# Adjuvant Systemic Therapy for Postmenopausal, Hormone Receptor-Positive Early Breast Cancer

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**KEYWORDS**

• Hormone receptor-positive breast cancer • Adjuvant endocrine therapy
• Recurrence score • Aromatase inhibitor

**KEY POINTS**

- Optimal selection of adjuvant therapy in HR+ early breast cancer requires accurate assessment of an individual's risk of recurrence.
- Clinical-pathologic staging and biological factors including genomic signatures combine to provide both prognostic and predictive information.
- Endocrine therapy (ET) with aromatase inhibitors for between 5 and 10 years is the mainstay of adjuvant therapy.
- De-escalation of chemotherapy use in HR+ EBC has followed integration of genomic profiling in node-negative/1 to 3 node-positive disease.
- In high-risk node-positive HR+ EBC, adjuvant abemaciclib for 2 years combined with ET further reduces recurrence risk.

## INTRODUCTION

Hormone receptor-positive (HR+) breast cancer is the most common subset of the disease in postmenopausal women presenting with early-stage disease, accounting for 75% of all cases.[1] HR+ breast cancer has a risk for both early and late recurrence, with at least half of all disease recurrences occurring more than 5 years after initial diagnosis, including a significant number more than 10 years after diagnosis.[2] Following locoregional breast surgery with/without radiotherapy, adjuvant systemic therapy is given to reduce the risk of recurrence (ROR) and enhance the chances of cure, and for HR+ early breast cancer (EBC) this has centered on endocrine therapy (ET) and chemotherapy. Twenty-five years ago, ET consisted of the antiestrogen tamoxifen given for up to 5 years to all patients with HR+ EBC regardless of

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menopausal status, and combination chemotherapy was recommended to patients based on clinical staging features such as node-positive disease, or those with node-negative disease but high tumor grade or large tumor size. Although tamoxifen alone for 5 years (compared with no ET) reduced ROR by 39% and improved survival by 30%,[3] the additional gains from chemotherapy were always much more modest. Despite that, chemotherapy was often given to all women with HR+ tumors larger than 1 cm, or to those with node-positive disease, albeit older patients (>75 years) tended not to be offered chemotherapy due to the short-term toxicity impact negating the minimal impact on recurrence risk and overall survival (OS).

Over the subsequent quarter of a century, there have been significant advances made in our understanding of HR+ breast cancer and its heterogeneous biology, together with improved ET options and longer durations of treatment, and more recently de-escalation strategies to identify those postmenopausal patients with HR+ EBC who do not need chemotherapy. The modern management of HR+ breast cancer involves a more in-depth assessment of an individual's ROR based on both clinical and biological features. The foundation of this assessment relies on the American Joint Committee for Cancer staging criteria, including tumor size and nodal involvement,[4] with a higher ROR being associated with higher anatomic stage and increased numbers of nodes.[5] The staging system has now been updated to incorporate biological factors such as tumor grade, receptor status, and also prognostic/predictive information provided by multigene assays.[4] This article reviews the criteria that are now used in clinical practice to assess ROR in HR+ EBC, the optimal ET strategies that are used for individual patients, and the role of systemic chemotherapy and the regimens used, together with the new developments including adjuvant CDK 4 and 6 inhibitors for high-risk node-positive EBC. In addition, future directions that may further individualize recurrence risk with a view to personalizing adjuvant therapies are discussed.

