Adjuvant Systemic Therapy: Endocrine Therapy

7

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Introduction

Adjuvant endocrine therapy (ET) is a major treatment modality for estrogen receptor (ER)-positive breast cancer. Among early-stage breast cancer patients, approximately 60% require adjuvant ET after chemotherapy (CT), 20% only require ET, and 20% only require CT. The antiestrogen drug tamoxifen was first introduced in the 1970s, and over the past 40 years, it has significantly improved overall survival (OS) in women with hormone receptor (HR)-positive early breast cancer. More recently, third-generation aromatase inhibitors (AIs) have been added to the repertoire of adjuvant ETs, and these inhibitors are superior to tamoxifen in reducing recurrence risk and improving OS in postmenopausal women.

Current ETs modulate or disrupt estrogen production or ER function/expression in breast cancer cells. In premenopausal women, the ovarian follicles are the main source of estrogen production. Ovarian estrogen production is regulated by the anterior pituitary gland, which produces luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH acts upon thecal cells to stimulate androgen synthesis, whereas FSH acts upon granulosa cells to stimulate the production of the enzyme aromatase, which converts testosterone and androstenedione to estradiol (E_2) and estrone, respectively, through aromatization. Pituitary LH and FSH production is in turn regulated by LH-releasing hormone (LHRH) (also known as gonadotropin-releasing hormone), which is produced in the hypothalamus. In postmenopausal women, estrogen production is dependent on peripheral aromatization, which predominantly occurs in the liver, adrenal glands, and adipose tissue. ET modulates or disrupts ER signaling by blocking pituitary LH/FSH production (LHRH agonists), blocking the ER (tamoxifen), degrading the ER (fulvestrant), or inhibiting peripheral estrogen production (AIs). Given their different modes of action, menopausal status is important in ET selection.

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Rationale of Endocrine Therapy

ERs belong to a family of nuclear steroid receptors that includes thyroid hormone, vitamin D, and retinoid receptors. ER phosphorylation, which occurs upon estrogen binding, induces a conformational change, resulting in receptor dimerization. The receptor complex binds to specific estrogen response elements in the promoters of target genes, resulting in the upregulation of target gene expression [1]. Two ERs, ERα and ERβ, have been described [2]. ERβ is broadly expressed in a variety of tissues, whereas ERα has a more restricted expression pattern (breast, ovary, uterus, and endometrium). The function and role of ERβ in breast cancer are not yet clear; thus, ER generally refers to ERα. The ER exerts both genomic and nongenomic effects in breast cancer. Genomic effects include the transcriptional activation of specific genes that are important for tumor cell growth and survival, whereas nongenomic effects include the activation of growth factor pathways, such as those of human epidermal growth factor receptor 2 (HER2) and insulin-like growth factor receptor, that enhance tumor growth. Growth factor receptor-linked kinases further activate the ER and its coactivators to augment ER-mediated transcriptional activity. This bidirectional crosstalk can cause ET resistance [3]. HR status is currently determined based on the immunohistochemical (IHC) expression of ER and progesterone receptor (PR). Tumors with any detectable (≥1%) ER and/or PR expression are considered HR positive. ER expression correlates with slower tumor growth, better differentiation, and longer natural history. By contrast, the absence of both ER and PR expression is associated with poorer prognosis and reduced OS rate. A positive response to hormone therapy is correlated with higher HR

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protein and mRNA expression levels [4]. For example, 60% of ER-positive/PR-positive patients were responsive to ET, compared with 30% of ER-positive/PR-negative patients and <10% of ER-negative/PR-negative patients. The updated results of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) clearly showed that the benefit of ET only occurs in ER-positive tumors and is strongest in tumors with high ER expression [5]. The benefit of adjuvant ET is very small in patients with HR-positive disease who have lymph node-negative cancers ≤0.5 cm or 0.6–1.0 cm in diameter with favorable prognostic features.

Determination of Endocrine Therapy Responsiveness

Endocrine-responsive breast cancer is a heterogeneous disease with a wide spectrum of clinical, pathologic, and molecular features. A variety of prognostic factors associated with recurrence risk in ER-positive breast cancer have emerged (Table 7.1). These factors provide information on the likelihood of tumor recurrence and on risk reduction with adjuvant ET. They may also help to estimate the absolute magnitude of treatment effects. However, to date, no single marker—aside from HR expression—is adequate for identifying patients who may benefit from adjuvant ET. Similarly, no single marker can identify the optimal ET for a given patient. Although molecular typing is an ideal method for assessing recurrence risk and treatment response, routine genetic profiling has not yet been established in clinical practice. IHC typing is still considered state of the art for assessing the risk of relapse and the potential benefits of specific therapies.

The evolving role of endocrine responsiveness in the selection of adjuvant breast cancer therapy is clearly seen in the consensus reports of the St. Gallen International Expert Consensus Meetings. In 2005, St. Gallen Conference panelists included endocrine responsiveness as the decisive criterion in adjuvant therapy selection [6]. Three categories (responsive, uncertain responsive, and unresponsive) were acknowledged and were later renamed as highly endocrine responsive, incompletely endocrine responsive, and endocrine nonresponsive [7]. The definitions of these categories rely mainly, but not exclusively, on the percentages of ER- and PR-positive tumor cells. High ER and PR expression and the absence of adverse biological factors (e.g., HER2 overexpression/amplification, high proliferation index, and high urokinase inhibitor type-1 level) denote highly endocrine-responsive tumors. Incompletely endocrine-responsive tumors are characterized by PR negativity, the presence of adverse biological factors, and extensive axillary lymph node invasion. At St. Gallen 2011, endocrine responsiveness was first linked to the intrinsic molecular breast cancer subtypes (Table 7.2) [8].

Table 7.1 Prognostic factors in HR-positive breast cancer

Tumor size
Nodal status
Tumor grade
Quantitative HR expression
HER2 status
Lymphovascular invasion
Proliferation status (e.g., Ki-67)
Multigene prognostic signatures (e.g., 21-gene recurrence score, PAM 50, Mamma Print)

Gene Expression Profiling

Breast cancer is a heterogeneous disease with diverse morphologies, molecular characteristics, and clinical behaviors. Gene expression profiling studies have identified several distinct breast cancer subtypes that differ markedly in prognosis and therapy response [8–10]. A list of the intrinsic genes that are used to differentiate subtypes includes ER, HER2, and proliferation-related genes as well as a unique cluster of genes called the basal cluster. The molecular subtypes include the following: (1) luminal subtype (luminal A and B) expresses genes associated with luminal epithelial cells of normal breast tissue and overlaps with ER-positive breast cancers as defined by clinical assays, (2) HER2-enriched subtype comprises the majority of clinically HER2-positive breast cancers, and (3) ER-negative subtype expresses low levels of HR-related genes.

The luminal A and luminal B subtypes comprise the majority of ER-positive breast cancers, with luminal A

Table 7.2 Clinicopathologic definitions of the intrinsic subtypes according to the 2011 St. Gallen International Expert Consensus Meeting

Intrinsic subtype	Clinicopathologic definition
Luminal A	ER and/or PR positive
	HER2 negative
	Ki-67 low
Luminal B (HER2 negative)	ER and/or PR positive
	HER2 negative
	Ki-67 high
Luminal B (HER2 positive)	ER and/or PR positive
	HER2 positive
	Ki-67 any

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The 2011 Saint Gallen Consensus Meeting defined as "low proliferation" tumors with a Ki67 index <14%. However, during the 2013 Saint Gallen Conference, the majority of panelists voted that a threshold of ≥20% was indicative of "high" Ki67 status. In March 2015, during the last Saint Gallen Conference, the use of the median Ki67 value from the local laboratory was proposed as the cutoff and accepted by the panel of experts

tumors being more common (40% vs. 20%, respectively, of all breast cancers). These subtypes have certain important molecular and prognostic distinctions. The clinicopathologic definitions of luminal A and B subtypes are shown below (Table 7.2). Luminal A tumors usually have high ER expression, low HER2 expression, and a low proliferation index (Ki-67). Compared with luminal A tumors, luminal B tumors have a lower ER expression, variable HER2 expression, and higher proliferation index. Luminal B tumors carry a worse prognosis than luminal A tumors.

Gene expression profiling has shed light on the complex molecular background of this disease and holds the potential for more accurate prognostication and patient stratification for therapy. Several genomic tests have been developed with the aim of improving prognostic information beyond that which is provided by classic clinicopathologic parameters [11–14]. Some of these tests are currently available in the clinic and are used to determine prognosis and, more importantly, to assist in determining the need for adjuvant chemotherapy, particularly in patients with ER-positive disease. The available data suggest that information generated from genomic tests has resulted in a change in decision-making in approximately 25–30% of cases.

Molecular signatures, such as the 21-gene recurrence score (RS) (Oncotype DX®) [11], the Amsterdam 70-gene prognostic profile (MammaPrint®) [12], Prosigna (PAM50) [14], and the Rotterdam/Veridex 76-gene signature [13], increase the prognostic value of conventional indicators in predicting breast cancer outcomes and treatment response. Oncotype DX is the most widely used of these assays. Oncotype DX can be performed using formalin-fixed paraffin-embedded tissue, whereas the other tests require fresh or frozen tissue. The predictive value of Oncotype DX has been validated in both premenopausal and postmenopausal women, and its use in node-negative, ER-positive breast cancer patients is suggested in the American Society of Clinical Oncology (ASCO) guidelines. MammaPrint and Oncotype DX have a similar predictive ability for clinical outcome [15]. The MammaPrint assay is approved by the Food and Drug Administration (FDA) for the assessment of recurrence risk in ER-positive and ER-negative breast cancer patients.

The Trial Assigning Individualized Options for Treatment (TAILORx) aims to validate the RS prospectively. This study recruited 10,273 node-negative patients with hormone receptor-positive and HER2-negative breast cancer. The RS determined the recommended adjuvant therapy. Of note, the cutoff scores for the respective risk groups were different from earlier studies (low-risk ≤10, intermediate-risk 11–25, and high-risk ≥26). This decision to change the cutoff scores was based on clinical consensus. The primary endpoint was disease-free survival (DFS). Only intermediate-risk patients underwent randomization of treatment. Low-risk patients were recommended endocrine therapy alone, whereas high-risk patients were recommended chemotherapy in combination with endocrine therapy. The results for the low-risk RS have been reported recently. A total of 1629 patients (15.9% of the trial population) had a low-risk RS. With endocrine therapy alone, these patients had excellent 5-year disease-free survival and distant recurrence-free survival rates of 93.8% and 99.3%, respectively [16]. The results for the intermediate-risk RS have also been presented in ASCO 2018. Women with intermediate-risk RS (11–25) were randomized to receive endocrine therapy or chemotherapy. In women with HR-positive, HER2-negative, AN-negative breast cancer and an RS of 11–25, adjuvant endocrine therapy was not inferior to chemotherapy in ITT analysis. According to this study, the findings suggest that chemotherapy may be spared in women with hormone receptor-positive, HER2-negative, node-negative breast cancer older than 50 years with an RS of 0–25 or 50 years or younger with an RS of 0–15, although some benefit of chemotherapy was found in some women 50 years of age or younger. The investigators found that, among patients age 50 or younger with a score of 16–25, there was some benefit of added chemotherapy; there were 2% fewer distant recurrences for those with an RS of 16–20 and 7% fewer for those with an RS of 21–25. Reporting on patients with high RS scores is pending.

The recently published phase 3 study MINDACT trial was designed to offer prospective evidence of the clinical utility of using the 70-gene signature in addition to standard clinical-pathological criteria to select patients for adjuvant chemotherapy. This trial randomized 6693 women with early-stage breast cancer and evaluated both the genomic risk (using the 70-gene signature) and the clinicopathological risk (using a modified version of Adjuvant! Online). Women at low clinical and genomic risk did not receive chemotherapy, whereas those at high clinical and genomic risk did. In patients with discordant risk results, either the genomic risk or the clinical risk was used to decide the use of chemotherapy. The 5-year rate of survival without distant metastasis for women deemed to be at high clinical risk, and low genomic risk was 94.7% (95% confidence interval, 92.5–96.2) for those not receiving chemotherapy, above the pre-defined threshold of 92%. The subset of patients who had ER-positive, human epidermal growth factor receptor 2-(HER-2)-negative, and either node-negative or node-positive disease had similar rates of survival without distant metastasis. Women at high clinical risk and low genomic risk for recurrence who were spared chemotherapy based on the 70-gene signature had a 5-year rate of survival without distant metastasis that was 1.5% points lower than the rate with chemotherapy (93.9% vs. 95.5%). These results indicate that approximately 46% of women with breast cancer who are at high clinical risk might not need chemotherapy [17].

21-Gene Recurrence Score in Lymph Node-Negative Patients Treated with Tamoxifen

The 21-gene assay includes 16 tumor-associated genes and five reference genes, which are used to compute an RS. Higher expression of favorable genes (e.g., *ER*, *glutathione S-transferase Mu 1*, and *BCL2-associated athanogene*) results in a lower RS because of a negative coefficient in the RS algorithm. Higher expression of unfavorable genes (CD68 and genes in the proliferation, HER2, and invasion groups) contributes to a higher RS because of a positive coefficient in the RS algorithm (Fig. 7.1). The 21-gene RS was validated in an independent dataset derived from 668 samples collected in the tamoxifen-treated arm of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, a prospective randomized clinical trial that examined the benefit of adjuvant tamoxifen in HR-positive, node-negative breast cancer. Although this population had a generally good prognosis, the rates of distant recurrence at 10 years were 7%, 14%, and 31% in patients with low (<18), intermediate [18–30], and high (>30) RSs, respectively (Table 7.3) [11]. The sensitivity of RS was 76.9% (95% CI 75.1–80.3), indicating that approximately 77% of patients who developed distant recurrence had a high or intermediate RS. The specificity was 55.4% (95% CI 54.1–56.8), indicating that 55% of patients with no recurrence had a low RS. The NSABP B-20 trial was performed to examine the benefit of concurrent tamoxifen and CT versus tamoxifen alone in node-negative, ER-positive breast cancer patients [18]. Tumor specimens from the tamoxifen-only arm were used as a training set for assay development [19]. In the tamoxifen-only arm, a high RS was almost five times more likely to occur in patients who developed distant recurrence at 10 years, whereas a low RS was five times more likely to occur in patients who did not develop distant recurrence at 10 years. RS sensitivity and specificity were 84% (95% CI 79–98) and 65% (95% CI 63–68), respectively. In a retrospective analysis of the NSABP B-14 and B-20 trials, RS was able to quantify recurrence risk as a continuous variable and predict tamoxifen and CMF responsiveness.

