Original Article

A look at current and potential treatment approaches for hormone receptor-positive, HER2-negative early breast cancer

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The heterogeneity of hormone receptor (HR)-positive, HER2-negative early breast cancers reinforces the importance of individualized, risk-adapted treatment approaches. Numerous factors contribute to the risk for recurrence, including clinical tumor features, individual biomarkers, and genomic risk. Current standard approaches for patients with HR-positive, HER2-negative, early stage disease focus on endocrine therapy and chemotherapy. The specific treatment regimen and duration of adjuvant therapy should be selected based on accurate risk assessment, tolerability of available therapies, and consideration for patient preferences. For patients with high-risk features, such as highly proliferative tumors, large tumor size, and significant nodal involvement, the risk for recurrence remains clinically significant despite appropriate adjuvant treatment with current standards of care. This has driven investigation into novel treatment approaches, including the addition of cyclin-dependent kinase 4 and 6 inhibitors to adjuvant endocrine therapy. Cyclin-dependent kinase 4 and 6 inhibition has demonstrated significant efficacy in patients with high-risk, HR-positive, HER2-negative, nonmetastatic breast cancer and now offers a new strategy to greatly improve outcomes in this difficult to treat patient population. ***Cancer* 2022;128:2209-2223**.

LAY SUMMARY:

- Hormone receptor (HR)-positive, HER2-negative early breast cancers are highly diverse and need to be managed differently for individual patients.
- The use of adjuvant endocrine therapy and chemotherapy should be driven by a patient's risk for recurrence, preferences, and risk for side effects.
- Patients with high-risk tumors have a persistently elevated risk for recurrence despite current standards of care.
- Emerging cyclin-dependent kinase 4 and 6 inhibitors are highly effective when added to endocrine therapy in high-risk, HR-positive early breast cancer and have the potential to improve patient outcomes in this difficult to treat patient population.

KEYWORDS: adjuvant therapy, breast cancer, chemotherapy, cyclin-dependent kinase (CDK), endocrine therapy, risk factors.

HETEROGENEITY OF HORMONE RECEPTOR-POSITIVE BREAST CANCERS

Hormone receptor (HR)-positive breast cancers make up a highly heterogeneous group of malignancies. These malignancies have a risk for both early and late recurrence, with at least one-half of disease recurrences occurring >5 years after initial diagnosis and some occurring well beyond 10 years after diagnosis.[1] Variations in tumor grade, expression of hormone receptors and proliferative genes (eg, Ki67), and genomic alterations all contribute to the diversity of early stage, HR-positive breast cancers. These characteristics are closely tied to intrinsic subtypes (luminal A and luminal B) and can provide valuable information regarding risk for recurrence and sensitivity to systemic therapies. However, between these 2 intrinsic subtypes lies a wide spectrum of HR-positive early breast cancers that have unique tumor biology and recurrence risk, reinforcing the importance of individualized treatment decisions (Table 1).[1]

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We acknowledge Tristin Abair, PhD, for her assistance writing the article and Trudy Grenon Stoddert, ELS, for her editorial assistance and assistance preparing the article for submission. Both were compensated by Medscape Education. The focus group and resulting article were supported by an educational grant from Lilly.

The findings and conclusions in this supplement are those of the authors and do not necessarily reflect the official position of the American Cancer Society, John Wiley & Sons, Inc., or the opinions of the journal editors.