## PROGNOSTIC FACTORS AND ASSESSING RISK OF RECURRENCE

Optimal selection of adjuvant systemic therapy in HR+ EBC requires an accurate assessment of an individual's risk for disease recurrence. After primary surgery, this can now be easily assessed by using both clinical and pathologic features that include tumor size, histologic grade, presence of vascular invasion, and extent of lymph node involvement, together with the biological information provided by estrogen receptor (ER) status, progesterone receptor (PgR) status, human epidermal growth factor receptor-2 (HER2) status, and information provided by various gene expression assays. Expression of the biomarkers ER and PgR assessed by immunohistochemistry (IHC), and HER2 assessed by IHC or in situ hybridization, combine to identify the breast cancer subtype and inform prognosis and the degree of benefit from adjuvant ET. High ER and/or PgR expression is predictive of benefit from ET, whereas lack of these markers is considered a poor prognostic marker.[5] Guidelines from the American Society of Clinical Oncology (ASCO) and College of American Pathologists recommend designating tumors as ER low positive if ER expression is 1% to 10%.[6] Expression of ER in the absence of PgR is associated with tumors that have higher grade and cell proliferation (so-called luminal B-like tumors) and have a worse prognosis, compared with tumors in which both ER and PgR are expressed at high levels, which are more likely to be grade 1 or 2 (luminal A tumors) (**Table 1**).[2] HER2 serves as both a prognostic marker and predictive marker for HER2-targeted therapies, and half of all HER2-positive tumors coexpress hormone receptors, albeit often at a lower quantitative level.

Genomic signatures have been developed based on patterns of tumor RNA expression in key genes involved in pathogenesis and correlate well with ER and PgR

**Table 1**
**Characteristics of intrinsic subtypes and the spectrum in-between for hormone receptor-positive, human epidermal growth factor receptor-2-negtive early breast cancer**

| Characteristic | Luminal a Subtype ⟷ | | Luminal B Subtype |
|---|---|---|---|
| Tumor grade | 1 (Well differentiated) | 2 (Moderately differentiated) | 3 (Poorly differentiated) |
| ER expression | +++ (Strong) | ++ to +++ | + to ++ (Weak to moderate) |
| PgR expression | ++ to +++ (Strong) | 0 to +++ | 0 to ++ (Negative to weak) |
| Ki67 index, % | <10 (Low) | 10–20 | >20 (High) |
| 21-Gene recurrence score[a] | <11 (Low) | 11 to 25 (Intermediate) | >25 (High) |
| Other genomic signatures[b] | Lower | Lower to higher | Higher |
| Breast cancer recurrence risk | Low (<10% risk over 10 years) | Lower to higher | Higher (>20% risk over 10 years) |

[a] The 21-gene recurrence score ranges from 0-100, with higher scores indicating a greater chance of recurrence and chemotherapy benefit.
[b] Other genomic signatures include the 7-gene signature (MammaPrint), PAM50 Risk of Recurrence (Prosigna), Breast Cancer Index, and EndoPredict.
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expression, histologic grade, cell proliferation, and moreover provide important information on prognosis and ROR (see **Table 1**). The most widely used genomic test is the 21-gene assay (Oncotype Dx) that evaluates 16 cancer-related genes and 5 reference genes assigning a recurrence score (RS) of 0 to 100. Initial retrospective studies validated this assay as a prognostic tool in patients with node-negative, HR-positive EBC and investigated whether it could be a predictive tool for adjuvant chemotherapy benefit. Patients with low RS (<11) had an excellent 9-year prognosis (>90% chance of being free of recurrence) and no benefit from chemotherapy, whereas high RS (>25) was associated with a much higher ROR, which was reduced in those given adjuvant chemotherapy.[7,8] For those with an intermediate score (RS 11–25), it was unclear whether there was any benefit from chemotherapy.

The subsequent prospective TAILORx study randomly assigned patients with node-negative disease and an intermediate RS of 11 to 25 to either ET alone or chemotherapy plus ET.[9] Nine-year invasive disease-free survival (iDFS), distant recurrence-free survival (DRFS), and OS were similar in both treatment arms, suggesting no benefit for chemotherapy in patients with an intermediate RS; this was especially the case in postmenopausal women, whereas subgroup analyses according to age suggested potential chemotherapy benefit in younger patients (aged $\leq$ 50 years) with an RS of 16 to 25. Subsequent refinement of prognosis has been provided by integrating RS with tumor grade and size with patient age into the RSClin tool, providing more accurate risk of distant recurrence than either RS or clinical-pathological features alone.[10] As such, in postmenopausal patients it became clear that in node-negative disease RS could be used to identify those patients who do not need chemotherapy, reserving it for those with biologically more aggressive breast cancer (RS > 25) as estimated by the 21-gene assay.