Table 7.3 Risk of distant recurrence at 10 years according to recurrence score in the NASBP B-14 validation study

Recurrence score	Risk group	*n*	10-year distant recurrence % (CI)
<18	Low	338	6.8 (4.0–9.6)
18–30	Intermediate	149	14.3 (8.3–20.3)
≥31	High	181	30.5 (23.6–37.4)

CI Confidence interval

21-Gene Recurrence Score in Lymph Node-Positive Patients Treated with Tamoxifen

In the Southwest Oncology Group (SWOG)-8814 (North American Breast Cancer Intergroup (INT) 0100) study, 1477 postmenopausal women with HR-positive, node-positive

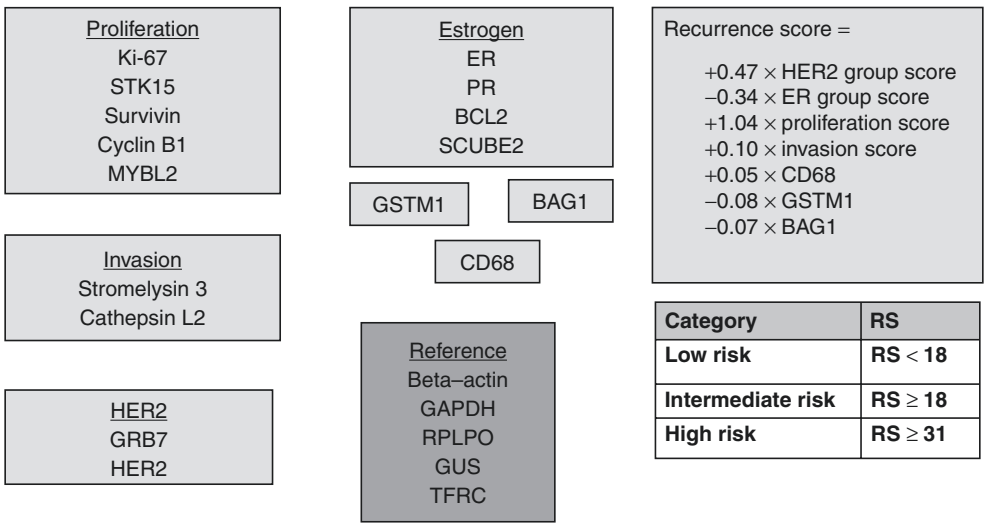


Fig. 7.1 Oncotype DX (Genomic Health, Redwood City, CA) recurrence score (*RS*): genes and algorithm. *HER* human epidermal growth factor receptor, *ER* estrogen receptor, *PR* progesterone receptor. *BAG 1* BCL2 Associated Athanogene 1, *BCL2* associated athanogene: BAG1, B-cell lymphoma 2, BCL2-associated athanogene, *ER* estrogen receptor, *HER2* epidermal growth factor receptor 2, *GAPDH* glyceraldehyde 3-phosphate dehydrogenase, *GRB7* growth factor receptor-bound protein 7, *GSTM1* glutathione S-transferase mu 1, *GUS* glucuronidase, *MYBL2* Myb-related protein B, *PR* progesterone receptor, *RPLPO* ribosomal large protein PO, *RS* recurrence score, *SCUBE2* signal peptide CUB domain EGF-like 2, *STK15* serine/threonine protein kinase 6, *TFRC* transferrin receptor

disease were randomized to receive tamoxifen alone or cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) plus tamoxifen. For patients treated with tamoxifen alone, the 10-year disease-free survival (DFS) rates were 60%, 49%, and 43% in the low, intermediate, and high RS groups, respectively. The continuous RS was prognostic for the first 5 years but not beyond 5 years [20]. Patients with high scores benefitted from CT, whereas those with low scores showed no benefit from CT regardless of the number of positive lymph nodes.

21-Gene Recurrence Score in Lymph Node-Positive and Node-Negative Patients Treated with Tamoxifen or Anastrozole

The Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial examined the predictive ability of RS for recurrence in CT-naive postmenopausal breast cancer patients with node-negative (n = 872) or node-positive (n = 432) disease. After combining the treatment arms, the 9-year distant recurrence rates were 4%, 12%, and 25% and 17%, 28%, and 49% for node-negative and node-positive patients in the low, intermediate, and high RS groups, respectively (both $p < 0.001$).

Determination of Menopausal Status

Definitions of menopause-associated terms and biomarkers used to assess menopausal status are provided in Boxes 7.1 [21–23] and 7.2 [24, 25], respectively. Menopausal status is generally assessed using clinical features such as age, menstrual history, and menopausal symptoms, and it may be confirmed by serum FSH and E_2 levels within the menopausal range. Elevated FSH and reduced E_2 levels generally confirm the clinical diagnosis of menopause. However, the use of

Box 7.1 Definitions of Primary Ovarian Insufficiency, Amenorrhea, Menopause, Menopausal Transition, and Perimenopause

Primary ovarian insufficiency (*POI*): Amenorrhea for at least 3 months and serum FSH and E_2 concentrations of >40 IU/L and <10 pg/mL, respectively, obtained twice at least 1 month apart in a woman aged <40 years [21]. The cause of ovarian dysfunction is inherent in the ovary. In most cases, an unknown mechanism leads to premature exhaustion of the resting pool of primordial follicles. POI may also result from genetic defects, autoimmunity, surgery, radiotherapy, or cytotoxic CT.

Amenorrhea: The absence of menses on a permanent, intermittent, or temporary basis. Amenorrhea is classified as primary or secondary. Primary amenorrhea is the failure of menses to occur by age 16 years. Secondary amenorrhea is defined as the absence of menses for more than three cycles or 6 months in a woman with previously normal menses. Amenorrhea may be due to pregnancy or caused by infections, uncontrolled diabetes mellitus, malnutrition, hypothalamic or thyroid dysfunction, hyperprolactinemia, or polycystic ovary syndrome. Secondary amenorrhea in conjunction with increased FSH levels often indicates ovarian insufficiency. However, gonadotropin cutoff values suggestive of ovarian insufficiency onset have not been established, likely due to the intermittent and sometimes erratic decline in ovarian function [21].

Menopause: The permanent cessation of menses resulting from the loss of ovarian follicle activity. Natural menopause can only be retrospectively established after 12 consecutive months of spontaneous amenorrhea. The mean age of natural menopause is 51 years, with a range of 40–60 years [21]. Postmenopause is characterized by markedly high FSH levels, low E_2 levels, and very low or undetectable inhibin-B and anti-Müllerian hormone (AMH) [22]. Varying menopause definitions have been used in breast cancer clinical trials. According to the National Comprehensive Cancer Network (NCCN), menopause is defined as bilateral oophorectomy, age ≥ 60 years, or age < 60 years with amenorrhea for ≥12 months in the absence of CT, tamoxifen, toremifene, or ovarian suppression and FSH and E_2 levels within postmenopausal range.

Menopausal transition: Menopausal transition typically begins in women in their mid-40s and precedes the final menses by 2–8 years (mean duration, 4 years). The endocrine changes underlying menopausal transition are predominantly the consequences of a marked decrease in ovarian follicle numbers. E_2 levels fall considerably, whereas estrone levels remain almost unchanged, reflecting peripheral aromatization of adrenal and ovarian androgens. The increase in FSH is greater than that of LH, presumably due to the loss of inhibins and estrogen feedback. Other significant changes include a decrease in inhibin-B levels during the early phase of the menstrual cycle and AMH levels.

Perimenopause: Perimenopause starts with menopausal transition and lasts throughout the 12 months of amenorrhea [23].

Box 7.2 Biomarkers for the Assessment of Menopausal Status

FSH: FSH is produced by the anterior pituitary gland in response to the pulsatile release of LHRH from the hypothalamus. FSH stimulates the growth of the small antral follicles and finally causes selection of the follicle with the most FSH receptors, which will become the dominant preovulatory follicle. Granulosa cells of the developing preovulatory follicles produce considerable amounts of E_2, which in turn exert negative feedback effect to decrease pituitary FSH secretion. The Stages of Reproductive Aging Workshop proposed FSH as the best predictive marker of menopause but did not establish a precise cutoff value to define menopausal status [24]. Elevated blood FSH levels reflect an age-dependent decrease in the follicle pool. FSH levels rise above 20 IU/L during the late perimenopausal phase; therefore, this level is often used as the cutoff value to determine ovarian reserve depletion. However, tamoxifen treatment in truly postmenopausal women may decrease FSH levels, even into the premenopausal range. Conversely, chemotherapy-induced amenorrhea (CIA) in premenopausal women may temporarily result in highly increased FSH levels; thus, folliculogenesis may resume later. Therefore, no absolute cutoff level of FSH can be provided above which folliculogenesis no longer occurs [25].

E_2: E_2 is mainly secreted by the late antral follicle and the ensuing corpus luteum. E_2 secretion is regulated by FSH and LH. Although E_2 levels <130 pmol/L are considered postmenopausal levels, values of 10–60 pmol/L have been reported. Furthermore, E_2 levels are higher in obese postmenopausal women because of the relatively high aromatase activity associated with the increased number of adipose cells. In contrast, E_2 levels are lower among smokers because nicotine and its metabolite cotinine are strong inhibitors of aromatase. In addition, hormone replacement therapy may lower FSH levels and increase E_2 levels up to 1 year after therapy cessation [25].

LH: LH levels increase with age, independent of E_2 levels, due to increased pituitary sensitivity to LHRH. During menopausal transition, LH increases slowly and reaches moderately elevated levels in postmenopause.

Antral follicle count (AFC), ovarian volume, and blood levels of FSH, E_2, inhibin-B, and AMH are used to evaluate ovarian reserve. AMH and AFC provide the most reliable assessment of the reproductive lifespan of the ovaries, fertility status, and risk of premature ovarian failure. Menstrual cycle irregularity, vasomotor symptoms, significantly elevated basal FSH, and undetectable inhibin-B levels are only short-term predictors of menopause (within 2 years) [27]. Low/undetectable AMH levels, low AFC, poor response to in vitro follicle stimulation, and rise in FSH during the early follicular phase indicate a limited ovarian reserve and risk of early menopause. However, these factors do not predict imminent menopause [27]. Although currently available enzyme-immunometric assays for AMH and FSH are highly sensitive (detection level, 0.05 ng/mL), the lowest level of detection is still not considered an absolute cutoff level to precisely mark menopause.

these biomarkers has several limitations. The transition toward menopause is highly variable, thus making it difficult to define diagnostic cutoff values for FSH/E_2. Therefore, single time point testing of FSH/E_2 levels is not sufficient to confirm menopause. Furthermore, FSH/estrogen levels are influenced by ETs. Tamoxifen increases circulating estrogens and decreases FSH levels [26]. AIs profoundly decrease estrogen levels and increase FSH levels in postmenopausal patients [26, 27]. Therefore, in these clinical settings, FSH/E_2 levels are not reliable surrogate markers of menopause.

Chemotherapy-Induced Amenorrhea/ Menopause

CT can cause significant changes in ovarian function by directly destroying the remaining functional follicles or indirectly promoting the loss of functional follicles through induction of ovarian fibrosis. CT can also lead to amenorrhea by inducing primary or hypergonadotropic hypogonadism [28]. CT is associated with the occurrence of POI. CT-induced POI results from an acceleration of the natural ovarian aging process caused by damage to the steroid-producing granulosa and theca cells and apoptotic death in a fraction of primordial follicles, which mainly impairs follicular development. The sensitivity of the ovaries to CT varies considerably (Table 7.4), with alkylating agents being the most commonly associated with permanent and irreversible gonadal damage [29]. The risk of CT-induced POI has been correlated with CT type, higher cumulative CT dose, and older age, and age > 40 years is the strongest predictor of both CIA and chemotherapy-induced menopause (CIM) [21, 23].

The estimated risk of CIA associated with single and combination CT regimens is shown in Table 7.4 [30]. Transient and prolonged amenorrhea are more frequently observed with CMF and cyclophosphamide, epirubicin, and 5-fluorouracil/CAF regimens compared with doxorubicin

Table 7.4 Estimated risk of permanent amenorrhea associated with single-agent and combination adjuvant regimens in early breast cancer

	Single-agent therapy	Combination therapy
High risk (>80%)	Cyclophosphamide	CMF, FEC, and FAC; six cycles in women aged ≥40 years
Intermediate risk	Cisplatin	CMF, FEC, and FAC; six cycles in women aged 30–39 years
	Carboplatin	AC and EC; four cycles in women aged ≥40 years
	Adriamycin	Taxane-containing combinations
	Taxanes	
Low risk (<20%) or no risk	Methotrexate	CMF, FEC, and FAC; six cycles in women aged <30 years
	5-Fluorouracil	AC and EC; four cycles in women aged <40 years
To be determined	Trastuzumab	
To be determined	Lapatinib	

Adapted from Lee et al. [30] with permission from the American Society of Clinical Oncology

AC adriamycin and cyclophosphamide, *CMF* cyclophosphamide, methotrexate, and fluorouracil, *EC* epirubicin and cyclophosphamide, *FAC* fluorouracil, adriamycin, and cyclophosphamide, *FEC* fluorouracil, epirubicin, and cyclophosphamide

and cyclophosphamide, presumably due to the higher cumulative dose of cyclophosphamide received [28]. The addition of taxanes increases the risk of CIA in many individuals, particularly in the first year of use [23, 31]. Tamoxifen use following CT significantly increases the rate and/or duration of CIA and slightly but significantly increases the CIM risk [23, 28, 32]. However, the mechanism by which tamoxifen influences CIA/CIM remains unclear. Tamoxifen may increase plasma E_2 levels and interfere with the hypothalamic–ovarian feedback loop that regulates estrogen synthesis [23].