DOI: 10.1002/cncr.34161, **Received:** December 13, 2021; **Revised:** January 31, 2022; **Accepted:** February 3, 2022, **Published online** May 10, 2022 in Wiley Online Library (wileyonlinelibrary.com)

TABLE 1. Characteristics of Intrinsic Subtypes in Hormone Receptor-Positive, HER2-Negative Early Breast Cancer[a]

Characteristic	Luminal A	Spectrum Between Luminal A and Luminal B Subtypes	Luminal B
Tumor grade	1 (well differentiated)	2 (moderately differentiated)	3 (poorly differentiated)
ER expression	+++	++ to +++	+ to ++
PgR expression	++ to +++	0 to +++	0 to ++
Ki67 index, %	<10	10-20	>20
Effect of endocrine therapy	+++	++ to +++	++ to +++
Effect of chemotherapy	0	0 to +	+++

Abbreviations: ER, estrogen receptor; HR, hormone receptor; PgR, progesterone receptor.
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ASSESSING RECURRENCE RISK IN PATIENTS WITH HR-POSITIVE EARLY BREAST CANCER

Adjuvant therapy options for HR-positive early breast cancers center on endocrine therapy and chemotherapy. Optimal treatment selection requires an accurate assessment of an individual's risk for disease recurrence. A higher risk of recurrence and a poorer prognosis are associated with large tumor size, increased numbers of nodes, high histologic grade, and vascular invasion.[2] The staging criteria from the American Joint Committee for Cancer was updated in 2018 to incorporate biologic factors such as tumor grade, estrogen receptor (ER) status, progesterone receptor (PgR) status, HER2 status, and multigene assays.[3]

Role for Individual Biomarkers

In addition to clinical factors, several biomarkers are important in determining risk for recurrence and appropriate adjuvant therapy. Expression of the biomarkers ER, PgR, and HER2 identifies the disease subtype and informs prognosis.[2,4] ER and PgR expression is evaluated using immunohistochemistry (IHC), and tumors are considered positive if ≥1% of cells show marker staining. High ER and/or PgR expression is predictive for benefit from endocrine therapy, and lack of these markers is considered a poor prognostic marker. Guidelines from the American Society of Clinical Oncology (ASCO) and the College of American Pathologists recommend designating tumors as *ER low positive* if ER expression is from 1% to 10%, recognizing that data are limited on the benefit of endocrine therapy for these tumors.[5] Expression of ER in the absence of PgR is associated with a worse prognosis (luminal B-like tumors) compared with tumors in which both markers are expressed. HER2 serves as both a prognostic marker and a predictive marker for HER2-targeted therapies and is assessed using IHC or in situ hybridization.[2]

Ki67 is a biomarker for the cell proliferation rate and is prognostic in HR-positive, HER2-negative breast cancers. Ki67 levels have been incorporated into the IHC definition of luminal-like tumors, with low Ki67 corresponding to luminal A-like tumors and high Ki67 corresponding to luminal B-like tumors.[2] IHC-based assessment of Ki67 can show considerable heterogeneity in the pattern of staining, and there is often significant variability in Ki67 testing between laboratories.[4,6] This reinforces the need for validation of testing methodologies and procedures to improve the reliability of results.

Another challenge to the implementation of Ki67 testing is lack of a clear consensus on the optimal cutoff points for low and high Ki67 index. The International Ki67 Working Group defines a low Ki67 as ≤5% and a high Ki67 as ≥30%, whereas the current European Society for Medical Oncology (ESMO) guidelines recommend cutoff levels of <10% for low Ki67 and >30% for high Ki67.[2,4] However, most luminal breast tumors have a Ki67 index that lies somewhere in between these values, making the interpretation of test results difficult.

In addition to its prognostic value, Ki67 is also predictive for response to both chemotherapy and endocrine therapy in the neoadjuvant setting.[2] The PEPI (preoperative endocrine prognostic index) score integrates Ki67 levels with pathologic tumor size, nodal status, and ER status to predict the risk for recurrence in surgical specimens after neoadjuvant endocrine therapy. As a research tool, this biomarker profile identified patients whose tumors were downstaged after neoadjuvant endocrine therapy who had a low risk of recurrence and may be less likely to benefit from adjuvant chemotherapy.[7]