More recently Oncotype Dx was also evaluated in node-positive patients (1 to 3 positive nodes) in the randomized phase 3 RxPONDER study, randomizing patients

with an RS of less than or equal to 25 to adjuvant ET with or without chemotherapy.[11] After 5 years of median follow-up, postmenopausal patients with an RS less than or equal to 25 did not benefit from adjuvant chemotherapy, whereas in younger, premenopausal women chemotherapy was associated with a 46% reduction in iDFS events compared with adjuvant ET alone, although it is unclear whether these benefits relate to the ovarian suppressive effects of cytotoxic therapy. These prospective data from 2 large trials have been deemed practice changing, resulting in a significant evidence-based de-escalation of systemic chemotherapy use in postmenopausal women with HR+ EBC.

Several other genomic panels assessing between 5 and 70 genes have been developed and evaluated in HR+ EBC in both prospective and retrospective studies, and all of them provide prognostic information on 10-year recurrence risk.[12] The 70-gene signature (MammaPrint) divides patient dichotomously into low and high genomic risk and was prognostic for time to distant metastasis and OS in retrospective validation studies[13]; this led to the prospective MINDACT trial, in which patients with discordant clinical and genomic risk were assigned to receive chemotherapy or not based solely on either their clinical or genomic risk group. The 5-year distant metastasis-free survival (DMFS) rate was 94.7% in patients with high clinical risk and low genomic risk treated with ET alone, suggesting the 70-gene signature could identify a group of patients (both node-negative and node-positive) who may not need adjuvant chemotherapy.[14] In particular, for postmenopausal patients aged greater than 50 years, an unplanned exploratory analysis in the HR+, HER2-negative subset showed similar 8-year DMFS with or without chemotherapy (90.2% vs 90.0%).

In postmenopausal women with ER-positive EBC the PAM-50 (Prosigna) signature evaluates 50 classifier genes and 5 control genes, categorizing HR+ breast tumors into intrinsic subtypes (ie, luminal A, luminal B, HER2-enriched, basal, normal) and assigning an ROR score ranging from 0 to 100. The PAM50 ROR score was prognostic in postmenopausal women for 10-year distant recurrence risk in patients with node-negative and node-positive disease from the ATAC and ABCSG-8 studies,[15] adding significant prognostic information compared with the 21-gene RS or IHC-based analysis of ER, PgR, HER2, and proliferation (Ki-67).[16] Likewise in postmenopausal women with HR+ EBC, the Breast Cancer Index, which combines a 5-gene prognostic molecular grade index with a 2-gene predictive biomarker ratio of HoxB13 and interleukin-17B receptor, was prognostic for both early and late recurrences in the Trans-ATAC study,[17] and predictive for benefit from extended adjuvant therapy in patients with node-negative or node-positive HR+ EBC.[18]

In terms of clinical utility, although the available gene expression assays vary with respect to the information they provide and populations assessed in the validation studies, they all provide additional prognostic information compared with clinical-pathologic factors alone. International guidelines all recommend the use of gene expression assays in patients with HR+ HER2-negative EBC with 0 to 3 positive nodes to assess the ROR and inform decisions regarding the use of adjuvant chemotherapy (**Table 2**), while not recommending any 1 genomic assay over another.[19,20] Although all the available assays provide valuable prognostic information, the 21-gene assay is currently the only one with prospective data supporting its ability to predict for chemotherapy benefit,[19] and the St Gallen International Consensus Guidelines have since recommended against routine use of chemotherapy for postmenopausal women with stage I or II (including 1–3 positive lymph nodes) HR+ breast cancers that had a lower-risk genomic signature (ie, Oncotype RS < 25) (see **Table 2**).[21] The Prosigna and Breast Cancer Index assays are useful

**Table 2**
**Adjuvant systemic therapy options for hormone receptor-positive human epidermal growth factor receptor-2-negative early breast cancer**

| Anatomic Stage | Tumor and Nodal Stage | Endocrine Therapy | Chemotherapy |
|---|---|---|---|
| Stage I | T1ab N0 | AI or Tam, 5 years | No |
| | T1c N0 | AI or Tam, 5 years | |
| Stage II | N0 (node negative) | Consider AI as extended therapy, especially after initial 2–5 years of Tam | Not indicated if favorable biology |
| | N1 (1–3+ LN) | Extended AI therapy | Only indicated for those within high genomic risk signature or unfavorable biology |
| Stage III | | Extended AI therapy | Yes |

*Abbreviations:* AI, aromatase inhibitor; LN, lymph node; Tam, Tamoxifen; TN, tumour size, nodal status.