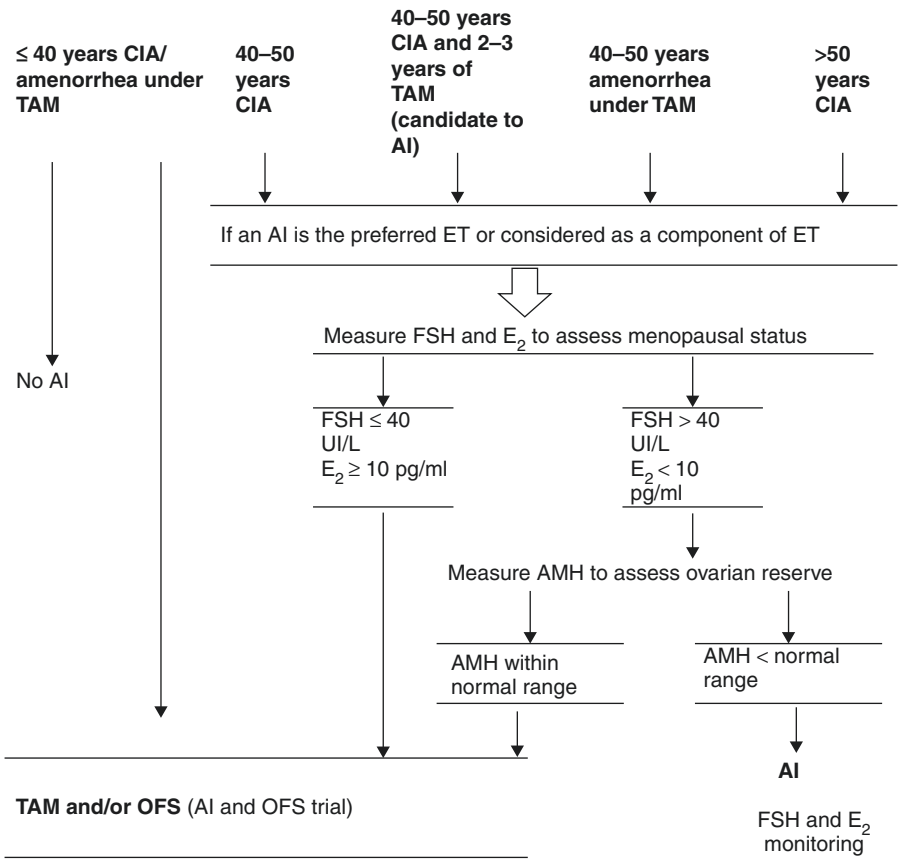
CIA complicates menopause assessment in premenopausal women with early breast cancer. In clinical practice, menopausal status in women with CIA may be determined only using hormonal evaluations and a nonvalidated pool of clinical data, including age, menstrual history, vasomotor symptoms, and the likelihood of gonadal toxicity from CT. The use of such criteria may lead to an inaccurate assessment of menopausal status. Furthermore, although many patients >40 years of age develop CIA, this type of ovarian failure may be temporary in a considerable number of patients. The percentage of women with CIA/oligomenorrhea who will later develop CIM is not yet known. Menstrual cycles and/or fertility may recover months to years after CT withdrawal. Resumption of menses is more likely to occur in younger women, those exposed to less gonadotoxic regimens, and those with a higher basal number of follicles. In fact, the remaining follicles may regrow from the primordial pool in 3–6 months, and gonadotropin levels may return to normal after CT withdrawal, especially in very young women [29]. However, individual CIM risk cannot be predicted. Thus, the use of both pre-CT and post-CT evaluations of ovarian reserve may better predict menopausal status.

Endocrine Therapy Selection According to Menopausal Status

Assessment of ovarian function is important in hormone-sensitive breast cancer patients who are eligible to receive adjuvant ET. Adjuvant AI treatment administered upfront or replacing tamoxifen is superior to tamoxifen alone in postmenopausal patients and has therefore become the standard of care in these patients. In contrast, adjuvant treatment with tamoxifen with or without ovarian suppression is recommended in premenopausal women. Tamoxifen can be safely given to premenopausal women; however, this is not the case for AIs. AIs interfere with androgen-to-estrogen conversion by blocking aromatase, thereby lowering E_2 levels in truly postmenopausal women. However, in the presence of functional ovaries, low levels of estrogen will enhance pituitary FSH production, thereby indirectly stimulating follicular aromatase production and subsequent E_2 production. Consequently, AI treatment in the absence of an LHRH agonist may be ineffective in postmenopausal women who were inaccurately classified as premenopausal. Moreover, in the case of CIA, AIs may promote recovery of ovarian function, leading to therapeutic failure and even to unwanted pregnancy.

The choice of adjuvant ET may be guided by age only in specific patient groups (Table 7.5). Women ≤40 years with CIA should not receive adjuvant ET with AIs alone. Estrogen depletion is the desired endocrine strategy in these patients. Their management should include oophorectomy or chemical ovarian suppression with combined LHRH agonist and tamoxifen. Serial monitoring of E_2 and gonadotropin levels should be performed in women 40–50 years of age with CIA. Women who have FSH and E_2 levels within the premenopausal range (≤40 IU/L and ≥10 pmol/L, respectively) should receive tamoxifen alone or tamoxifen plus ovarian suppression. In patients with hormone levels indicative of postmenopausal status (FSH > 40 IU/L and E_2 < 10 pmol/L), AMH assessment may be useful to detect any residual ovarian function. AI may be cautiously administered to patients whose AMH levels are below the lower limits of normal range. In addition, serial hormone monitoring should be performed (with a reasonable timing of 4 months between consecutive measurements) to achieve ongoing confirmation of menopausal status. For patients whose levels remain within the postmenopausal range, AI can be continued. Otherwise, tamoxifen alone or in combination with ovarian suppression

Table 7.5 Suggested practical approaches to determine the appropriateness of adjuvant AI therapy in breast cancer patients with CIA or tamoxifen-induced amenorrhea



Adapted from Torino et al. [23] with permission from BioScientifica, Ltd.
AI aromatase inhibitor, *AMH* anti-Müllerian hormone, *CIA* chemotherapy-induced amenorrhea, *E2* estradiol, *ET* endocrine therapy, *FSH* follicle-stimulating hormone, *OFS* ovarian function suppression, *TAM* tamoxifen

is the appropriate ET. The same approach should be used in premenopausal women >40 years of age with CIA who may start AI after 2–3 years of tamoxifen. Likewise, in women who develop tamoxifen-induced amenorrhea and are suitable candidates for switching to an AI, it is advisable to perform serial high-quality evaluations of E_2, FSH, and AMH. The switch can only be safely made in cases with confirmed menopausal status. Women >50 years of age at the time of CT with CIA lasting >6 months may receive AI if hormone assessment has provided enough certainty of menopausal status. However, tamoxifen should replace AI in patients whose E_2 levels continue to rise [23].

Adjuvant Endocrine Therapy for Premenopausal Women

Approximately 60% of premenopausal breast cancers are ER positive. Adjuvant ET is an integral component of ER-positive breast cancer therapy. Patients with ER- and/or PR-positive invasive breast cancers should be considered for adjuvant ET regardless of age, lymph node status, or adjuvant CT use [33]. Features that are indicative of uncertain endocrine responsiveness include low levels of HR immunoreactivity, PR negativity, poor differentiation (grade 3), high proliferation index (Ki-67), HER2 overexpression, and high gene RS. In the absence of these features, tumors are considered highly endocrine responsive. Patients with tumors of different degrees of endocrine responsiveness may receive Et alone or in combination with CT. The type of treatment selected is determined by multiple factors including ER and PR status, nodal status, histological grade, and peritumoral vascular invasion (Table 7.6) [34]. Patients with tumors of uncertain endocrine responsiveness are usually treated with a combination of ET and CT. Endocrine strategies in premenopausal women include ER blockade with tamoxifen, temporary ovarian suppression with LHRH agonists, or permanent ovarian suppression with oophorectomy or radiotherapy. Tamoxifen is the mainstay of ET in premenopausal women. The benefit of ovarian suppression has not been clearly demonstrated; however, prospective studies are currently ongoing. The use of AIs as single agents is contraindicated because the reduced feedback of estrogen to the hypothalamus and pituitary may increase gonadotropin secretion and

Table 7.6 Threshold for treatment modalities according to the 2009 St. Gallen Consensus Conference

Clinicopathologic feature	Relative indication for chemoendocrine therapy	Factor not useful for decision	Relative indication for endocrine therapy alone
ER and PR levels	Low		High
Histological grade	3	2	1
Proliferation index[a]	High	Intermediate	Low
Nodal status	Positive (≥4 involved nodes)	Positive (1–3 involved nodes)	Negative
PVI	Present		Absent
pT size, cm	>5	2.1–5	≤2
Patient preference	Use all available treatments		Avoid chemotherapy-related side effects
Multigene signature assay score[b]	High	Intermediate	Low

Adapted from Goldhirsch et al. [34] with permission of Oxford University Press
ER estrogen receptor, *HER2* epidermal growth factor receptor 2, *PR* progesterone receptor, *pT* pathological tumor size (i.e., size of the invasive component), *PVI* peritumoral vascular invasion
[a]Conventional measures of proliferation include assessment of the Ki-67 labeling index (low, ≤15%; intermediate, 16%–30%; high, >30%) and frequency of mitosis. The reliability of these measures will vary in different geographic settings. First-generation gene signatures consist of ER, HER2, and proliferation-related genes. A meta-analysis indicated that much of the prognostic information in these signatures resides in their sampling of proliferative genes, but their respective total scores may be the only form in which information is provided at present and are the only format that could be used in this component of assessment of relative indications for chemotherapy
[b]The European Society for Medical Oncology Panel agreed that validated multigene tests, if readily available, could assist in deciding whether to add chemotherapy in cases where its use was uncertain after consideration of conventional markers

stimulate the ovary, thereby leading to an increase in androgen substrates and aromatase. However, concurrent AI and ovarian suppression with an LHRH agonist, surgery, or radiotherapy may also be considered.

Tamoxifen

Until recently, tamoxifen has been the gold standard for the adjuvant treatment of ER-positive breast cancer in both premenopausal and postmenopausal women. The 2011 EBCTCG meta-analysis, which compared 5 years of tamoxifen treatment to no ET in premenopausal and postmenopausal women, was instrumental in establishing the efficacy of adjuvant tamoxifen [5]. Tamoxifen treatment resulted in a 39% reduction in breast cancer recurrence compared with placebo (relative risk [RR] 0.61, 95% CI 0.57–0.65), which translated into a 15-year absolute reduction of 13% (33% vs. 46%, respectively). This outcome was observed in both node-negative and node-positive patients. Tamoxifen treatment also resulted in a 30% reduction in breast cancer mortality risk (RR 0.70, 95% CI 0.64–0.75), which translated into a 15-year absolute reduction of 9% (24% vs. 33% in the placebo group). The magnitude of benefit was similar between women <45 and 55–69 years of age. Tamoxifen also reduced the risks of local recurrence (RR 0.54) and of contralateral breast cancer (RR 0.62).

Timing of Tamoxifen Therapy

Concurrent tamoxifen interferes with the cytotoxicity of CT in cancer cell lines in vitro [35, 36]. The SWOG-8814 (INT 0100) randomized trial investigated the timing of tamoxifen in 1558 patients receiving CT [37]. At a median follow-up of 9.94 years, CAF plus 5 years of tamoxifen was superior to tamoxifen alone, and CAF plus sequential tamoxifen was more effective than CAF plus concurrent tamoxifen. Based on these results, tamoxifen should be given sequentially and not concurrently with CT.

Duration of Tamoxifen Therapy

For decades, tamoxifen for 5 years has been the standard ET for premenopausal women [38]. Tamoxifen for more than 5 years has not been shown to be more beneficial than tamoxifen for 5 years in two North American and Scottish trials [39, 40]. However, the results of the ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) and Adjuvant Tamoxifen—To Offer More (aTTom) trials have recently changed this paradigm. The ATLAS trial aimed to assess the further benefit of continuing tamoxifen for 10 years in women with HR-positive breast cancer who had completed 5 years of tamoxifen. Premenopausal and postmenopausal women ($n = 6846$) were randomly assigned to receive either 5 years of additional tamoxifen or no further therapy. Extended tamoxifen reduced breast cancer recurrence by 25% (617 vs. 711 patients, respectively; $p < 0.01$) and breast cancer deaths by 29% (331 vs. 397 patients, respectively; $p = 0.001$), but it did not increase nonbreast cancer mortality. These benefits were only observed after 10 years of tamoxifen use. In the extended tamoxifen arm, 1% and 0.2% increases in endometrial cancer incidence and related deaths, respectively, in women aged >50 years were observed [41]. In the aTTom trial, 6953 women with ER-positive ($n = 2755$) or ER-untested ($n = 4198$; estimated to be 80% ER-positive) invasive breast cancer who had completed 5 years of

tamoxifen were randomized to stop tamoxifen or continue tamoxifen to year 10. Extended tamoxifen reduced breast cancer recurrence (580/3468 vs. 672/3485; $p = 0.003$) in a time-dependent manner. The rate ratio was 0.99 (95% CI 0.86–1.15), 0.84 (95% CI 0.73–0.95), and 0.75 (0.66–0.86) during years 5–6, years 7–9, and later years, respectively. Longer treatment also reduced breast cancer recurrence-related mortality (392 vs. 443 deaths; $p = 0.05$) and overall mortality (849 vs. 910 deaths; $p = 0.1$). The rate ratios were 1.03 (95% CI 0.84–1.27) during years 5–9 and 0.77 (95% CI 0.64–0.92) during the later years for breast cancer recurrence-related mortality and 1.05 (95% CI 0.90–1.22) during years 5–9 and 0.86 (95% CI 0.75–0.97) during the later years for overall mortality. Nonbreast cancer mortality was not significantly affected (457 vs. 467 deaths; rate ratio 0.94 [95% CI 0.82–1.07]). However, extended tamoxifen treatment also increased the incidence of endometrial cancer (102 vs. 45 patients; rate ratio 2.20 [95% CI 1.31–2.34]; $p < 0.0001$) and endometrial cancer-related deaths (37 [1.1%] vs. 20 [0.6%] deaths; absolute hazard ratio [HR] 0.5; $p = 0.02$) compared with 5 years of tamoxifen. The aTTom trial also demonstrated that, compared with 5 years of tamoxifen, continuing tamoxifen to 10 years in patients with ER-positive disease yielded further reductions in recurrence from year 7 onward and breast cancer mortality after year 10.

In a recent meta-analysis of extended adjuvant tamoxifen in early breast cancer (eight trials including 29,138 patients), more than 5 years of tamoxifen significantly improved OS (odds ratio [OR] 0.89; 95% CI 0.80–0.99; $p = 0.03$), breast cancer-specific survival (OR 0.78; 95% CI 0.69–0.9; $p = 0.0003$), and recurrence-free survival (RFS; OR 0.72; 95% CI 0.56–0.92; $p = 0.01$) compared with 5 years of tamoxifen. Locoregional and distant relapses were reduced by 36% and 13%, respectively. Compared with 5 years of tamoxifen, additional adjuvant ET reduced the risk of death and relapse in ER-positive breast cancer patients by 10% and 30%, respectively. Combining the results of the aTTom and ATLAS trials enhanced the significance of the recurrence ($p < 0.0001$), breast cancer mortality ($p = 0.002$), and OS ($p = 0.005$) benefits. Taken together, these studies indicate that, compared with tamoxifen for 5 years, 10 years of adjuvant tamoxifen reduces breast cancer mortality by approximately one-third in the first 10 years following diagnosis and by one-half in subsequent years [42].