Dynamic changes in Ki67 during short-term (2-week) preoperative endocrine therapy can identify patients who are endocrine-sensitive versus those who may have endocrine-resistant disease and should be considered for adjuvant chemotherapy or other treatment strategies. The predictive value of Ki67 was demonstrated in the phase 3 POETIC trial (ClinicalTrials.gov identifier NCT02338310) in postmenopausal patients with

TABLE 2. Genomic Tests for Early Breast Cancer[a]

Test	Prognostic Information Provided	Predictive Information Provided	Type of Supporting Data	Clinical Use in HR-Positive, HER2-Negative Early Breast Cancer
21-Gene assay (Oncotype DX)	10-y recurrence risk	Adjuvant chemotherapy benefit	Prospective trials (TAILORx, RxPONDER, WSG PlanB, ADAPT)	• Node-negative or node-positive (1-3 lymph nodes) • Premenopausal or postmenopausal
70-Gene assay (MammaPrint)	10-y recurrence risk	Not determined	Prospective trial (MINDACT)	• Node-negative or node-positive (1-3 lymph nodes) • Premenopausal or postmenopausal
50-Gene assay (PAM50; Prosigna)	10-y recurrence risk	Not determined	Retrospective	• Node-negative or node-positive (1-3 lymph nodes) • Postmenopausal
12-Gene assay (EndoPredict)	10-y recurrence risk	Not determined	Retrospective	• Node-negative or node-positive (1-3 lymph nodes) • Premenopausal or postmenopausal
Breast Cancer Index	10-y recurrence risk and late recurrence risk (5-10 y)	Extended adjuvant endocrine therapy benefit	Retrospective	• Node-negative or node-positive (1-3 lymph nodes) • Premenopausal or postmenopausal

Abbreviation: HR, hormone receptor.
[a]See National Comprehensive Cancer Network[10]; Kittaneh et al, 2020[11]; and Laws et al, 2021.[12]

HR-positive, HER2-negative early breast cancer. Those who had a reduction in Ki67 levels to ≤10% after neoadjuvant endocrine therapy demonstrated a 5-year recurrence risk of 8.4%, compared with 21.5% for those who had persistently high Ki67 levels after neoadjuvant therapy.[8] This has led to ongoing studies, such as POETIC-A in HR-positive early breast cancer (ClinicalTrials.gov identifier NCT04584853), which is integrating repeat Ki67 assessment at diagnosis and after 2 weeks on neoadjuvant endocrine therapy to identify early tumor response or resistance.[9]

Gene Expression Assays in HR-Positive Early Breast Cancer

An important limitation of individual biomarkers like ER, PgR, and Ki67 is the potential for interlaboratory variability, as well as subjective human interpretation of results. Gene expression analysis can overcome some of these challenges, providing an automated approach to the evaluation of tumor biology. Each of the available assays differs with respect to the type of information provided and the specific patient populations used to validate the assays (Table 2).[10-12] These characteristics should be carefully considered when selecting which genomic test will be most beneficial to inform adjuvant treatment decisions.[10-12]

The 21-Gene Assay (Oncotype DX)

The 21-gene assay evaluates 16 cancer-related genes and 5 reference genes, assigning a recurrence score (RS) from 0 to 100. Initial retrospective studies validated this assay as a prognostic and predictive tool in patients with node-negative, HR-positive early breast cancer, although uncertainty remained regarding the benefit of chemotherapy among patients in the intermediate-risk RS group.[13,14] The prospective TAILORx study (ClinicalTrials.gov identifier NCT00310180) was designed to address this question, randomly assigning patients with node-negative disease and an intermediate-risk RS of 11 to 25 to either endocrine therapy alone or chemotherapy plus endocrine therapy. Nine-year invasive disease-free survival (iDFS), distant recurrence-free survival (RFS), and overall survival (OS) were similar in both treatment arms, suggesting no benefit from chemotherapy among patients in the intermediate-risk RS group. However, subgroup analyses according to age suggested a potential benefit in younger patients (aged ≤50 years) with an RS of 16 to 25.[15]