Historically, the St Gallen Panel has favored AI-based therapy in higher-risk tumors defined by T and N stage, grade, and Ki67 score.

Extended therapy implies 10 years of treatment, although some studies indicate that 10 years may not offer benefit beyond that seen with 7 to 8 years of endocrine therapy.

*Favorable biology*: Lower-risk genomic signature (eg, RS $\leq$25 [node-positive] or 16–25 [node-negative], or 70-gene signature "low"); strongly ER-positive with low to intermediate grade, and/or lower baseline Ki-67, or decrease in Ki-67 with preoperative exposure to endocrine therapy (dynamic Ki-67).

*Unfavorable biology*: Higher-risk genomic signature (eg, recurrence score >25 or 70-gene signature "high"); lower ER expression, intermediate to high grade, and/or higher baseline Ki-67, or lack of decline in Ki-67 with preoperative exposure to endocrine therapy (dynamic Ki-67).

*Adapted from* Burstein HJ, Curigliano G, Thurlimann B, et al. Customising local and systemic therapies for women with early breast cancer: the St Gallen International Consensus Guidelines for treatment of early breast cancer. Ann Oncol. 2021 Oct;32(10):1216-1235.021.

to assess risk for late recurrences in HR+ EBC, which may be useful in determining candidates for extended adjuvant ET.

## ADJUVANT ENDOCRINE THERAPY IN POSTMENOPAUSAL HORMONE RECEPTOR-POSITIVE EARLY BREAST CANCER

The Early Breast Cancer Trialists' Collaborative Group meta-analyses first showed that 5 years of adjuvant tamoxifen significantly reduced risk of disease recurrence and improved OS in HR+ EBC, even in tumors in which ER expression is low (ie, between 1% and 10%).[3] Tamoxifen provides equivalent benefit in luminal A and luminal B tumors and reduces local-regional recurrence, even in small breast cancers less than 1 cm in size.[22] The extent of ER expression determined by IHC together with coexpression of PgR strongly correlates with endocrine sensitivity and degree of benefit from adjuvant ET with tamoxifen.[23]

Approximately 20 years ago, new options for adjuvant endocrine treatment in postmenopausal women arose following trials that compared 5 years of aromatase inhibitors (AIs) with 5 years of tamoxifen in HR+ EBC.[24] The AIs letrozole, anastrozole, and exemestane all block conversion of androgens to estrogens in postmenopausal women, suppressing estrogen levels by 90% resulting in significant antiproliferative effects in HR+ breast cancer cells.[25] Long-term follow-up from the ATAC and BIG 1-98 adjuvant trials in postmenopausal HR+ EBC showed that 5 years of adjuvant anastrozole or letrozole significantly reduced distant recurrences compared with 5 years of tamoxifen.[26,27] Likewise, for premenopausal or perimenopausal women who initially start on tamoxifen but then are confirmed as postmenopausal and switch to an AI, this sequencing strategy is superior to tamoxifen alone.[25,27] However, for

women with small stage I or IIA node-negative HR+ EBC (often detected by mammographic screening) the numerical advantage for AIs over tamoxifen is minimal (2%–3% reduction is ROR at 10 years), whereas the quantitative benefit is much greater for AIs over tamoxifen in higher-risk disease as determined by anatomic stage or adverse biological features,[25,28] or by histologic type such as invasive lobular breast cancer.[29] Given the overall improved efficacy results, most postmenopausal patients with HR+ EBC are now treated with AIs as initial therapy, although in very-low-risk disease tamoxifen is still a very reasonable option (see **Table 2**).