The optimal duration of ET for premenopausal women to balance the potential benefits and side effects associated with treatment has yet to be determined. ET significantly affects reproductive options in premenopausal women because women are counseled not to become pregnant while undergoing adjuvant ET. Young women receiving ET may also experience menopausal symptoms, such as hot flashes, vaginal dryness, and sexual dysfunction. Tamoxifen is associated with an increased risk of thromboembolic events (1–2% increased risk of deep venous thrombosis and threefold increased risk of pulmonary embolism), increased vaginal bleeding, and threefold increased risk of endometrial cancer. However, the absolute increase in endometrial cancer is <1%, and almost all of the cancers that develop are stage I adenocarcinomas.

Tamoxifen Resistance

The expression of growth factor receptors, such as HER2, is associated with the development of tamoxifen resistance in breast cancer. Selected studies suggest that HER2-positive breast cancers may be less sensitive to some ETs, whereas other studies have failed to confirm this finding [43–46]. A retrospective analysis of tumor blocks collected in the ATAC trial indicated that HER2 amplification is a marker of relative endocrine resistance independent of ET type [47]. Some studies suggest that PR negativity in ER-positive tumors may be associated with increased growth factor expression, more aggressive tumor phenotype, and tamoxifen resistance. By contrast, higher levels of ER expression predict greater tamoxifen benefits. Other factors that may contribute to tamoxifen resistance include variable expression of ERα and ERβ isoforms, interference with coactivator and corepressor binding, alternative splicing of *ER* mRNA variants, modulators of ER expression (e.g., epidermal growth factor and its receptors, such as epidermal growth factor receptor 1 and HER2), and inherited drug-metabolizing *CYP2D6* genotypes. CYP2D6 converts tamoxifen to endoxifen, the major active tamoxifen metabolite. Over 100 allelic variants of *CYP2D6* have been reported. In the Breast International Group (BIG) 1-98 and ATAC trials, *CYP2D6* genotype status was shown to not influence breast cancer recurrence after tamoxifen use [48, 49]. Given the limited and conflicting evidence at this time, the NCCN Breast Cancer guidelines do not recommend CYP2D6 testing as a tool to determine the optimal adjuvant endocrine strategy.

Ovarian Suppression

The ovaries are the main site of estrogen production in premenopausal women. Therefore, ovarian ablation/suppression is an endocrine therapeutic option to consider in young women with ER-positive disease. Irreversible ovarian ablation may be accomplished by surgical oophorectomy or ovarian irradiation. Radiation is seldom used because of its side effects. Adjuvant CT frequently results in permanent amenorrhea and thus represents an indirect form of ovarian ablation. Chemical castration with LHRH is a reversible approach. Chemical ovarian suppression utilizes LHRH agonists to suppress LH and FSH release from the pituitary and reduce ovarian estrogen production. Goserelin, leuprolide, and triptorelin are also used for chemical ovarian suppression; however, only goserelin has been approved by the FDA. The advantage of chemical suppression is that it is a

simple, reversible outpatient therapy. The disadvantages are restoration of estrogen production at the time of drug withdrawal, injection site reactions, and menopausal symptoms. The optimal form of ovarian suppression (surgical oophorectomy, ovarian irradiation, or chemical suppression) in the adjuvant setting is unknown because of the absence of direct comparison studies. Ovarian ablation therapy is the oldest type of breast cancer therapy. Beatson first reported its use in the palliation of young women with metastatic disease in 1896.

The role of adjuvant ovarian ablation/suppression in premenopausal women with HR-positive breast cancer remains undetermined. The combined analysis of the early studies in the 1995 overview from the EBCTCG demonstrated that ovarian ablation as a single intervention reduces breast cancer recurrence and increases survival in women <50 years of age [50]. Of the 12 randomized trials included in the analysis, 7 trials compared ovarian ablation and no CT, and 5 trials compared ovarian ablation combined with CT. By indirect comparison, the efficacy of ovarian ablation was similar to that of adjuvant CT and tamoxifen. The EBCTCG also performed a meta-analysis of randomized studies of ovarian ablation/suppression alone versus no adjuvant treatment in women >50 years. The annual odds of recurrence and death were reduced in favor of ovarian ablation/suppression over no adjuvant treatment. Reductions of 25% and 29% in recurrence and death rates, respectively, were observed in women <40 years of age, and a 29% reduction in both recurrence rate and death rate was observed in women 40–49 years of age [51]. An analysis of ovarian suppression versus no adjuvant therapy showed no significant reductions in recurrence (HR reduction −28.4; 95% CI −50.5 to 3.5; $p = 0.08$) or death (HR reduction −22; 95% CI −44.1 to 6.4; $p = 0.11$) [52]. The following findings emerged from this meta-analysis. (1) As single agents, LHRH agonists such as goserelin, leuprolide, and triptorelin showed a trend toward a lower risk of breast cancer recurrence compared with no further systemic treatment (HR 0.72, 95% CI 0.49–1.04). A trend toward a reduction in mortality was also observed (HR 0.82, 95% CI 0.47–1.43), although the analysis was likely underpowered for this outcome. (2) The combination of LHRH agonist and tamoxifen showed a trend toward a lower risk of recurrence (HR 0.85, 95% CI 0.67–1.09) and mortality (HR 0.84, 95% CI 0.59–1.19) compared with tamoxifen alone (3). The risks of recurrence (HR 1.04, 95% CI 0.92–1.17) and mortality (HR 0.90, 95% CI 0.79–1.10) did not differ between LHRH agonist plus non-anthracycline-containing adjuvant CT and adjuvant CT alone. These results suggest that LHRH agonists have limited efficacy in patients who receive non-anthracycline-based chemotherapy. This limitation is perhaps due to the high rate of treatment-induced suppression caused by CT regimens such as CMF. However, ovarian suppression may provide an additional benefit for women who are treated with contemporary anthracycline-based regimens. There is no definitive evidence of any additional benefit with the use of LHRH agonists administered as an alternative to or along with tamoxifen. LHRH agonists should be given for at least 2 years. However, the timing and optimal duration of treatment are still a matter of debate. Data comparing the efficacy of monthly and trimonthly formulations of LHRH agonists are lacking. However, monthly goserelin and trimonthly leuprolide have similar effects on E_2 and FSH levels [53]. Thus, to date, selected studies have suggested the benefits of ovarian ablation/suppression in the adjuvant treatment of premenopausal women with HR-positive breast cancer.

Ovarian suppression has also been studied with either tamoxifen or the AI exemestane in premenopausal patients in a combined analysis of the SOFT (Suppression of Ovarian Function Trial) and TEXT (Tamoxifen and Exemestane Trial) trials; exemestane use was associated with a significant reduction in the risk of recurrence compared with tamoxifen. In women who did not need chemotherapy, 5 years of tamoxifen was sufficient to reduce recurrence risk, and ovarian function suppression is not advised in this group. However, in the cohort that remained premenopausal after CT (average age, 40 years), ovarian suppression added to tamoxifen achieved a 22% reduction in risk of recurrence versus tamoxifen alone. The combination of exemestane plus ovarian function suppression was even better, with a 35% reduction in risk of recurrence versus that in tamoxifen alone. The 5-year event-free survival was 78% for tamoxifen alone, 82.5% for tamoxifen plus ovarian function suppression, and 85.7% for exemestane plus ovarian function suppression [51, 54]. In the SOFT study presented at ASCO 2018, adding ovarian function suppression to tamoxifen significantly decreased the relative risk of disease-free survival events by 24% versus tamoxifen-alone in the overall population after a median of 8 years of follow-up, resulting in a 4.2% absolute benefit at 8 years. The absolute benefit was greater in women who remained premenopausal after receiving chemotherapy before starting ovarian suppression. The clinical benefit was particularly clear in women under age 35, with an 8.6% absolute benefit at 8 years. After a median follow-up of 9 years, the combined analysis of the TEXT and SOFT studies confirmed statistically significant improvements in disease outcomes with exemestane versus tamoxifen used in combination with ovarian suppression. Adjuvant exemestane plus ovarian function suppression, compared with tamoxifen plus ovarian function suppression, showed sustained absolute improvements in disease-free survival and freedom from distant recurrence of 4.0% and 2.1% at 8 years, respectively. Women with HER2-negative breast cancer experienced the greatest clinical benefit, especially those who also received adjuvant chemotherapy due to a higher risk of recurrence. In these higher-risk groups, the

absolute improvements in disease-free survival and freedom from distant recurrence were 7–9% and 5–7% across TEXT and SOFT, respectively, with exemestane plus ovarian suppression. No difference in overall survival after a median follow-up of 9 years was observed when comparing the two groups treated with ovarian suppression [55]. Based on the results of the SOFT and TEXT trials, the NCCN Panel has included ovarian suppression plus an aromatase inhibitor for 5 years as an adjuvant endocrine therapy option for premenopausal women with hormone receptor-positive breast cancer at higher risk of recurrence (e.g., young age, high-grade tumor, lymph node involvement).

In addition, randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant CT in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of CIA.

The abrupt interruption of ovarian function is a significant problem in young premenopausal patients. Adverse events may include severe menopause-related signs and symptoms, psychological distress, impaired quality of life, sexual dysfunction, changes in personal and family relationships, and bone loss. Ovarian ablation alone is not recommended as an alternative to any other form of systemic therapy, except in the specific cases of patients who are candidates for other forms of systemic therapy but who for some reason will not pursue other systemic therapies (e.g., patients who cannot tolerate other forms of systemic therapy or patients who choose no other form of systemic therapy).

Ovarian Ablation/Suppression Versus Chemotherapy

Studies of ovarian ablation/suppression alone versus CMF alone have generally demonstrated similar antitumor efficacy in premenopausal patients with HR-positive tumors, whereas superior outcomes were achieved with CMF in HR-negative patients (Table 7.7) [52, 56–63]. The benefits of ovarian suppression/ablation may be greater in younger premenopausal patients.

Ovarian Ablation/Suppression Plus Tamoxifen Versus Chemotherapy

In general, studies of ovarian ablation/suppression plus tamoxifen versus CT alone have shown no differences in recurrence or survival rates in premenopausal women (Table 7.7) [51, 64–66].

Chemotherapy Plus Ovarian Suppression/Ablation with or Without Tamoxifen

Clinical trials evaluating the efficacy of ovarian suppression as combination or sequential therapy in premenopausal women with HR-positive breast cancer are shown in Table 7.8 [56, 61, 67]. A large intergroup trial compared the efficacy of adjuvant CAF, CAF plus ovarian suppression with goserelin (CAF-Z), and CAF-Z plus tamoxifen (CAF-ZT) in premenopausal women with HR-positive, node-positive breast cancer [56]. Time to recurrence (TTR) and OS were similar between the CAF and CAF-Z groups. TTR (HR 0.73; 95% CI 0.59–0.90; $p < 0.01$), but not OS, was improved in the CAF-Z group compared with the CAF-ZT group (HR 0.91; 95% CI 0.71–1.15; $p = 0.21$). This study did not include a CAF plus tamoxifen arm; therefore, the contribution of goserelin to the improved TTR in the CAF-ZT arm could not be assessed. The addition of ovarian suppression/ablation has also been subjected to meta-analysis by the EBCTCG [51]. They found that the addition of ovarian suppression/ablation to CT did not result in significant reductions in annual recurrence or mortality rates in women <40 and 40–49 years of age.

Currently, there is no evidence that ovarian suppression/ablation is superior to tamoxifen, except perhaps in women

Table 7.7 Randomized trials of adjuvant chemotherapy versus ovarian ablation/suppression with or without tamoxifen

Study	Patients	*n*	Treatment	Outcome
ZEBRA [58]	N^+, $HR^{+/-}$	1640	CMF × 6 vs. Z × 2 years	No difference in HR^+; CMF better in HR^-
IBCSG VIII [61]	N^-, $HR^{+/-}$	706	CMF × 6 vs. Z × 2 years	No difference in HR^+; CMF better in HR^-
Scottish Cancer Trial Breast Group [62]	$N^{+/-}$	332	CMF × 6–8 vs. OA (XRT/surg)	No difference
TABLE [63]	N^+, HR^+	600	CMF × 6 vs. leuprorelin acetate × 2 years	No difference
GROCTA 02 [64]	N^+, HR^+	244	CMF × 6 vs. Z × 2 years + TAM × 5 years	No difference
FASG 06 [65]	N^+, HR^+	333	FEC × 6 vs. triptorelin × 3 years + TAM × 3 years	No difference
ABCSG 5 [66]	Stage I/II, HR^+	1045	CMF × 6 vs. Z × 3 years + TAM × 5 years	DFS better with Z + TAM

ABCSG Austrian Breast Cancer Study Group, *CMF* cyclophosphamide, methotrexate, and fluorouracil, *FAC* fluorouracil, doxorubicin, and cyclophosphamide, *FASG* French Adjuvant Study Group, *FEC* fluorouracil, epirubicin, and cyclophosphamide, *GROCTA* Italian Breast Cancer Adjuvant Study Group, HR^+ hormone receptor-positive, HR^- hormone receptor-negative, *IBCSG* International Breast Cancer Study Group, N^+ node positive, N^- node negative, *OA* ovarian ablation, *surg* oophorectomy, *TABLE* Takeda Adjuvant Breast cancer study with Leuprorelin Acetate, *TAM* tamoxifen, *XRT* ovarian radiation, *Z* goserelin, *ZEBRA* Zoladex Early Breast Cancer Research Association

Table 7.8 Clinical trials evaluating the efficacy of ovarian suppression as combination or sequential therapy in premenopausal women with hormone receptor-positive breast cancer

Study	*n*	Treatment	Outcome
INT 0101 [56]	1503	CAF (6×)[a] vs. CAF (6×) → Z (5 years) vs. CAF (6×) → Z + TAM (both 5 years)	DFS, OS, TTR: CAF → Z + TAM > CAF → Z > CAF
IBCSG VIII [61]	1063	CMF (6×) vs. Z (24 months) vs. CMF (6×) → Z (18 months)	DFS (ER-negative tumors): CMF > Z, DFS (ER-positive tumors): CMF = Z CMF → Z > CMF CMF → Z > Z OS: no difference
ZIPP [67]	2710	After standard CT/RT Z vs. TAM vs. Z + TAM vs. No treatment	RFS and OS: Z > no Z

CAF cyclophosphamide, doxorubicin, and 5-fluorouracil, *CMF* cyclophosphamide, methotrexate, and 5-fluorouracil, *CT* chemotherapy, *DFS* disease-free survival, *ER* estrogen receptor, *IBCSG* International Breast Cancer Study Group, *INT* North American Breast Cancer Intergroup, *OS* overall survival, *RFS* recurrence-free survival, *RT* radiotherapy, *TAM* tamoxifen, *TTR* time to recurrence, *Z* goserelin, *ZIPP* Zoladex in Premenopausal Patients
[a]Six cycles

who have not developed CIM. Ovarian ablation should not be routinely added to systemic CT, tamoxifen, or combined tamoxifen and CT. However, women <40 years of age and patients who do not become amenorrheic after CT may especially benefit from ovarian suppression with an LHRH agonist. The best use of LHRH agonists (concurrent or sequential with CT) is unknown. The combination of LHRH agonist plus AI or AI alone is not indicated in premenopausal patients outside clinical trials. Some women are offered treatment with ovarian suppression in association with AI therapy because of intolerance to or contraindications for tamoxifen.