Secondary analyses of the TAILORx trial factoring in clinical risk showed that, in younger patients (aged ≤50 years) with an RS of 16 to 20, chemotherapy benefit was evident in those who had high, but not low, clinical risk. Patients with an RS of 21 to 25 showed a chemotherapy benefit regardless of the clinical risk. It is unclear whether the benefit from chemotherapy in younger patients with breast cancer may be largely because of chemotherapy-induced, premature menopause rather than direct cytotoxic effects.[16] The emerging RSClin tool combines RS with tumor grade, tumor size, and patient age and recently demonstrated significantly superior prognostication with regard to the risk for distant recurrence compared with the RS or the clinical-pathologic risk alone.[17]

Oncotype DX was evaluated in node-positive patients (1-3 positive nodes) in the randomized, phase 3 RxPONDER study (ClinicalTrials.gov identifier NCT01272037), randomizing patients with an RS ≤25 to receive adjuvant endocrine therapy with or without chemotherapy. After a median

follow-up of 5 years, the 21-gene RS was not predictive for chemotherapy benefit in the intent-to-treat population with an RS ≤25 (hazard ratio, 1.02). Although postmenopausal patients with an RS ≤25 did not appear to benefit from adjuvant chemotherapy, premenopausal patients had a 46% decrease in iDFS events and a 53% decrease in deaths when chemotherapy was added to adjuvant endocrine therapy.[18] Again, it is unclear whether the benefits of chemotherapy in younger, premenopausal women was because of its ovarian-suppressive effects.

The prospective phase 3 West German Study Group PlanB trial (ClinicalTrials.gov identifier NCT01049425) also evaluated Oncotype DX in patients with clinically high-risk, pathologic N0 (pN0)/pN1 early breast cancer, seeking to identify patients with genomically low-risk disease who may be unlikely to benefit from adjuvant chemotherapy. Patients with an RS ≤11 received adjuvant endocrine therapy alone without chemotherapy and demonstrated excellent 5-year disease-free survival (DFS) (94%) and 5-year OS (99%) rates compared with 94% and 97%, respectively, in patients with an RS of 12 to 25 who received endocrine therapy and chemotherapy. The RS also added valuable predictive information for patients with intermediate Ki67 levels (between 10% and 40%), supporting the use of this genomic assay to inform treatment decisions for patients with HR-positive, HER2-negative early breast cancer.[19]

On the basis of data from the POETIC study demonstrating that a dynamic Ki67 response to preoperative endocrine therapy could predict for improved outcomes, the phase 3 West German Study Group ADAPT HR-positive/HER2-negative trial (ClinicalTrials.gov identifier NCT01779206) examined the integration of this biomarker with Oncotype DX in patients with intermediate-risk or high-risk, luminal early breast cancer. Patients who had 0 to 3 positive lymph nodes, an RS of 12 to 25, and a response to preoperative endocrine therapy (evidenced by a posttreatment Ki67 level ≤10%) had a 5-year iDFS comparable to that of patients who had 0 to 3 positive lymph nodes and an RS ≤11 (92.6% vs 93.9%, respectively). Five-year distant DFS and OS were also similar between these 2 groups, suggesting a dynamic Ki67 response; and the Oncotype DX RS can identify patients with <3 positive lymph nodes and an RS ≤25 who can safely be spared adjuvant chemotherapy. Of note, subgroup analyses suggested that patients with 3 positive lymph nodes and an RS of 12 to 25 may have poorer outcomes and should be considered for adjuvant chemotherapy.[20]

The 70-Gene Signature (MammaPrint)