An equally important consideration to efficacy when deciding between AIs and tamoxifen is their difference in side effects and patient tolerability. Both therapies can enhance menopausal vasomotor symptoms such as hot flashes and night sweats that can disturb sleep and contribute to fatigue. Tamoxifen can cause vaginal discharge, increase the risk for deep vein thrombosis, and cause endometrial cancer, whereas AIs commonly cause arthralgia, vaginal dryness, and hair thinning and may accelerate osteoporosis. These symptoms may affect patient compliance for patients required to take these medications for a minimum of 5 years.[30] For women in whom an AI is associated with an unacceptable side effect profile, switching to another class of AI (ie, from letrozole to exemestane) or to tamoxifen may be better tolerated, while exercise or acupuncture can also reduce musculoskeletal symptoms.[31] The reverse sequence of an AI-tamoxifen is as effective as tamoxifen-AI sequence (distant recurrence-free interval at 8 years: 88.7% vs 88.1%),[32] suggesting it is a safe strategy to offer patients unable to tolerate an AI long term. Likewise, data from the phase 3 SOLE trial also showed that short treatment breaks after an initial 5 years of AI therapy in postmenopausal patients are feasible with similar benefit for intermittent (9 months on, 3 months off) versus continuous dosing of letrozole, and will not compromise long-term benefit.[33] These different treatment strategies and interventions to manage toxicities are important considerations to maximize patient compliance during adjuvant ET.

One important feature of HR+ EBC is the ongoing annual ROR beyond 5 years, which although small is constant, such that recurrences up to 10 or even 20 years later will occur, being more frequent in those with higher nodal and tumor stage or higher grade,[34] or adverse biological features as determined by genomic signatures[35]; this has led to several studies of extended adjuvant ET comparing 10 versus 5 years of treatment. These studies have demonstrated improved disease-free survival when extended AI therapy was given for 5 additional years following an initial 5 years of tamoxifen, an AI, or sequential tamoxifen-AI therapy.[36] Whether 10 years is needed in all patients is not clear, and the ABCSG-16 study showed a similar benefit for 2 additional years of AI therapy instead of 5 years, suggesting that therapy could be stopped at 7 years without compromising outcomes.[37] A meta-analysis of almost 25,000 patients showed that extending ET beyond 5 years significantly reduced recurrence, but it also reported differential benefit based on the degree of nodal involvement. Five years of additional AI therapy reduced recurrence by 1.1% in node-negative patients, 3.8% in those with 1 to 3 positive nodes, and 7.7% in those with 4 or more positive nodes.[38] As such, International Consensus Guidelines[21] now recommend that 5 years of ET (tamoxifen or an AI) may be sufficient for stage I/IIA low-risk breast cancers, whereas patients with higher-stage disease and increased nodal involvement should be strongly considered for extended-duration ET for a minimum of 7 to 8 years that includes an AI for some or all of that period (see **Table 2**).

## ADJUVANT CHEMOTHERAPY IN POSTMENOPAUSAL HORMONE RECEPTOR-POSITIVE EARLY BREAST CANCER

The true role of adjuvant chemotherapy in HR+ EBC has become better defined in recent years, especially in postmenopausal women in whom there has been significant de-escalation of use following the introduction of genomic signatures to define chemotherapy benefit in patients with lower anatomic stage. Nodal status remains a strong prognostic factor and marker of risk, but importantly does not define that chemotherapy is required. Patients with HR+ breast cancer who have a higher clinical stage (ie, extensive nodal burden or stage III disease) do probably have significant risk to warrant adjuvant chemotherapy use regardless of their genomic signature,[21] albeit the absolute chemotherapy benefit in low genomic risk/high clinical stage may be minimal as shown in the MINDACT study.[14] Unlike other subtypes of breast cancer such as triple-negative or HER2-positive EBC, neoadjuvant (preoperative) chemotherapy has a low chance of inducing a complete pathologic response, but still may be warranted to improve surgical options by downstaging those with large T3 node-positive breast cancers.

