuma K, Ohashi Y, *et al.* Health-related quality of life and psychological distress of breast cancer patients after surgery during a phase III randomized trial comparing continuation of tamoxifen with switching to anastrozole after adjuvant tamoxifen for 1–4 years: N-SAS BC 03. *Breast Cancer Res Treat* 2011;127:143–52.
87. Iwata H, Ohsumi S, Aogi K, *et al.* Long-term follow-up data of the side effect profile of anastrozole compared with tamoxifen in Japanese women: findings from N-SAS BC03 trial [abstract P2-13-07]. *Cancer Res* 2012;72:.
88. Markopoulos C, Dafni U, Misitzi J, *et al.* Extended adjuvant hormonal therapy with exemestane has no detrimental effect on the lipid profile of postmenopausal breast cancer patients: final results of the ATENA lipid substudy. *Breast Cancer Res* 2009;11:R35.
89. Markopoulos C, Chrissochou M, Michailidou A, *et al.* Effect of exemestane on the lipidemic profile of post-menopausal operable breast cancer patients following 5–7 years of adjuvant tamoxifen: preliminary results of the ATENA substudy. *Anticancer Drugs* 2005;16:879–83.
90. Jakesz R, Greil R, Gnant M, *et al.* Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. *J Natl Cancer Inst* 2007;99:1845–53.
91. Mamounas EP, Jeong JH, Wickerham DL, *et al.* Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol* 2008;26:1965–71.
92. Members of the Breast Cancer Disease Site Group. *The Role of Aromatase Inhibitors in Adjuvant Therapy for Postmenopausal Women with Hormone Receptor-Positive Breast Cancer*. Evidence-based series 1-18. Toronto, ON: Cancer Care Ontario; 2012. [Available online at: <https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13882>; cited October 18, 2012]
93. Burstein HJ, Prestrud AA, Seidenfeld J, *et al.* on behalf of the American Society of Clinical Oncology. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol* 2010;28:3784–96.
94. Helwick C. Exemestane and anastrozole comparable in MA.27 final analysis. *The ASCO Post* 2011;2(2):6. [Report of presentation by Goss PE, Ingle JN, Chapman JAW, *et al.* Final analysis of NCIC CTG MA.27: a randomized phase III trial of exemestane versus anastrozole in postmenopausal women with hormone receptor positive primary breast cancer (abstract S1-1). Presented at the 2010 San Antonio Breast Cancer Symposium; San Antonio, TX, U.S.A.; December 8–12, 2010]
95. Medical Education Network (MEDNET). Aromatase inhibitors as upfront endocrine therapy in early breast cancer [Web article]. Vaudreuil, QC: MEDNET; n.d. [Available at: <http://www.mednet.ca/en/report/aromatase-inhibitors-as-upfront-endocrine-therap.html>; cited May 28, 2012; report of presentation by Goss PE, Ingle JN, Chapman JAW, *et al.* Final analysis of NCIC CTG MA.27: a randomized phase III trial of exemestane versus anastrozole in postmenopausal women with hormone receptor positive primary breast cancer. Presented at the 2010 San Antonio Breast Cancer Symposium; San Antonio, TX, U.S.A.; December 9–12, 2010]
96. Hershman DL, Cheung AM, Chapman JW, *et al.* Effects of adjuvant exemestane versus anastrozole on bone mineral density: two-year results of the NCIC CTG MA.27 bone companion study [abstract 518]. *J Clin Oncol* 2011;29: [Available online at: <http://meetinglibrary.asco.org/content/84625-102>; cited January 23, 2015]
97. Goss PE, Ingle JN, Pritchard KI, *et al.* Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27—a randomized controlled phase III trial. *J Clin Oncol* 2013;31:1398–404.
98. Goss PE, Hershman DL, Cheung AM, *et al.* Effects of adjuvant exemestane versus anastrozole on bone mineral density for women with early breast cancer (MA.27B): a companion analysis of a randomised controlled trial. *Lancet Oncol* 2014;15:474–82.
99. Monnier A. FACE: the barefaced facts of AI potency. *Cancer Manag Res* 2010;2:267–76.
100. Kaura S, Dranitsaris G. Letrozole or anastrozole for the treatment of hormone positive breast cancer: a clinical comparison using indirect statistical techniques [abstract 224P]. *Ann Oncol*