The 70-gene includes a core set of 70 genes that were found to be significantly associated with disease outcome. This genomic assay divides patients dichotomously into low and high genomic risk groups and was prognostic for the time to distant metastasis and OS in retrospective validation studies.[21,22] This led to the prospective MINDACT trial (ClinicalTrials.gov identifier NCT00433589), in which patients with discordant clinical and genomic risk were assigned to either receive or not receive chemotherapy based solely on either their clinical risk group or their 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 who received endocrine therapy alone, suggesting that the 70-gene signature can identify a group of patients who may not need adjuvant chemotherapy. The results were consistent in patients who had HR-positive, HER2-negative breast cancer compared with those who had other disease subtypes. Results were also consistent in patients with node-negative or node-positive disease.[22]

An unplanned exploratory analysis in the HR-positive, HER2-negative subset showed similar 8-year DMFS with or without chemotherapy in patients aged >50 years (90.2% vs 90.0%). In younger patients (aged ≤50 years), an absolute DMFS benefit of 5% was observed in patients randomly assigned to chemotherapy (93.6% vs 88.6% for those receiving endocrine therapy alone). Nodal status did not influence chemotherapy benefit in this patient population. Similar to the TAILORx and RxPonder studies, investigators speculated that the benefit observed in younger patients could be due to chemotherapy-induced ovarian function suppression (OFS).[23]

The PAM50 Gene Expression Signature (Prosigna)

The PAM50 signature evaluates 50 classifier genes and 5 control genes, categorizing breast tumors into intrinsic subtypes and assigning a risk of recurrence (ROR) score ranging from 0 to 100 in postmenopausal women with ER-positive early breast cancer. The PAM50 ROR score was prognostic for 10-year distant recurrence risk in patients with node-negative and node-positive disease from the ATAC (ClinicalTrials.gov identifier NCT00849030) and ABCSG-8 (ClinicalTrials.gov identifier NCT00291759) studies.[24-26] The ROR score also added significant prognostic information compared with the 21-gene RS or an IHC-based analysis of ER, PgR, HER2, and Ki67

(IHC4).[26] Additional data from a Danish cohort study also showed that the ROR score could identify patients with node-positive disease and a low risk of recurrence who could be spared chemotherapy.[27]

The 12-Gene Assay (EndoPredict)

The 12-gene EndoPredict assay combines a 12-gene molecular score with tumor size and nodal status to create an EPclin score, which designates patients as either low risk or high risk for recurrence.[28] EndoPredict is prognostic for the 10-year risk of recurrence in patients with node-negative or node-positive, HR-positive early breast cancer and was initially validated in patients treated with endocrine therapy alone, without chemotherapy.[29] Recent studies have also shown that this 12-gene assay is prognostic in patients treated with chemoendocrine therapy and is predictive for benefit from neoadjuvant chemotherapy or endocrine therapy.[28,30]

Breast Cancer Index

The Breast Cancer Index combines a 5-gene prognostic molecular grade index with a 2-gene predictive biomarker ratio of HoxB13 and interleukin-17B receptor. The resulting score ranges from 0 to 10 and designates patients as having a low or high risk of recurrence.[11] An analysis of patients from the TransATAC study (International Standard Randomized Controlled Trial Number 18233230) showed that the Breast Cancer Index was prognostic for both early and late recurrences but suggested that this assay was particularly useful for the prediction of late recurrences in years 5 to 10 after initial diagnosis.[31] Data from the MA.17 trial (ClinicalTrials.gov identifier NCT00003140) and the aTTom trial (ClinicalTrials.gov identifier NCT00003678) demonstrated that the Breast Cancer Index was predictive for benefit from extended adjuvant therapy in patients with node-negative or node-positive, HR-positive early breast cancer.[32,33] In contrast, the Breast Cancer Index was not predictive for benefit from extended letrozole in patients with HR-positive, HER2-negative early breast cancer in a recent analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-42 trial (ClinicalTrials.gov identifier NCT00382070).[34]