Adjuvant Endocrine Therapy for Postmenopausal Women

In general, the following three groups of women can safely be considered postmenopausal: women >60 years of age, women who have undergone a bilateral ovariectomy, and women <60 years of age with intact uteri who are not using oral contraceptives or hormone replacement therapy and have been amenorrheic for at least 1 year prior to their breast cancer diagnosis. Women who experience regular menses without using oral contraceptives or hormone replacement therapy can be classified as premenopausal. Strictly stated, in all other cases, ovarian activity cannot be excluded, and menopausal status is therefore considered uncertain. Approximately 75% of breast cancers are diagnosed in postmenopausal women, and 80% of these cancers are HR positive [68]. Third-generation AIs, including anastrozole, letrozole, and exemestane, block estrogen synthesis by inhibiting aromatase. Because these AIs do not block ovarian estrogen production, their use is limited to postmenopausal women.

A number of studies have compared AIs with tamoxifen in the adjuvant setting using either a head-to-head (i.e., randomly assigning patients to 5 years of either drug) or switched schedule approach (i.e., initial tamoxifen for 2–3 years followed by either an AI for 2–3 years or continued tamoxifen for a total of 5 years). The use of AIs in either approach reduces breast cancer recurrence rates compared with tamoxifen alone; however, the effect on survival is less clear [69]. Two large randomized studies showed no significant differences in recurrence or survival between upfront and switching AI therapy [70–72]. Randomized studies have also demonstrated that extended ET with 3–5 years of an AI following 5 years of tamoxifen decreases relapse rates and may improve survival, especially in women with nodal involvement [73–75]. Given the improved outcomes observed with the use of AIs compared with tamoxifen alone, both the ASCO and NCCN recommend the incorporation of AIs at some point in the treatment of postmenopausal women with HR-positive breast cancer [76]. Sequential rather than concurrent administration of cytotoxic and endocrine therapies should be used. The concurrent use of tamoxifen and anthracyclines has been shown to have detrimental effects, whereas the concurrent use of AIs and CT has not been investigated [8].

Several studies have evaluated AIs as initial adjuvant therapy, sequential therapy following 2–3 years of tamoxifen, and extended therapy following 4.5–6 years of tamoxifen in postmenopausal women with early-stage breast cancer. Two prospective randomized clinical trials have provided evidence of an OS benefit in patients with early-stage breast cancer receiving initial adjuvant ET with tamoxifen followed by sequential anastrozole (HR 0.53; 95% CI 0.28–0.99; $p = 0.045$) or exemestane (HR 0.83; 95% CI 0.69–1.00; $p = 0.05$ [excluding patients with ER-negative disease])

compared with those receiving ET with tamoxifen alone [77, 78]. In addition, the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) MA.17 trial demonstrated that, compared with placebo, extended letrozole therapy provided a survival advantage in women with axillary lymph node-positive, but not lymph node-negative, ER-positive breast cancer [73]. However, no survival differences have been reported for patients receiving initial adjuvant therapy with an AI versus first-line tamoxifen treatment [79, 80]. Tamoxifen and AIs have different side effect profiles, although both can cause hot flashes, night sweats, and vaginal dryness. AIs are more commonly associated with musculoskeletal symptoms, osteoporosis, and increased rates of bone fracture, whereas tamoxifen is associated with an increased risk of uterine cancer and deep venous thrombosis. However, randomized trials have demonstrated that bisphosphonates and denosumab, a receptor activator of nuclear factor kappa B ligand (RANKL) inhibitor, can ameliorate AI-associated bone loss [81, 82].

Upfront Aromatase Inhibitor Therapy

Two large randomized trials, the ATAC [79, 83] and BIG 1-98 [66, 76], compared initial adjuvant ET with either tamoxifen or an AI in postmenopausal breast cancer patients (Table 7.9). In these trials, randomization occurred before the initiation of adjuvant therapy, and analyses included all events during the 5-year period.

The double-blind, placebo-controlled ATAC trial evaluated the efficacy and safety of anastrozole, tamoxifen, or anastrozole plus tamoxifen as initial adjuvant therapy after surgery in 9366 postmenopausal women with localized HR-positive breast cancer. Anastrozole was superior to both tamoxifen and combined tamoxifen and anastrozole [83–85]. At a median follow-up of 120 months, fewer recurrences occurred in patients receiving anastrozole compared with those receiving tamoxifen [79, 83]. DFS, the primary endpoint, was also significantly longer in patients receiving anastrozole (HR 0.86; 95% CI 0.78–0.95; $p = 0.003$). No differences in survival were observed. Although the greatest relative reductions in DFS, TTR, and contralateral breast cancer were observed in the first 2 years of active therapy, these benefits were sustained throughout the entire follow-up period and after treatment completion. Patients in the combined tamoxifen and anastrozole group gained no additional benefit over those in the tamoxifen group, suggesting a possible deleterious effect from the weak estrogenic effect of tamoxifen in patients with near-complete elimination of their endogenous estrogen levels [85]. The ATAC trial subprotocols show a number of important findings, including a lesser effect of anastrozole compared with tamoxifen on endometrial tissue [86]; similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting no significant impairment in overall quality of life [87]; a greater loss of bone mineral density with anastrozole [88]; a small pharmacokinetic interference of anastrozole in the presence of tamoxifen, with unclear significance [89]; and no evidence of an interaction between prior CT and anastrozole [90].

The BIG 1-98 trial, a phase III, double-blind, randomized trial, compared the efficacy of 5 years of tamoxifen, 5 years of letrozole, 2 years of tamoxifen followed by 3 years of letrozole, and 2 years of letrozole followed by 3 years of tamoxifen in 8010 postmenopausal women. An early analysis compared tamoxifen alone versus letrozole alone, including those patients in the sequential arms during their first 2 years of treatment only [80]. This analysis (25.8-month median follow-up) showed that 5 years of letrozole significantly improved DFS (HR 0.81; $p = 0.003$) and distant DFS (DDFS) (HR 0.73; $p = 0.001$) compared with 5 years of tamoxifen. These results led to the unblinding of the tamoxifen-alone arm, and 25.2% of patients selectively crossed over to letrozole, which has complicated subsequent intention-to-treat analyses of the monotherapy arms. The updated report (76-month median follow-up) included both an intention-to-treat analysis and a censored weighted modeling analysis at the time of crossover. Significant improvements in DFS and DDFS in favor of letrozole over tamoxifen and a nonsignificant improvement in OS (HR 0.87; 95% CI 0.75–1.02; $p = 0.08$) were still observed. However, in an updated analysis of the BIG 1-98 trial that accounted for women who crossed over from tamoxifen to letrozole after study unblinding, a significant, although modest, improvement in survival was observed in the letrozole arm compared with the tamoxifen arm (HR 0.82, 95% CI 0.70–0.95), resulting in an absolute difference of 1.4% at 5 years [91]. The overall incidence of cardiac adverse events was similar between the letrozole and tamoxifen arms (4.8% vs. 4.7%, respectively). However, the incidence of grade 3–5 cardiac

Table 7.9 Comparative efficacy of upfront aromatase inhibitor for 5 years versus tamoxifen for 5 years in early breast cancer

Study	ATAC [83]	BIG 1-98 [70]
Number of patients	6241	4922
Median follow-up, months	120	76
Disease-free survival		
HR	0.86[a]	0.88
p value	0.003[a]	0.03
Difference in 5-year disease-free survival, %	2.8	2.9
Time to distant recurrence		
HR	0.85[a]	0.85
p value	0.02[a]	0.05
Overall survival		
HR	0.95[a]	0.87
p value	0.4[a]	0.08

ATAC Anastrozole, Tamoxifen, Alone or in Combination, *BIG* Breast International Group, *HR* hazard ratio
[a]ER-negative patients excluded

adverse events was significantly higher in the letrozole arm, whereas the overall incidences of all-grade and high-grade (grade 3–5) thromboembolic events were significantly higher in the tamoxifen arm [92]. In addition, a higher incidence of bone fractures was observed in the letrozole arm than in the tamoxifen arm (9.5% vs. 6.5%, respectively) [93].

The magnitude of any additional benefit from an AI may depend on the risk of relapse. Retrospective analyses of the BIG 1-98 trial suggest that patients with low-risk tumors (i.e., small, low-grade tumors without lymphatic vascular invasion or nodal involvement; strong positive HR expression; and low Ki-67) may do equally well on tamoxifen or an AI [94]; however, this outcome has not been established in a prospective trial. Thus, given the numerous randomized trials demonstrating superior outcomes with AI versus tamoxifen monotherapy, most patients should receive an AI during the first 5 years of adjuvant therapy when possible [95].

Switching from Tamoxifen to Aromatase Inhibitor Versus Continued Tamoxifen

Several trials (Table 7.10) have evaluated the efficacy of switching to an AI after 2–3 years of tamoxifen versus 5 years of tamoxifen alone in an attempt to preempt the potential development of tamoxifen resistance and minimize the long-term side effects of 5-year AI and tamoxifen monotherapies. The largest of these studies, the Intergroup Exemestane Study (IES), compared the switch to exemestane after 2–3 years of tamoxifen versus 5 years of tamoxifen alone. Postmenopausal breast cancer patients who had completed a total of 2–3 years of tamoxifen ($n = 4724$) were randomized to receive either continued tamoxifen or exemestane to complete a total duration of 5 years of ET [96]. At a median follow-up of 55.7 months, sequential exemestane therapy was superior to tamoxifen alone in terms of DFS (HR 0.76; 95% CI 0.66–0.88; $p = 0.0001$). A significant difference in OS was only found in patients with ER-positive tumors (HR 0.83; 95% CI 0.69–1.00; log rank $p = 0.05$). In the most recent update (91-month median follow-up), the benefit in those patients who switched to exemestane has been sustained.

The Italian Tamoxifen Anastrozole (ITA) trial randomized 448 postmenopausal women with breast cancer who had completed 2–3 years of tamoxifen to either continue tamoxifen or switch to anastrozole to complete a total of 5 years of ET [97]. Updated results from this study showed that the HR for relapse-free survival was 0.56 (95% CI 0.35–0.89; $p = 0.01$), and the p value for OS analysis remained at 0.1 [98]. A meta-analysis ($n = 4006$) of the Austrian Breast and Colorectal Cancer Study Group (ABCSG) 8, Arimidex–Nolvadex (ARNO) 95, and ITA trials showed a significant improvement in OS (HR 0.71; $p = 0.04$) with anastrozole switching therapy in postmenopausal women with hormone-sensitive disease [99, 100]. In the ARNO 95 and ITA trials, only patients who were relapse-free after 2–3 years of tamoxifen were randomized, whereas the ABCSG 8 study randomized patients at diagnosis. An additional meta-analysis of these studies ($n = 9015$) demonstrated that AI switching therapy resulted in a significant 29% proportional decrease in recurrence rate (absolute decrease of 3.1% at 5 years and 3.6% at 8 years), a significant 22% proportional decrease in breast cancer mortality rate (absolute decrease of 0.7% at 5 years and 1.7% at 8 years), and a reduction in overall mortality rate (absolute decrease of 2.2% at 8 years; $p = 0.004$) [69]. An update of the ABCSG 8 trial (60-month median follow-up) showed a modest, statistically nonsignificant improvement in the primary endpoint of RFS and a significant improvement in the defined exploratory endpoint of distant relapse-free survival.

Table 7.10 Comparative efficacy of 2–3 years of tamoxifen followed by 2–3 years of aromatase inhibitor versus 5 years of tamoxifen alone

Study	IES [96]	ARNO 95 [100]	ITA [97, 98]	ABCSG 8 [100]
Number of patients	4724	979	448	3714
Median follow-up, months	55.7	30.1	64	72
Disease-free survival				
HR	0.76	0.66	0.56	0.79
p value	0.0001	0.49	0.01	0.038
Overall survival				
HR	0.83	0.53	0.56	0.77
p value	0.05	0.045	0.1	0.025

ABCSG Austrian Breast Cancer Study Group, *ARNO* Arimidex–Nolvadex, *HR* hazard ratio, *IES* Intergroup Exemestane Study, *ITA* Italian Tamoxifen Anastrozole

Switching from Tamoxifen to Aromatase Inhibitor Versus Upfront Aromatase Inhibitor

The use of upfront or switching AI therapy has been addressed in two large randomized trials, the Tamoxifen Exemestane Adjuvant Multicenter (TEAM) and the BIG 1-98 trials. The TEAM trial evaluated exemestane [72], and the BIG 1-98 trial evaluated letrozole [70, 71]. Neither trial demonstrated any significant difference in recurrence or survival rates between the upfront and switch arms. The TEAM trial compared exemestane alone versus 2.5–3 years of tamoxifen followed by exemestane to complete a total of 5 years of ET [72]. This trial was initially designed to compare 5 years of tamoxifen monotherapy to 5 years of exemestane monotherapy. However, based on the favorable results of the IES, the study design was changed to a switch trial consisting of 9229 postmenopausal patients. At the end of 5 years, 85% of patients in the sequential group versus 86% of patients in the exemestane group were disease-free (HR 0.97; 95% CI 0.88–1.08; $p = 0.60$). This finding is consistent with data from the BIG 1-98 trial, in which tamoxifen followed by letrozole, letrozole followed by tamoxifen, and letrozole alone showed a similar efficacy at a 71-month median follow-up.

Extended Adjuvant Endocrine Therapy

Late recurrences are common in HR-positive breast cancer, and a continual risk of relapse exists throughout a 15-year time span despite 5 years of ET. The risk of breast cancer recurrence after 5 years of endocrine therapy was evaluated in a meta-analysis by the EBCTCG. In that meta-analysis, breast cancer recurrence occurred at a steady rate throughout the study period from 5 to 20 years and was strongly correlated with the original tumor size, nodal status, and tumor grade [101]. The rationale for evaluating AI as extended adjuvant therapy is based on the observation that ER-positive patients continue to exhibit significant residual risk for recurrence and death long after the initial 5 years of tamoxifen therapy. Several trials including the large MA.17 trial and the smaller ABCSG 6 and NSABP B-33 trials have also demonstrated that extended ET with 3–5 years of an AI following 5 years of tamoxifen decreases relapse rates and may affect survival, especially in women with nodal involvement (Table 7.11) [73–75, 102].