Biological information in HR+ EBC is very likely to be a more powerful predictor than clinical stage for benefit from adjuvant therapies (both endocrine and cytotoxic). The European Society for Medical Oncology (ESMO) and St Gallen Consensus Guidelines recommend consideration of adjuvant chemotherapy for patients with luminal A tumors who also have a high disease burden ($\geq$4 lymph nodes, $\geq$T3) as well as those with luminal B proliferative tumors, whereas patients with low-grade luminal A tumors and low genomic risk likely derive minimal (if any) benefit from adjuvant chemotherapy and should be treated with adjuvant ET alone.[5,21] For those HR+ tumors that are either node-negative or have low nodal burden (1–3 nodes, N1) but have some increased clinical risk features (size, grade, vascular invasion), a gene expression profile is strongly considered to determine both the prognosis and whether chemotherapy is indicated.[5,21] The National Comprehensive Cancer Network guidelines list the Oncotype Dx 21-gene assay as the preferred testing option for node-negative disease and postmenopausal patients with node-positive disease, strongly recommending adjuvant chemotherapy in all patients with stage I or II HR+ disease with a high-risk genomic signature (RS $\geq$26).[19] In contrast, based on data from the TAILORx and RxPONDER trials in node-negative and node-positive HR+ disease, respectively, adjuvant chemotherapy does not provide significant benefit in postmenopausal patients with 3 or less positive nodes and a low-risk genomic signature (RS < 26) (see **Table 2**).[9,11]

Standard adjuvant chemotherapy regimens for breast cancer have historically included anthracyclines, alkylators, and in the last 20 years taxanes. There are geographic differences in the preferred regimens for HR+ breast cancer, and some parts of the world have seen a shift away from the use of anthracyclines. In patients with HR+, node-negative disease, docetaxel plus cyclophosphamide (TC) was more effective that a taxane plus doxorubicin/cyclophosphamide (TaxAC), whereas patients with HR+ disease with a high tumor burden showed benefit from the addition of anthracyclines.[39] Other studies have shown similar benefit for 4 cycles of epirubicin/cyclophosphamide followed by docetaxel (EC-T) versus 6 cycles of TC in patients with EBC, regardless of HR status.[40] As such, 4 cycles of a nonanthracycline-based regimen (ie, TC), 4 cycles of an anthracycline regimen (AC/EC), or 12 weeks of weekly paclitaxel are all common adjuvant choices for low- to intermediate-risk HR+ breast cancer, whereas a sequential anthracycline-taxane regimen, such as accelerated EC $\times$ 4 followed by weekly paclitaxel $\times$12, is commonly used for high-risk HR+ disease. Adverse events (AEs) associated with chemotherapy are always an important consideration

when selecting adjuvant therapy. Both anthracyclines and taxanes are commonly associated with alopecia, and anthracyclines have a smaller risk for serious events such as cardiac damage, whereas taxanes can cause peripheral neuropathy. In older (>70 years) postmenopausal patients with higher-risk HR+ EBC, a balanced discussion of the quantitative adjuvant benefits versus any potential harms from chemotherapy is especially important in shared decision making with individual patients.

## ADDITIONAL ADJUVANT SYSTEMIC THERAPIES IN HIGHER-RISK HORMONE RECEPTOR-POSITIVE EARLY BREAST CANCER

Despite current locoregional and systemic treatments for HR+ EBC, one-fifth of patients will still experience disease recurrence within the first 10 years.[24] For postmenopausal patients with HR+ EBC, additional therapy in the form of bisphosphonates such as zoledronic acid every 6 months for 3 years has been shown to not only mitigate the risk of osteoporosis from ET with AIs but also reduce the risk of disease recurrence.[41] Clinical and pathologic factors in HR+ EBC that are associated with recurrence risk include larger tumor size, extent of nodal involvement, and higher grade of tumor, which indicates more proliferative disease (ie, luminal B with a high Ki-67 index).[42] In patients with HR+ disease with more than 4 positive nodes, or if 1 to 3 nodes are involved additional risk factors such as grade 3 disease or large tumor size greater than 5 cm, the risk of early recurrence in the first 5 years can be up to 20% and as high as those with triple-negative EBC.[43] For this high-risk HR+ patient population, there is a need for more effective adjuvant treatment approaches.