- 2010;21(suppl 8):viii81. [Available online at http://annonc.oxfordjournals.org/content/21/suppl_8/viii78.full.pdf; cited March 6, 2012]
101. Rugo H, Kaura S, Dranitsaris G. Application of number needed to treat (NNT) to compare benefit: letrozole or anastrozole for the prevention of early recurrences in postmenopausal women with early stage breast cancer [abstract 195P]. *Ann Oncol* 2008;19(suppl 8):viii81. [Available online at http://annonc.oxfordjournals.org/content/19/suppl_8/viii77.full.pdf; cited March 6, 2012]
 102. Tjan-Heijnen VC, Smorenburg CH, de Graaf H, *et al.* Recovery of ovarian function in breast cancer patients with chemotherapy-induced amenorrhea receiving anastrozole in the Dutch DATA study [abstract PD04-2]. *Cancer Res* 2011;71(suppl):.
 103. Colleoni M. The SOLE trial: International Breast Cancer Study Group (IBCSG 35-07) and Breast International Group (BIG 1-07) study of letrozole extension [abstract OT2-02-1]. *Cancer Res* 2011;71(suppl):.
 104. Iwata H, Ohtani S, Fujisawa T, *et al.* N-SAS BC06: a phase III study of adjuvant endocrine therapy with or without chemotherapy for postmenopausal breast cancer patients who responded to neoadjuvant letrozole (LET): the New Primary Endocrine-Therapy Origination Study (NEOS) [abstract TPS654]. *J Clin Oncol* 2013;31. [Available online at: <http://meetinglibrary.asco.org/content/113458-132>; cited January 23, 2015]
 105. Taira N, Iwata H, Hasegawa Y, *et al.* Health-related quality of life and psychological distress during neoadjuvant endocrine therapy with letrozole to determine endocrine responsiveness in postmenopausal breast cancer. *Breast Cancer Res Treat* 2014;145:155–64.
 106. Beatson GT. Classics in oncology. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. *CA Cancer J Clin* 1983;33:108–21 [Reprint of articles in: *Lancet* 1896;148:104–7,162–5]
 107. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2006;24:5769–79.
 108. Cuzick J, Ambroisine L, Davidson N, *et al.* on behalf of the LHRH-Agonists in Early Breast Cancer Overview group. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet* 2007;369:1711–23.
 109. Eisen A, Messersmith H, Franek J, Trudeau M on behalf of the Breast Cancer Disease Site Group. *Adjuvant Ovarian Ablation in the Treatment of Premenopausal Women with Early Stage Invasive Breast Cancer*. Evidence-based series 1-9. Toronto, ON: Cancer Care Ontario; 2010. [Available online at: <https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=75982>; cited May 23, 2012]
 110. Goel S, Sharma R, Hamilton A, Beith J. LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. *Cochrane Database Syst Rev* 2009;CD004562.
 111. Gnant M, Mlineritsch B, Schippinger W, *et al.* Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009;360:679–91. [Erratum in: *N Engl J Med* 2009;360:379]
 112. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, *et al.* Long-term follow-up in ABCSG-12: significantly improved overall survival with adjuvant zoledronic acid in premenopausal patients with endocrine-receptor-positive early breast cancer [abstract S1-2]. *Cancer Res* 2011;71(suppl):.
 113. Gnant M, Mlineritsch B, Stoeger H, *et al.* Overall survival with adjuvant zoledronic acid in premenopausal breast cancer patients with complete endocrine blockade: long-term results from ABCSG-12 [abstract 520]. *J Clin Oncol* 2011;29. [Available online at: <http://meetinglibrary.asco.org/content/83575-102>; cited January 23, 2015]
 114. Kaufman M. SABCS: mixed findings fail to clarify role of bisphosphonates. London, U.K.: CancerNetwork; 2011. [Available online at: <http://www.cancernetwork.com/print/article/10165/2004594>; cited September 7, 2012]
 115. Ribí K, Luo W, Bernhard J, *et al.* on behalf of the SOFT investigators and the International Breast Cancer Study Group. Patient-reported endocrine symptoms, sexual functioning and quality of life (QoL) in the IBCSG SOFT trial: adjuvant treatment with tamoxifen (T) alone versus T plus ovarian function suppression (OFS) in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC) [abstract S3-09]. Presented at the 2014 San Antonio Breast Cancer Symposium; San Antonio, TX, U.S.A.; December 9–13, 2014. [Available online at: http://www.abstracts2view.com/sabcs14/view.php?nu=SABCS13L_182; cited January 14, 2015]
 116. Francis PA, Regan MM, Fleming GF, *et al.* on behalf of the SOFT investigators and the International Breast Cancer Study Group. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014; [Epub ahead of print].
 117. Tevaarwerk AJ, Wang M, Zhao F, *et al.* Phase III comparison of tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node-negative, hormone receptor-positive breast cancer (E-3193, INT-0142): a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2014;32:3948–58.
 118. Masuda N, Iwata H, Rai Y, *et al.* Monthly versus 3-monthly goserelin acetate treatment in pre-menopausal patients with estrogen receptor-positive early breast cancer. *Breast Cancer Res Treat* 2011;126:443–51.
 119. Paridaens RJ, Gelber S, Cole BF, *et al.* Adjuvant! Online estimation of chemotherapy effectiveness when added to ovarian function suppression plus tamoxifen for premenopausal women with estrogen-receptor-positive breast cancer. *Breast Cancer Res Treat* 2010;123:303–10.
 120. Thurlimann B, Price KN, Gelber RD, *et al.* Is chemotherapy necessary for premenopausal women with lower-risk node-positive, endocrine responsive breast cancer? 10-Year update of International Breast Cancer Study Group trial 11-93. *Breast Cancer Res Treat* 2009;113:137–44.
 121. Hackshaw A, Baum M, Fornander T, *et al.* Long-term effectiveness of adjuvant goserelin in premenopausal women with early breast cancer. *J Natl Cancer Inst* 2009;101:341–9.
 122. Sverrisdóttir A, Johansson H, Johansson U, *et al.* Interaction between goserelin and tamoxifen in a prospective randomised clinical trial of adjuvant endocrine therapy in premenopausal breast cancer. *Breast Cancer Res Treat* 2011;128:755–63.
 123. Castiglione-Gertsch M, O'Neill A, Price KN, *et al.* on behalf of the International Breast Cancer Study Group. Adjuvant

- chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node–negative breast cancer: a randomized trial. *J Natl Cancer Inst* 2003;95:1833–46.
124. Davidson NE, O'Neill AM, Vukov AM, *et al*. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). *J Clin Oncol* 2005;23:5973–82.
 125. Zujewski JA, Kamin L. Trial assessing individualized options for treatment for breast cancer: the TAILORX trial. *Future Oncol* 2008;4:603–10.
 126. Gonzalez–Angulo AM, Barlow WE, Gralow J, *et al*. SWOG S1007: a phase III, randomized clinical trial of standard adjuvant endocrine therapy with or without chemotherapy in patients with one to three positive nodes, hormone receptor (HR)–positive, and HER2–negative breast cancer with recurrence score (RS) of 25 or less [abstract TPS104]. *J Clin Oncol* 2011;29. [Available online at: <http://meetinglibrary.asco.org/content/76547-102>; cited January 23, 2015]
 127. Bartlett J, Canney P, Campbell A, *et al*. Selecting breast cancer patients for chemotherapy: the opening of the UK OPTIMA trial. *Clin Oncol (R Coll Radiol)* 2013;25:109–16.
 128. Bachelot TD, Chabaud S, Martin AL, Lemonnier J, Campone M, Andre F. UNIRAD: multicenter, double-blind, phase III study of everolimus plus ongoing adjuvant therapy in ER+, HER2–breast cancer [abstract TPS653]. *J Clin Oncol* 2013;31. [Available online at: <http://meetinglibrary.asco.org/content/112509-132>; cited January 23, 2015]
 129. Chavez–MacGregor M, Barlow WE, Gonzalez–Angulo AM, *et al*. A phase III randomized, placebo–controlled clinical trial evaluating the use of adjuvant endocrine therapy +/- one year of everolimus in patients with high-risk, hormone receptor–(HR) positive and HER2–negative breast cancer: SWOG/NSABP S1207 [abstract OT2-04]. *Cancer Res* 2012;72(suppl):.
 130. Chavez–MacGregor M, Barlow WE, Gonzalez–Angulo AM, *et al*. Phase III randomized, placebo–controlled clinical trial evaluating the use of adjuvant endocrine therapy with or without one year of everolimus in patients with high-risk, hormone receptor–(HR) positive and HER2–neu–negative breast cancer: SWOG/NSABP S1207 [abstract TPS657]. *J Clin Oncol* 2013;31. [Available online at: <http://meetinglibrary.asco.org/content/118004-132>; cited January 23, 2015]
 131. Nofech–Mozes S, Vella ET, Dhesy–Thind S, Hanna W. *Guideline on Hormone Receptor Testing in Breast Cancer*. Evidence-based series 22-1. Toronto, ON: Cancer Care Ontario; 2011. [Available online at: <https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=98566>; cited October 5, 2012]
 132. Nofech–Mozes S, Vella ET, Dhesy–Thind S, *et al*. Systematic review on hormone receptor testing in breast cancer. *Appl Immunohistochem Mol Morphol* 2012;20:214–63.
 133. Nofech–Mozes S, Vella ET, Dhesy–Thind S, Hanna WM. Cancer Care Ontario guideline recommendations for hormone receptor testing in breast cancer. *Clin Oncol* 2012;24:684–96. [Available online at: <http://www.clinicaloncologyonline.net/article/S0936-6555%2812%2900127-6/abstract>; cited October 5, 2012]
 134. Zhang N, Moran MS, Huo Q, Haffty BG, Yang Q. The hormonal receptor status in breast cancer can be altered by neoadjuvant chemotherapy: a meta-analysis. *Cancer Invest* 2011;29:594–8.
 135. van de Ven S, Smit VT, Dekker TJ, Nortier JW, Kroep JR. Discordances in ER, PR and HER2 receptors after neoadjuvant chemotherapy in breast cancer. *Cancer Treat Rev* 2011;37:422–30.
 136. Lindstrom LS, Karlsson E, Wilking UM, *et al*. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. *J Clin Oncol* 2012;30:2601–8.

Correspondence to: Andrea Eisen, Division of Medical Oncology, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, T2038, Toronto, Ontario M4N 3M5.

E-mail: andrea.eisen@sunnybrook.ca

* Durham Regional Cancer Centre, Oshawa, ON.
† Program in Evidence-Based Care, Cancer Care Ontario; and Department of Oncology, McMaster University, Hamilton, ON.

‡ Sunnybrook Health Science Centre, Toronto, ON.
§ Cancer Centre of Southeastern Ontario, Kingston General Hospital, and Queen's University, Kingston, ON.

|| The Ottawa Hospital Cancer Centre and University of Ottawa, Ottawa, ON.