The MA.17 trial evaluated the benefit of extended adjuvant ET with letrozole in postmenopausal patients who had completed 5 years of tamoxifen (Box 7.3). At a median follow-up of 2.5 years, extended letrozole treatment resulted in fewer recurrences and fewer new contralateral breast cancers (HR 0.58; 95% CI 0.45–0.76; $p < 0.001$) compared with placebo. No difference in OS was demonstrated (HR 0.82; 95% CI, 0.57–1.19; $p = 0.30$), although a survival advantage was observed in the subset of patients with axillary lymph node-positive disease (HR 0.61; 95% CI 0.38–0.98; $p = 0.04$). However, in an updated analysis (64-month median follow-up) that adjusted for patients in the placebo arm who crossed over to letrozole after study unblinding, a significant 24–39% proportional decrease in mortality was observed in patients who received letrozole after tamoxifen [73]. A formal

Table 7.11 Comparative efficacy of extended adjuvant therapy of 5 years of tamoxifen followed by 3–5 years of aromatase inhibitor versus 5 years of tamoxifen alone

Study	NCIC-CTG MA.17 [73]	ABCSG-6a [74]	NSABPB-33 [75]
Number of patients	5187	852	1562
Median follow-up, months	64	62	30
Disease-free survival			
HR	0.68	0.62	0.68
p value	0.0001	0.031	0.07
Overall survival			
HR	0.98	0.89	NR
p value	0.853	0.57	

ABCSG Austrian Breast Cancer Study Group, *HR* hazard ratio, *NCIC-CTG* National Cancer Institute of Canada Clinical Trials Group, *NR* not recorded, *NSABP* National Surgical Adjuvant Breast and Bowel Project

Box 7.3 Evidence of the Efficacy of Adjuvant AI Therapy from the 2010 EBCTCG Meta-analysis and MA.17 Trial

Single-agent therapy—The 2010 EBCTCG meta-analysis compared adjuvant AI vs. tamoxifen in 9856 women (mean follow-up of 6 years). AI treatment resulted in (1) a reduction in recurrence risk within 5 years (rate ratio 0.77; $p < 0.001$), which translated into a 3% absolute reduction in the 5-year recurrence risk (12% vs. 15%, respectively), and (2) a nonsignificant reduction in the risk of breast cancer death (rate ratio 0.89; $p > 0.1$), which translated into a 1% absolute reduction in the 5-year breast cancer mortality rate (7% vs. 8%, respectively).

Switching therapy—A second analysis compared switching to AI vs. continued tamoxifen in 9015 women (mean follow-up of 4 years). After 2–3 years of tamoxifen, patients were randomly assigned to receive AI or continued tamoxifen to complete a total of 5 years of ET. Switching therapy resulted in (1) a reduction in recurrence risk at 6 years (8% vs. 11%, respectively; rate ratio 0.71; $p < 0.001$) and (2) a reduction in the 5-year breast cancer mortality rate (6% vs. 8%, respectively; rate ratio 0.79; $p = 0.004$).

Extended therapy—A third adjuvant AI strategy is to initiate a 5-year course of AI after the completion of 5 years of tamoxifen. Evidence to support extended therapy comes from the MA.17 trial. In this trial, 5187 postmenopausal women (node-positive, 46%; ER-positive, 98%) who had completed 5 years of adjuvant tamoxifen were randomly assigned to receive letrozole or placebo for 5 years. At a median follow-up of 64 months, letrozole improved DFS (HR 0.68, 95% CI 0.45–0.61) and OS (HR 0.51, 95% CI 0.42–0.61). Interestingly, women in the placebo arm who switched to letrozole after study unblinding still experienced an improvement in DFS despite the substantial interval between therapies (median, 2.8 years).

Similar benefits in DFS have been reported with tamoxifen followed by 3 years of anastrozole and 5 years of exemestane [74, 75]. In the extension study of the ABCSG 6 trial, 852 HR-positive postmenopausal patients who were disease-free and received 5 years of adjuvant tamoxifen were randomized to 3 years of anastrozole ($n = 387$) or no further therapy ($n = 469$). At a median follow-up of 62.3 months, anastrozole significantly reduced the recurrence risk compared with no further treatment (HR 0.62; 95% CI 0.40–0.96; $p = 0.031$) [74]. The results of the ABCSG-6a trial confirmed the benefit

of extended adjuvant anastrozole treatment, showing a 38% decrease in recurrence risk. However, these findings should be viewed cautiously because of the limited statistical power and the lower than expected recruitment rate. Despite the limitations of the NSABP B-33 trial (premature closing and crossover from placebo to exemestane in some patients), the intention-to-treat analysis showed an improvement in DFS at 4 years with exemestane [75].

quality-of-life analysis demonstrated reasonable preservation of life quality during extended ET, although some women experienced ongoing menopausal symptoms and loss of bone mineral density [103, 104]. In conclusion, the MA.17 study demonstrated that extended adjuvant treatment with letrozole after tamoxifen significantly improved DFS and distant metastasis-free survival in lymph node-positive and node-negative patients and extended OS in lymph node-positive patients.

The recently reported MA.17R trial randomized women who had already completed 5 years of aromatase inhibitor therapy with or without previous tamoxifen to a further 5 years of letrozole or placebo. DFS was significantly improved in the extended letrozole group, with similar quality of life, but bone fracture rates were higher. The 5-year DFS rate was 95% for the letrozole arm compared with 91% for the placebo arm [hazard ratio 0.66, 95% CI (0.48–0.91); $p < 0.01$] [105].

Several studies investigated the efficacy and safety of additional treatment with AIs after a sequential regimen of tamoxifen and an AI for 5 years [106, 107]. However, results from NSABP-B42, the DATA trial, and the IDEAL trial have not confirmed the benefit for recurrence-free survival observed in MA17R.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B42 study presented at the San Antonio Breast Cancer Symposium in 2016 investigated the efficacy of 5 years of letrozole after an initial 5 years of endocrine therapy including an AI. This therapy could be either AI monotherapy or sequenced with tamoxifen. In contrast to the findings of the MA.17R trial, the difference in DFS between the control and placebo groups did not reach statistical significance [7-year DFS 84.7% vs. 81.3%, HR 0.85, $p = 0.048$, statistical significance level 0.0418]. For OS, a significant difference between the control and placebo groups was also not observed [91.8% vs. 92.3%, HR 1.15, $p = 0.22$]. However, patients under extended endocrine therapy were significantly less frequently affected by distant recurrence [HR 0.72, $p = 0.03$]; a risk reduction of 28% was observed. Furthermore, a significantly longer BC-free interval (BCFI), defined as time to recurrence or contralateral BC as the first event, was observed in the letrozole group [incidence of BCFI events 6.7% vs. 10.0%, HR 0.71, $p = 0.003$].

The Different Durations of Anastrozole and Tamoxifen (DATA) trial presented at the San Antonio Breast Cancer Symposium in 2016 was designed to investigate the effect of extended AI therapy after TAM. In this multicenter phase III trial, 1660 postmenopausal women with HR^+ EBC who underwent 2–3 years of TAM therapy were randomized to 6 or 3 years of anastrozole daily. The 5-year adapted DFS did not differ significantly [83.1% vs. 79.4%, HR 0.79, $p = 0.07$] [106].

The Investigation on the Duration of Extended Adjuvant Letrozole (IDEAL) multicenter phase III trial from the Netherlands randomized patients to 2.5 or 5 years of letrozole after 5 years of hormone therapy. The median follow-up was 6.5 years. No significant difference in 5-year DFS was observed between patients with 2.5 years or 5 years of extended letrozole therapy [88.4% vs. 87.9%, HR 0.96, $P = 0.70$]. The 5-year OS also did not differ significantly between these groups [93.5% vs. 92.6%, HR 1.08, $P = 0.59$] [107]. In a recent meta-analysis of extended endocrine therapy that included the abovementioned trials, women with positive nodal status seemed to receive greater benefit from extended endocrine therapy (node-positive HR 0.72 versus node-negative HR 0.83). Similarly, a greater benefit of extended endocrine therapy was observed in women with a larger tumor size and those with both ER and PR expression versus single-receptor expression. A greater effect was also observed in patients who received adjuvant chemotherapy compared with that of those who did not [108].

Other trials have evaluated less intensive extended endocrine regimens and suggested their equivalence with extended therapy for an additional 5 years. The SOLE study was recently presented at the ASCO annual meeting in June 2017. This phase III trial included 4884 postmenopausal women with HR^+, N^+ early-stage BC with the purpose of investigating the effect of a new therapeutic concept of letrozole [109]. The trial was designed to assess the role of continuous versus intermittent letrozole intake. After 5 years of adjuvant endocrine therapy, patients were randomized to 5 years of either continuous ($n = 2441$) or intermittent ($n = 2443$) letrozole administration with mandatory 3-month treatment-free intervals. After 60 months of follow-up, similar 5-year DFS rates were observed in patients with intermittent and continuous letrozole administration [85.8% vs. 87.5%, HR 1.08, $p = 0.31$]. Extending AI after the initial 5 years of any endocrine therapy was also assessed (Table 7.12).

Table 7.12 Extending AI after initial 5 years of any endocrine therapy

Trial	No. of patients	Prerandomization therapy	Randomization	HR for DFS	HR for OS
MA.17R [105]	1918	3–5 ys TAM + 5ys AI	Letrozol (5 ys)	0.66 (p = 0.01)	0.97 (p = ns)
			Placebo		
NSABP B42	3923	5 ys (or TAM sequenced to AI)	Letrozol (5 ys)	0.85 (p = ns)	1.15 (p = ns)
			Placebo		
IDEAL [107]	1824	5 ys AI or TAM or TAM sequenced to AI	Letrozol (5 ys)	0.92 (p = ns)	1.04 (p = ns)
			Letrozol (2.5 ys)		
DATA [106]	1660	2–3 ys TAM	Anastrazol (6 ys)	0.79 (p = 0.07)	0.91 (p = ns)
			Anastrazol (3 ys)		
SOLE [109]	4884	5 ys AI or TAM or TAM sequenced to AI	Letrozol (5 ys-cont)	1.08 (p = ns)	0.05 (p = ns)
			Letrozol (5 ys-int)		

HR hazard ratio, *DFS* disease-free survival, *OS* overall survival, *ns* nonsignificant, *NSABP* National Surgical Adjuvant Breast and Bowel Project, *IDEAL* Investigation on the Duration of Extended Adjuvant Letrozole, *DATA* Different Durations of Anastrozole and Tamoxifen, *ys* years

Table 7.13 Criteria used for adjuvant endocrine therapy selection in postmenopausal women [76, 112]

Adjuvant endocrine therapy	Criteria for therapy selection			
5 years of AI (up to 10 years [76]) Preferred	1. Higher risk of early relapse (e.g., larger tumor size or several positive nodes) 2. History or risk of thromboembolic event 3. Patient on a CYP2D6 inhibitor	→	If muscle/joint discomfort or other adverse effects, use an alternative AI	If unable to tolerate AI, use tamoxifen to complete at least 5 years
Switch from tamoxifen (2–3 years) to AI (2–3 years) to complete a total of 5 years of endocrine therapy (up to 10 years [76]) Preferred	1. Significant osteopenia/ osteoporosis 2. Musculoskeletal and/or joint discomfort 3. Hypercholesterolemia/heart disease	→	AI may be continued up to 5 years if tolerated High proliferative rate (Ki-67) High grade Lower ER/PR level HER2 amplification Presence of LVI	
5 years of tamoxifen (up to 10 years [76]) Less preferred	AI contraindicated or declined by patient	→	5 years of AI if appropriate or consider 5 years of tamoxifen if AI use is still not an option	

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AI aromatase inhibitor, *ER* estrogen receptor, *LVI* lymphovascular invasion, *PR* progesterone receptor

Biomarkers for Endocrine Therapy Selection

No single biomarker can reliably predict the optimal ET for use in a given patient. The prognostic significance of ER and PR levels, PR negativity, HER2 overexpression, Ki-67 level, and 21-gene RS has been examined. In the initial exploratory analysis of the ATAC trial, a greater benefit of anastrozole compared with tamoxifen in the PR-negative subgroup was suggested. A subsequent central analysis using 2006 of 5880 specimens showed that quantitative expression of ER, PR, and HER2 was not useful in identifying patients who would benefit from anastrozole. The TEAM trial showed that, in patients receiving exemestane, ER and PR expression levels predicted DFS, relative risk of relapse increased with decreased ER and PR expression, and PR status did not predict treatment response. In the BIG 1-98 trial, more relapses occurred in the first 2 years in women who received tamoxifen followed by letrozole than in those who received letrozole alone (4.4% vs. 3.1%, respectively). This increased risk of relapse was particularly evident in women with >3 involved nodes ($p < 0.001$), tumors ≥2 cm in size ($p = 0.001$), or vascular invasion ($p = 0.02$). A retrospective analysis demonstrated that these factors in conjunction with ER and PR levels, Ki-67 labeling index, and HER2 status may be useful in guiding the selection of letrozole or tamoxifen [94]. IHC analysis of the nuclear antigen Ki-67 is used to estimate the proliferative activity of tumor cells. Studies have demonstrated the prognostic value of Ki-67 in predicting response and clinical outcomes [110]. One small study suggested that analyzing Ki-67 after short-term ET may be useful in selecting patients who are resistant to ET and may benefit from additional interventions [111]. However, these data require greater analytic and clinical validation. Patients at the highest risk of recurrence benefited the most from AI treatment for 5 years, whereas relapse rates in those at lowest risk did not differ among patients treated with tamoxifen, letrozole, or a switch approach [112]. A summary of the criteria used for adjuvant ET selection in postmenopausal women is shown in (Table 7.13).

Comparison of Letrozole, Anastrozole, and Exemestane Efficacy

According to the evidence to date, AIs exhibit very similar activity. Although letrozole leads to more complete aromatase inhibition [113] and lower serum estrogen levels [104, 114] than anastrozole, the clinical importance of these findings is unclear. To date, indirect comparisons between adjuvant trials suggest that letrozole, anastrozole, and exemestane have similar benefits when compared with tamoxifen. In addition, a neoadjuvant study showed that letrozole, anastrozole, and exemestane similarly suppress the proliferation marker Ki-67 and preoperative endocrine prognostic index scores [115].