Cyclin-dependent kinases (CDKs) are involved in cell cycle regulation in HR+ breast cancer, and in recent years orally active and potent inhibitors of CDK4 and CDK6 combined with ET have been approved as treatment of HR+ advanced breast cancer.[44] Three randomized trials of adjuvant CDK4/6 inhibitors added to ET in high-risk HR+ EBC have been undertaken and reported results. Palbociclib was investigated in the adjuvant setting in the phase 3 PALLAS study, which evaluated the addition of 2 years of palbociclib to tamoxifen or an AI versus ET alone in patients with stage II or III HR+, HER2-negative EBC.[45,46] The primary end point of iDFS was not improved in the investigational arm at the second interim analysis, and palbociclib treatment was discontinued for futility. The second trial to report was the double-blind, placebo-controlled, randomized phase 3 PENELOPE-B trial, which enrolled women with high-risk HR+ HER2-negative primary breast cancer with residual invasive disease after taxane-containing neoadjuvant chemotherapy.[47] At the final analysis, the addition of 1 year of palbociclib to adjuvant ET failed to demonstrate improved iDFS (hazard ratio, 0.93; 95% confidence interval, 0.74–1.17).

In contrast, the third randomized phase 3 trial monarchE demonstrated a significant benefit from the addition of adjuvant abemaciclib to ET in patients with HR+ HER2-negative, node-positive, high-risk EBC.[48] High-risk disease was defined as 4 or more positive nodes or 1 to 3 positive nodes with either a grade 3 tumor, a tumor greater than or equal to 5 cm in size, or high proliferation rate (Ki-67 level $\geq$20%). More than 95% of these high-risk patients had received chemotherapy and 56% were postmenopausal, and they received standard ET with or without 2 years of abemaciclib. A preplanned interim analysis after 15.5 months' follow-up demonstrated a statistically significant improvement in iDFS (primary endpoint) with the addition of abemaciclib,[48] and at the updated analysis after a median of 27 months' follow-up the hazard ratio had strengthened to 0.696 ($P < .0001$).[49] The benefit was consistent across patient subgroups (including the postmenopausal group), and abemaciclib reduced the risk of DRFS by 31.3%. A high Ki-67 (>20%) was clearly prognostic

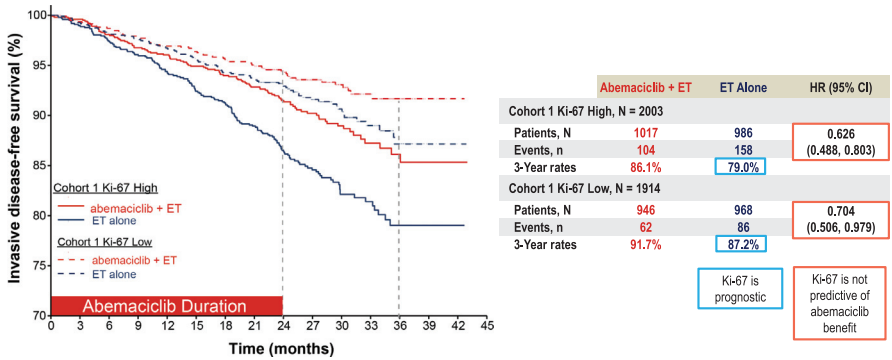


**Fig. 1.** Prognostic but not predictive effect of Ki-67 in Cohort 1 of monarchE trial. Figure depicts invasive disease-free survival according to treatment arm among patients enrolled into Cohort 1 in teh monarchE trial, subdivided by baseline tumor Ki-67 with high Ki-67 greater than 20%, low Ki-67 less than 20%. ET, endocrine therapy; HR, hazard ratio. (*Adapted from* Harbeck N, Burstein HJ, Hurvitz SA, et al. A look at current and potential treatment approaches for hormone receptor-positive, HER2-negative early breast cancer. Cancer 2022;128 Suppl 11:2209–23. doi:10.1002/cncr.34161.)

with a 3-year iDFS rate for the ET alone control arm of 79% for high Ki-67 and 87% for low Ki-67, with added benefit from abemaciclib in both high and low Ki-67 groups (**Fig. 1**).[49] Abemaciclib had a manageable safety profile, and the most common AEs were gastrointestinal (diarrhea, nausea, abdominal pain), fatigue, and measured cytopenias.[48,49] Most AEs started early, and for those who required therapy interruption/dose reduction, thereafter they were able to remain on therapy. On the basis of these data, abemaciclib has recently been approved in many countries in combination with ET for the adjuvant treatment of high-risk HR+ EBC, and whereas in the United States approval has initially been restricted to those with node-positive disease and also high Ki-67,[50] in clinical practice updated ASCO guidelines have endorsed its use in the wider node-positive high-risk monarchE trial population.[51]