The NCIC-CGC MA.27 study compared the efficacy and safety of 5 years of exemestane, a steroidal AI that binds irreversibly to aromatase, to that of anastrozole, a nonsteroidal AI that forms reversible bonds, in 7576 postmenopausal women [116]. At a median follow-up of 4.1 years, the 4-year event-free survival was 91% for exemestane and 91.2% for anastrozole (stratified HR 1.02; 95% CI, 0.87–1.18; $p = 0.85$). The overall DDFS and disease-specific survival rates were also similar. In all, 31.6% of patients discontinued treatment because of adverse effects, concomitant disease, or study refusal. Osteoporosis/osteopenia, hypertriglyceridemia, vaginal bleeding, and hypercholesterolemia were less frequent in response to exemestane, whereas mild liver function abnormalities and rare episodes of atrial fibrillation were less frequent in response to anastrozole. Vasomotor and musculoskeletal symptoms were similar between the arms. Compliance is a major issue for the use of all chronic medications, including adjuvant ET. Given the adverse effects of both tamoxifen and AIs and the uncertain survival benefit of any particular approach, the schedule that leads to better compliance is likely to have the most benefit. For some patients, a switch approach may offer the best balance between efficacy and toxicity [117]. The Femara versus Anastrozole Clinical Evaluation (FACE) trial was recently reported to assess the potential differences in efficacy and safety between the nonsteroidal AIs anastrozole and letrozole in postmenopausal women with HR-positive, node-positive breast cancer. The 5-year estimated DFS rate was 84.9% for letrozole versus 82.9% for anastrozole arm (hazard ratio, 0.93; $P = 0.3$). Exploratory analysis showed similar DFS for letrozole and anastrozole in all evaluated subgroups. The 5-year estimated overall survival rate was 89.9% for letrozole versus 89.2% for anastrozole arm (hazard ratio, 0.98; $P = 0.8$) [118].

Optimal Timing of Aromatase Inhibitor Therapy

Studies have consistently demonstrated that the use of third-generation AIs as initial adjuvant therapy, sequential therapy, or extended therapy lowers recurrence risk, including ipsilateral breast tumor recurrence, contralateral breast cancer, and distant metastatic disease, in postmenopausal women with HR-positive breast cancer. However, a direct comparison of these strategies is not possible given the differences in design and patient populations among studies. All three adjuvant strategies have shown similar antitumor efficacy and toxicity profiles in randomized studies. The benefit of upfront and switching adjuvant AI therapy was established in the 2010 EBCTCG meta-analysis. Two separate analyses were performed: (1) AI versus tamoxifen monotherapy and (2) switching to AI after 2–3 years of tamoxifen versus continued tamoxifen. The findings of this meta-analysis are summarized in Box 7.3. Upfront or switching AI therapy improved DFS compared with 5 years of tamoxifen. In contrast, AI-containing regimens had no clear impact on OS. However, a modest OS benefit was observed in all switching studies, yielding an absolute gain in survival at 8 years.

The current version of the NCCN Guideline (2019 V1) recommends the following adjuvant ET options for postmenopausal women with early breast cancer: 5 years of AI as initial adjuvant therapy (category 1), 2–3 years of AI followed by tamoxifen to complete 5 years of adjuvant ET (category 1), 2–3 years of tamoxifen followed by an AI to complete 5 years (category 1) or 5 years of AI alone B, or 5 years of tamoxifen followed by 5 years of AI (category 1). The use of tamoxifen alone for 5 years or longer is limited to postmenopausal women who decline AI treatment or have a contraindication to AIs. Patients who experience intolerable adverse effects on the initial adjuvant AI therapy and switch to tamoxifen after 2 years have similar outcomes to those who complete 5 years of AI therapy [71]. Switching to a different AI is reasonable because 39% of patients are able to tolerate an alternative AI [119].

In conclusion, AI use, either upfront or after 2–3 years of tamoxifen, should be recommended for the majority of breast cancer patients. When choosing between upfront and switch strategies, it is reasonable to weigh the potential added benefit of AIs in reducing early relapse in the patients who are most likely to suffer tamoxifen and AI toxicities [120]. Support from prospective studies for the preferential use of upfront AI in patients with greater tumor burdens or more aggressive tumor biology would be extremely useful [94].

Optimal Duration of Adjuvant Endocrine Therapy

Because of the chronic nature of HR-positive disease, the risk of recurrence remains after 5 years. The optimal duration of adjuvant ET is not yet known but should be more than 5 years. It is unclear how the results of the extended adjuvant ET trials, such as the MA.17, should be incorporated into

practice because AIs are used at some point in the first 5 years of breast cancer therapy. Because 5 years of an AI is effective after 5 years of tamoxifen use and because recurrence is decreased every year of AI use, it is logical to assume that 5 years of an AI would also be effective after 2–3 years of tamoxifen. Therefore, up to 5 years of AI treatment is reasonable after switching from tamoxifen regardless of when the switch is made. However, current data support a total of 8–10 years of ET when AIs are used after 2–3 years of tamoxifen. Currently, ASCO 2019 guideline recommends 10 years of therapy for high risk postmenopausal women [76]. Extended duration of tamoxifen has been shown to improve disease-free survival and overall survival in the ATLAS and aTTom trials. However, in postmenopausal women, AIs have been shown to be more effective than tamoxifen. Accordingly, it is recommended that adjuvant endocrine therapy in postmenopausal women with early breast cancer include an AI. Recently, the DATA, IDEAL, and NSABP B42 trials showed that extended adjuvant endocrine therapy with AIs beyond 5 years in postmenopausal women with early breast cancer reduced the occurrence of secondary breast tumors but had no or only a small impact on distant metastasis-free survival. Furthermore, the toxicity of adjuvant AIs led to gradually decreasing compliance rates and long-term toxicities associated with non-breast cancer-related deaths.

Conclusion

Adjuvant ET remains a mainstay of therapy for women with ER-positive breast cancer. A summary of the 2019 NCCN (Version 1.2019) and ASCO 2019 recommendations regarding the use of AIs and tamoxifen in the adjuvant setting is provided in Boxes 7.4 and 7.5, respectively. Adjuvant ET has

Box 7.4 Summary of the 2019 NCCN Breast Cancer Panel Recommendations for Adjuvant Endocrine Therapy (NCCN Guidelines Version 1. 2019 Breast Cancer)

- Endocrine strategies in premenopausal women include ER blockade with tamoxifen, temporary ovarian suppression with LHRH agonists, or permanent ovarian suppression with oophorectomy or radiotherapy. Premenopausal women should not be given AIs as an initial adjuvant therapy outside the confines of a clinical trial. Women who are premenopausal at diagnosis and become amenorrheic after CT may have continued estrogen production from the ovaries without menses. Serial assessment of circulating LH, FSH, and E_2 levels to confirm postmenopausal status is mandatory in this subset of women if AI therapy is considered. Tamoxifen with or without ovarian suppression for 5 years has been the standard ET for premenopausal women (category 1). In women who are postmenopausal at the time of completion of 5 years of tamoxifen (including those who have become postmenopausal during the 5 years of tamoxifen therapy), extended therapy with continued tamoxifen for 5 years (category 2A) or an AI for up to 5 years (category 1) is recommended. For those who remain premenopausal after the initial 5 years of tamoxifen, continued tamoxifen therapy for up to 10 years is recommended based on the data from the ATLAS trial (category 2A). AI for 5 years + ovarian suppression may be considered as an alternative option based on the SOFT and TEXT clinical trial outcomes.
- The following adjuvant ET options are recommended for women who are postmenopausal at diagnosis: initial adjuvant therapy with an AI for 5 years (category 1), AI for 2–3 years followed by tamoxifen to complete a total of 5 years of adjuvant ET (category 1), tamoxifen for 2–3 years followed by an AI to complete a total of 5 years (category 1) or 5 years of an AI (category 2B), or tamoxifen for 4.5–6 years followed by 5 years of an AI (category 1) or consideration of tamoxifen for up to 10 years (category 2A). The use of tamoxifen alone for 5 years (category 1) or up to 10 years (category 2A) is limited to postmenopausal women who decline or have a contraindication to AIs.
- Small, HR-positive tumors (those less than 0.5 cm in greatest diameter that do not involve the lymph nodes) have such favorable prognoses that adjuvant ET is of minimal benefit (category 2B).
- IHC analysis of the nuclear antigen Ki-67 estimates the proliferative activity of tumor cells. Studies have demonstrated the prognostic value of Ki-67 in predicting response and clinical outcome. Standardization of tissue handling and processing is required for improving the reliability and prognostic value of Ki-67 analysis. To date, there is no conclusive evidence that Ki-67 alone, especially baseline Ki-67, is useful in ET selection. Therefore, Ki-67 assessment is not currently recommended.
- The cytochrome P-450 enzyme CYP2D6 converts tamoxifen to endoxifen. Because of the limited and conflicting evidence at this time, CYP2D6 testing for adjuvant ET selection is not recommended. When prescribing a selective serotonin reuptake inhibitor, it is reasonable to avoid potent and intermediate CYP2D6 inhibitors, particularly paroxetine and fluoxetine, if an appropriate alternative exists.

Box 7.5 Summary of the ASCO 2019 Recommendations Specific for Adjuvant Endocrine Therapy

1. *Treatment of choice in premenopausal patients with HR-positive early breast cancer*: Women with HR-positive breast cancer who are premenopausal or perimenopausal at the time of diagnosis should be offered adjuvant ET with tamoxifen for an initial duration of 5 years. After 5 years, women should receive additional therapy based on menopausal status. Premenopausal and perimenopausal women and those with unknown or undetermined menopausal status should be offered continued tamoxifen for a total duration of 10 years. Women who have become definitively postmenopausal should be offered the choice of continued tamoxifen for a total duration of 10 years or switching to up to 5 years of an AI to complete a total of up to 10 years of adjuvant ET.
2. *Optimal duration of tamoxifen*: Five trials have evaluated tamoxifen treatment for longer than 5 years; three showed positive results. The two largest studies with the longest reported follow-up now show a breast cancer survival advantage with longer durations (10 years) of tamoxifen use. The beneficial effects of tamoxifen become more pronounced with longer duration. Thus, a minimum of 5 years of extended treatment (i.e., 10 years since diagnosis) is needed to observe clinical benefit. In addition to modest gains in survival, extended therapy with tamoxifen for 10 years was associated with lower risks of recurrence and of contralateral breast cancer compared with 5 years. Extended tamoxifen did not affect non-breast cancer mortality in the studies examined. Consistent with previous reports on the effects of adjuvant ET, only patients with ER-positive tumors appear to benefit from extended therapy with tamoxifen.
3. *What is the appropriate sequence of adjuvant ET in postmenopausal patients*? Postmenopausal women who are intolerant of either tamoxifen or AIs should be offered an alternative adjuvant ET. Women who have received an AI but discontinued treatment at less than 5 years may be offered tamoxifen for a total of 5 years. Women who have received tamoxifen for 2–3 years should be offered the option of switching to an AI for up to 5–8 years to complete a total of up to 7–10 years of adjuvant ET. Women who have received 5 years of tamoxifen or AI as adjuvant ET should be offered additional adjuvant ET. Postmenopausal women should be offered continued tamoxifen for a total of up to 10 years or the option of switching to up to 5 years of an AI to complete a total of up to 10 years of adjuvant ET. Premenopausal and perimenopausal women and those with unknown or undetermined menopausal status should be offered an additional 5 years of tamoxifen to complete a total of 10 years of adjuvant ET.
4. *Determination of ET responsiveness*: Tumor size, nodal status, ER expression, PR expression, and HER2 expression are well-established predictors of breast cancer recurrence. However, robust biomarkers that are capable of predicting early versus late recurrence, the most appropriate ET (tamoxifen vs. AI), and the need for extended adjuvant ET are not available.
5. *Subsets of patients who are more likely to benefit from an AI* versus *tamoxifen*: Currently, no subgroups have been well identified as being more likely to benefit from an AI versus tamoxifen. Most analyses are retrospective and mix predictive and prognostic factors. Tamoxifen is recommended for male patients because of the lack of AI data. The predictive value of CYP2D6 for tamoxifen response is unknown. Thus, CYP2D6 genotype testing is not recommended for treatment selection. However, caution is needed in patients taking tamoxifen with CYP2D6-interacting agents. CYP2D6-interacting agents should not be used in combination with tamoxifen if alternative choices exist.
6. *Risks associated with adjuvant AI therapy*: Toxicity, the presence of comorbidities, and patient preference should be taken into account in treatment selection. Switching therapy should be considered if there is poor adherence or intolerable toxicity. Although serious adverse events are rare, these agents have different and unique toxicity profiles that should be considered when recommending a specific treatment. AI use is associated with increased risk of cardiovascular disease, bone disorders, hypercholesterolemia, and hypertension, whereas tamoxifen is more often associated with gynecologic side effects, flushing, endometrial lesions, and venous thromboembolic events.
7. *Interchangeability of AIs*: There are no clinically relevant differences among AIs. Therefore, patients intolerant of one AI can be switched to another.

made a major contribution in reducing recurrence risk and improving OS in ER-positive disease. In premenopausal women, tamoxifen remains the standard treatment. Currently, up to 10 years of tamoxifen can be safely administered, especially in women who remain premenopausal. The addition of an LHRH agonist to tamoxifen treatment represents another choice. Patients who are considered to be perimenopausal should be initially treated like premenopausal patients. Depending on their serum hormone levels, these patients can be safely switched to an AI therapy once the E_2 and FSH

levels prove the establishment of postmenopausal status. In postmenopausal women, several sequences of endocrine treatment are available. The AI therapy can be induced upfront or sequentially by switching from AI to TAM and vice versa. Because women with ER-positive breast cancer have a long-term risk of relapse, emerging data demonstrating further survival gains with extended adjuvant ET are particularly relevant and indicate that the full potential of currently available endocrine agents has not yet been realized. Ongoing AI studies will further help to define the benefit of extended ET. However, the benefit is likely to vary based on recurrence risk; thus, a move from a one-size-fits-all strategy to a risk-adaptive strategy is needed.

The St. Gallen Consensus Conference 2017 and 2019 panels were almost unanimous that some postmenopausal patients can be treated with tamoxifen alone. Most of the panelists believed that an aromatase inhibitor should be used at some point during the course of adjuvant therapy. Factors that favored the use of an aromatase inhibitor include node positivity, high ki67, high grade, lobular histology, and her two positivity. The Panel recommended longer durations of therapy in women with moderate to high risk of recurrence, typically defined as stage II or III breast cancers.