## FUTURE DIRECTIONS FOR ADJUVANT SYSTEMIC THERAPIES IN HORMONE RECEPTOR-POSITIVE EARLY BREAST CANCER

Although there has been significant progress in applying knowledge about the biology of HR+ breast cancer to the estimation of risk and selection of appropriate adjuvant systemic therapies, the information on relative risk reduction from adding any given therapy is generated from clinical trials of hundreds of patients with HR+ breast cancer. This is a heterogeneous disease with a spectrum of biological features (see **Table 1**), and in clinical practice there remains limited ability to accurately predict response or resistance on an individual basis to any adjuvant therapy whether it be endocrine based, cytotoxic, or targeted such as CDK 4/6 inhibitors. Providing a more personalized prediction of benefit from adjuvant systemic therapies could further refine treatment selection and improve clinical outcomes.

One such approach in HR+ postmenopausal EBC is to use a short exposure for 2 to 4 weeks to ET with an AI, and measure change in cancer cell proliferation (dynamic Ki-67) before and after ET with the resulting 2-week Ki-67*post* score that integrates both predictive and prognostic information in HR+ EBC.[52] The predictive value of dynamic Ki-67 for postmenopausal women with HR+ EBC was demonstrated in the phase 3 POETIC trial in which those with a reduction in Ki-67 levels to less than 10% after 2 weeks of an

AI had a 5-year recurrence risk of 8.4%, compared with 21.5% for those with persistently high Ki-67 after neoadjuvant therapy.[53] Likewise, complete cell cycle arrest with Ki-67*post* less than 2.7% has been shown as strongly prognostic for those patients with an excellent prognosis on adjuvant ET alone.[54] More recently the ADAPT trialists examined the integration of this biomarker with Oncotype Dx in postmenopausal patients with node-negative/1 to 3 node-positive (pN0/pN1) HR+ EBC.[55] Patients with an RS of 12 to 25 and response to preoperative ET (evidenced by post Ki-67 $\leq$ 10% after 3 weeks ET) had comparable 5-year iDFS to those with an RS of less than or equal to 11 (92.6% vs 93.9%). Although Oncotype Dx RS can already identify pN0/pN1 postmenopausal patients with an RS less than or equal to 25 who can safely be spared adjuvant chemotherapy,[9,11] the addition of dynamic Ki-67 yields additional information about endocrine response that might provide a more accurate risk assessment and improved decision making.[52] As such ongoing phase 3 trials (APAPT-cycle and POETIC-A) are prospectively testing whether those patients with HR+ EBC with either negative or low nodal burden who do not suppress Ki-67 with preoperative ET can gain benefit from the addition of adjuvant CDK4/6 inhibitors.[12]

## SUMMARY

Since the introduction of adjuvant tamoxifen for HR+ EBC nearly 40 years ago, which was the first adjuvant systemic therapy to significantly improve clinical outcome in this form of breast cancer,[3] substantial progress has been made in both a deeper understanding of the biology of HR+ EBC that is now used to inform assessment of risk and prognosis and more effective adjuvant systemic therapies. For postmenopausal HR+ EBC ET remains the mainstay of treatment, with extended duration for many and the addition of targeted CDK 4/6 inhibitors for those with node-positive high-risk disease, and de-escalation of chemotherapy for those in whom it is unlikely to be of benefit. As such, systemic adjuvant therapy is now highly tailored and individualized for this most common form of breast cancer.

## CLINICS CARE POINTS

- Accurate assessment of risk in HR+ postmenopausal breast cancer should include clinical-pathologic staging, biological information from receptor status, and where indicated genomic profiling to ascertain both prognosis and predictive benefit from adjuvant therapy.
- ET with AIs or tamoxifen is used in all HR+ postmenopausal EBC for between 5 and 10 years depending on the level of risk and tolerability.
- Shared decision making about adjuvant chemotherapy should discuss relative risk reduction and toxicity, and for postmenopausal women with N0 or N1 disease and an Oncotype recurrence score of less than 25, chemotherapy is not indicated
- Adjuvant abemaciclib should be considered for high-risk node-positive HR+ EBC to further reduce risk

## DISCLOSURE

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