References

1. Osborne CK, Schiff R, Fuqua SA, Shou J. Estrogen receptor: current understanding of its activation and modulation. Clin Cancer Res. 2001;7:4338s–42s; discussion 4411s–4412s.
2. Kumar R, Thompson EB. The structure of the nuclear hormone receptors. Steroids. 1999;64:310–9.
3. Shou J, Massarweh S, Osborne CK, et al. Mechanisms of tamoxifen resistance: increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer. J Natl Cancer Inst. 2004;96:926–35.
4. Osborne CK, Yochmowitz MG, Knight WA 3rd, McGuire WL. The value of estrogen and progesterone receptors in the treatment of breast cancer. Cancer. 1980;46:2884–8.
5. Davies C, Godwin J, Gray R, et al. 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.
6. Goldhirsch A, Coates AS, Gelber RD, et al. First–select the target: better choice of adjuvant treatments for breast cancer patients. Ann Oncol. 2006;17:1772–6.
7. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol. 2007;18:1133–44.
8. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes–dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol. 2011;22:1736–47.
9. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000;406:747–52.
10. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98:10869–74.
11. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004;351:2817–26.
12. van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med. 2002;347:1999–2009.
13. Wang Y, Klijn JG, Zhang Y, et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. Lancet. 2005;365:671–9.
14. Filipits M, Nielsen TO, Rudas M, et al. The PAM50 risk-of-recurrence score predicts risk for late distant recurrence after endocrine therapy in postmenopausal women with endocrine-responsive early breast cancer. Clin Cancer Res. 2014;20:1298–305.
15. Fan C, Oh DS, Wessels L, et al. Concordance among gene-expression-based predictors for breast cancer. N Engl J Med. 2006;355:560–9.
16. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med. 2015;373:2005–14.
17. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med. 2016;375:717–29.
18. Fisher B, Redmond C. Systemic therapy in node-negative patients: updated findings from NSABP clinical trials. National Surgical Adjuvant Breast and Bowel Project. J Natl Cancer Inst. Monographs. 1992;11:105–16.
19. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006;24:3726–34.
20. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol. 2010;11:55–65.
21. De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. Lancet. 2010;376:911–21.
22. Knauff EA, Eijkemans MJ, Lambalk CB, et al. Anti-Mullerian hormone, inhibin B, and antral follicle count in young women with ovarian failure. J Clin Endocrinol Metab. 2009;94:786–92.
23. Torino F, Barnabei A, De Vecchis L, et al. Recognizing menopause in women with amenorrhea induced by cytotoxic chemotherapy for endocrine-responsive early breast cancer. Endocr Relat Cancer. 2012;19:R21–33.
24. Soules MR, Sherman S, Parrott E, et al. Stages of reproductive aging workshop (STRAW). J Womens Health Gend Based Med. 2001;10:843–8.
25. 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.
26. 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 HOBOE trial. J Clin Oncol. 2009;27:3192–7.
27. Lambalk CB, van Disseldorp J, de Koning CH, Broekmans FJ. Testing ovarian reserve to predict age at menopause. Maturitas. 2009;63:280–91.
28. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J Clin Oncol. 1996;14:1718–29.
29. Sonmezer M, Oktay K. Fertility preservation in young women undergoing breast cancer therapy. Oncologist. 2006;11:422–34.
30. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24:2917–31.

31. Najafi S, Djavid GE, Mehrdad N, et al. Taxane-based regimens as a risk factor for chemotherapy-induced amenorrhea. Menopause. 2011;18:208–12.
32. Swain SM, Land SR, Ritter MW, et al. Amenorrhea in premenopausal women on the doxorubicin-and-cyclophosphamide-followed-by-docetaxel arm of NSABP B-30 trial. Breast Cancer Res Treat. 2009;113:315–20.
33. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet. 1998;351:1451–67.
34. Goldhirsch A, Ingle JN, Gelber RD, et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol. 2009;20:1319–29.
35. Sutherland RL, Green MD, Hall RE, et al. Tamoxifen induces accumulation of MCF 7 human mammary carcinoma cells in the G0/G1 phase of the cell cycle. Eur J Cancer Clin Oncol. 1983;19:615–21.
36. Hug V, Hortobagyi GN, Drewinko B, Finders M. Tamoxifen-citrate counteracts the antitumor effects of cytotoxic drugs in vitro. J Clin Oncol. 1985;3:1672–7.
37. Albain KS, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. Lancet. 2009;374:2055–63.
38. Lonning PE. Evolution of endocrine adjuvant therapy for early breast cancer. Expert Opin Investig Drugs. 2010;19(Suppl 1):S19–30.
39. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst. 1996;88:1529–42.
40. Stewart HJ, Forrest AP, Everington D, et al. Randomised comparison of 5 years of adjuvant tamoxifen with continuous therapy for operable breast cancer. The Scottish Cancer Trials Breast Group. Br J Cancer. 1996;74:297–9.
41. Davies C, Pan H, Godwin J, et al. 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.
42. Petrelli F, Coinu A, Cabiddu M, et al. Five or more years of adjuvant endocrine therapy in breast cancer: a meta-analysis of published randomised trials. Breast Cancer Res Treat. 2013;140:233–40.
43. Piccart MJ, Di Leo A, Hamilton A. HER2: a 'predictive factor' ready to use in the daily management of breast cancer patients? Eur J Cancer. 2000;36:1755–61.
44. Arpino G, Green SJ, Allred DC, et al. HER-2 amplification, HER-1 expression, and tamoxifen response in estrogen receptor-positive metastatic breast cancer: a southwest oncology group study. Clin Cancer Res. 2004;10:5670–6.
45. Berry DA, Muss HB, Thor AD, et al. HER-2/neu and p53 expression versus tamoxifen resistance in estrogen receptor-positive, node-positive breast cancer. J Clin Oncol. 2000;18:3471–9.
46. Mass R. The role of HER-2 expression in predicting response to therapy in breast cancer. Semin Oncol. 2000;27:46–52; discussion 92–100.
47. Dowsett M, Allred C, Knox J, et al. Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the Arimidex, Tamoxifen, Alone or in Combination trial. J Clin Oncol. 2008;26:1059–65.
48. Regan MM, Leyland-Jones B, Bouzyk M, et al. CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the breast international group 1-98 trial. J Natl Cancer Inst. 2012;104:441–51.
49. Rae JM, Drury S, Hayes DF, et al. CYP2D6 and UGT2B7 genotype and risk of recurrence in tamoxifen-treated breast cancer patients. J Natl Cancer Inst. 2012;104:452–60.
50. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: overview of the randomised trials. Lancet. 1996;348:1189–96.
51. Puhalla S, Brufsky A, Davidson N. Adjuvant endocrine therapy for premenopausal women with breast cancer. Breast. 2009;18(Suppl 3):S122–30.
52. Cuzick J, Ambroisine L, Davidson N, et al. 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.
53. Aydiner A, Kilic L, Yildiz I, et al. Two different formulations with equivalent effect? Comparison of serum estradiol suppression with monthly goserelin and trimonthly leuprolide in breast cancer patients. Med Oncol. 2013;30:354.
54. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med. 2014;371:107–18.
55. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. N Engl J Med. 2018;379:122–37.
56. 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.
57. Ejlertsen B, Mouridsen HT, Jensen MB, et al. Similar efficacy for ovarian ablation compared with cyclophosphamide, methotrexate, and fluorouracil: from a randomized comparison of premenopausal patients with node-positive, hormone receptor-positive breast cancer. J Clin Oncol. 2006;24:4956–62.
58. Kaufmann M, Jonat W, Blamey R, et al. Survival analyses from the ZEBRA study. Goserelin (Zoladex) versus CMF in premenopausal women with node-positive breast cancer. Eur J Cancer. 2003;39:1711–7.
59. Schmid P, Untch M, Wallwiener D, et al. Cyclophosphamide, methotrexate and fluorouracil (CMF) versus hormonal ablation with leuprorelin acetate as adjuvant treatment of node-positive, premenopausal breast cancer patients: preliminary results of the TABLE-study (Takeda Adjuvant Breast cancer study with Leuprorelin Acetate). Anticancer Res. 2002;22:2325–32.
60. von Minckwitz G, Graf E, Geberth M, et al. CMF versus goserelin as adjuvant therapy for node-negative, hormone-receptor-positive breast cancer in premenopausal patients: a randomised trial (GABG trial IV-A-93). Eur J Cancer. 2006;42:1780–8.
61. Castiglione-Gertsch M, O'Neill A, Price KN, et al. 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.
62. Scottish Cancer Trials Breast Group and ICRF Breast Unit, Guy's Hospital, London. Adjuvant ovarian ablation versus CMF chemotherapy in premenopausal women with pathological stage II breast carcinoma: the Scottish trial. Lancet. 1993;341:1293–8.
63. Schmid P, Untch M, Kosse V, et al. Leuprorelin acetate every-3-months depot versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant treatment in premenopausal patients with node-positive breast cancer: the TABLE study. J Clin Oncol. 2007;25:2509–15.
64. Boccardo F, Rubagotti A, Amoroso D, et al. Cyclophosphamide, methotrexate, and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: results of the Italian Breast Cancer Adjuvant Study Group 02 randomized trial. boccardo@hp380.ist.unige.it. J Clin Oncol. 2000;18:2718–27.

65. Roche H, Kerbrat P, Bonneterre J, et al. Complete hormonal blockade versus epirubicin-based chemotherapy in premenopausal, one to three node-positive, and hormone-receptor positive, early breast cancer patients: 7-year follow-up results of French Adjuvant Study Group 06 randomised trial. Ann Oncol. 2006;17:1221–7.
66. Jakesz R, Hausmaninger H, Kubista E, et al. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer–Austrian Breast and Colorectal Cancer Study Group Trial 5. J Clin Oncol. 2002;20:4621–7.
67. Baum M, Hackshaw A, Houghton J, et al. Adjuvant goserelin in pre-menopausal patients with early breast cancer: results from the ZIPP study. Eur J Cancer. 2006;42:895–904.
68. Anderson WF, Chatterjee N, Ershler WB, Brawley OW. Estrogen receptor breast cancer phenotypes in the Surveillance, Epidemiology, and End Results database. Breast Cancer Res Treat. 2002;76:27–36.
69. 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.
70. Mouridsen H, Giobbie-Hurder A, Goldhirsch A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med. 2009;361:766–76.
71. Regan MM, Neven P, Giobbie-Hurder A, et al. 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.
72. van de Velde CJ, 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.
73. 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.
74. 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.
75. 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.
76. Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KA, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO Clinical Practice Guideline Focused Update. J Clin Oncol. 2019;37(5):423–38.
77. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet. 2007;369:559–70.
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. Forbes JF, Cuzick J, Buzdar A, et al. 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.
80. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med. 2005;353:2747–57.
81. Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. J Clin Oncol. 2007;25:829–36.
82. Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol. 2008;26:4875–82.
83. Cuzick J, Sestak I, Baum M, et al. 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.
84. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet. 2002;359:2131–9.
85. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet. 2005;365:60–2.
86. Duffy S, Jackson TL, Lansdown M, et al. The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: first results of the endometrial sub-protocol following 2 years of treatment. Hum Reprod. 2006;21:545–53.
87. Fallowfield L, Cella D, Cuzick J, et al. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. J Clin Oncol. 2004;22:4261–71.
88. Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. J Clin Oncol. 2008;26:1051–7.
89. Dowsett M, Cuzick J, Howell A, Jackson I. Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the 'Arimidex and tamoxifen alone or in combination' (ATAC) trial. Br J Cancer. 2001;85:317–24.
90. Buzdar AU, Guastalla JP, Nabholtz JM, et al. Impact of chemotherapy regimens prior to endocrine therapy: results from the ATAC (Anastrozole and Tamoxifen, Alone or in Combination) trial. Cancer. 2006;107:472–80.
91. 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.
92. Mouridsen H, Keshaviah A, Coates AS, et al. Cardiovascular adverse events during adjuvant endocrine therapy for early breast cancer using letrozole or tamoxifen: safety analysis of BIG 1-98 trial. J Clin Oncol. 2007;25:5715–22.
93. Rabaglio M, Sun Z, Price KN, et al. Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. Ann Oncol. 2009;20:1489–98.
94. Viale G, Regan MM, Dell'Orto P, et al. 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.
95. Aydiner A, Tas F. Meta-analysis of trials comparing anastrozole and tamoxifen for adjuvant treatment of postmenopausal women with early breast cancer. Trials. 2008;9:47.
96. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med. 2004;350:1081–92.
97. 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.

98. 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.
99. Jonat W, Gnant M, Boccardo F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol. 2006;7:991–6.
100. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet. 2005;366:455–62.
101. Pan H, Gray R, Braybrooke J, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med. 2017;377:1836–46.
102. Jin H, Tu D, Zhao N, et al. 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.
103. Perez EA, Josse RG, Pritchard KI, et al. Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17. J Clin Oncol. 2006;24:3629–35.
104. Whelan TJ, Goss PE, Ingle JN, et al. Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. J Clin Oncol. 2005;23:6931–40.
105. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med. 2016;375:209–19.
106. Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. Lancet Oncol. 2017;18:1502–11.
107. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al. Optimal duration of extended adjuvant endocrine therapy for early breast cancer; results of the IDEAL trial (BOOG 2006-05). J Natl Cancer Inst. 2018;110:40–8.
108. Goldvaser H, AlGorashi I, Ribnikar D, et al. Efficacy of extended adjuvant therapy with aromatase inhibitors in early breast cancer among common clinicopathologically-defined subgroups: a systematic review and meta-analysis. Cancer Treat Rev. 2017;60:53–9.
109. Colleoni M, Luo W, Karlsson P, et al. Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018;19:127–38.
110. Dowsett M, Nielsen TO, A'Hern R, et al. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst. 2011;103:1656–64.
111. Dowsett M, Smith IE, Ebbs SR, et al. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. J Natl Cancer Inst. 2007;99:167–70.
112. Tung N. What is the optimal endocrine therapy for postmenopausal women with hormone receptor-positive early breast cancer? J Clin Oncol. 2013;31:1391–7.
113. Geisler J, Haynes B, Anker G, et al. Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study. J Clin Oncol. 2002;20:751–7.
114. Dixon JM, Renshaw L, Young O, et al. Letrozole suppresses plasma estradiol and estrone sulphate more completely than anastrozole in postmenopausal women with breast cancer. J Clin Oncol. 2008;26:1671–6.
115. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype–ACOSOG Z1031. J Clin Oncol. 2011;29:2342–9.
116. 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.
117. Amir E, Seruga B, Niraula S, et al. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. J Natl Cancer Inst. 2011;103:1299–309.
118. O'Shaughnessy J. A decade of letrozole: FACE. Breast Cancer Res Treat. 2007;105(Suppl 1):67–74.
119. Henry NL, Azzouz F, Desta Z, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. J Clin Oncol. 2012;30:936–42.
120. Aydiner A. Meta-analysis of breast cancer outcome and toxicity in adjuvant trials of aromatase inhibitors in postmenopausal women. Breast. 2013;22:121–9.