GUIDELINE RECOMMENDATIONS AND CLINICAL USE OF GENOMIC ASSAYS

The available gene expression assays vary with regard to the information they provide and the specific patient populations used for assay validation, requiring careful interpretation of results. Uncertainty also remains regarding the applicability of these assays in certain patient populations, including patients who have small tumors and lower-risk clinical features. Despite the limitations of current gene expression assays, genomic testing provides additional prognostic information and is likely superior to basing adjuvant treatment decisions on anatomic staging alone. Breast cancer guidelines from the National Comprehensive Cancer Network (NCCN), the ASCO, and the ESMO recommend the use of gene expression assays in patients with HR-positive, HER2-negative early breast cancer who have 0 to 3 positive lymph nodes to assess the risk of recurrence and inform decisions regarding the use of adjuvant chemotherapy.[2,10,35] Current guidelines do not emphasize any specific genomic assay over another, and there is significant regional variability in the selection and use of these assays, with each institution often having a preferred test they use most often.[11]

Clinicians need to understand the information provided by each genomic assay and the unique differences between these tests. For instance, whereas all the available gene expression 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.[10] The Prosigna, EndoPredict, and Breast Cancer Index assays can assess risk for late recurrences, which may be useful in determining candidates for extended adjuvant therapy. The investigational EPclin and RSClin scores combine genomic profiling with other clinical factors (eg, tumor size, tumor grade), which may further improve risk assessment and subsequent treatment decisions.[11]

Patients should be well informed of the benefits and limitations of gene expression assays before testing. For cases in which anatomic staging does not strongly support the decision between chemoendocrine therapy and endocrine therapy alone, genomic assays can offer additional insight on the risk of recurrence and potential benefit from chemotherapy. Unfortunately, many HR-positive early breast cancers are classified as intermediate-risk, and treatment decisions for this group remain challenging. In addition, there is continued uncertainty regarding whether the benefit for adjuvant chemotherapy observed in younger patients is primarily due to chemotherapy-induced ovarian suppression or cytotoxic effects. If chemotherapy-induced ovarian suppression is the primary mechanism of action, then premenopausal patients could reasonably be offered ovarian suppression instead of

adjuvant chemotherapy.[10] Testing should not be considered if the results will not affect clinical decision making, such as a patient who refuses or is ineligible for adjuvant chemotherapy or a patient whose clinical features strongly indicate a need for chemotherapy.[11]

PERSPECTIVES ON CURRENT TREATMENT APPROACHES FOR HR-POSITIVE EARLY BREAST CANCER

Both endocrine therapy and chemotherapy play an important role in the treatment of HR-positive, HER2-negative early breast cancers. In addition to careful risk assessment, adjuvant treatment selection should also be based on tolerability of available therapies and consideration of patient preferences and treatment goals.

Adjuvant Endocrine Therapy

Tamoxifen

Tamoxifen is commonly used in both premenopausal and postmenopausal patients with HR-positive breast cancer.[2,10] On the basis of data from meta-analyses, adjuvant tamoxifen significantly reduces disease recurrence and improves survival, even in tumors that have ER expression as low as 1%.[36] Tamoxifen provides equivalent benefit in luminal A and luminal B tumors and reduces locoregional recurrence, even in breast cancers <1 cm in size.[37,38]

Aromatase inhibitors

The aromatase inhibitors (AIs) anastrozole, letrozole, and exemestane are used primarily in postmenopausal patients and have demonstrated superior efficacy compared with tamoxifen in this patient population.[39] Long-term follow-up from the ATAC study and the BIG 1-98 trial (ClinicalTrials.gov identifier NCT00004205) showed that 5 years of adjuvant anastrozole or letrozole significantly reduced distant recurrences compared with 5 years of tamoxifen.[40,41] Sequencing tamoxifen and AI therapy for a total of 5 years (2-3 years each) also demonstrated superiority to 5 years of tamoxifen alone in reducing distant recurrence, suggesting that the use of an AI at any point during adjuvant therapy can reduce the risk of recurrence.[39]

Ovarian function suppression

Uncertainty remains regarding the optimal use of OFS in premenopausal patients with HR-positive breast cancer. Data from the SOFT trial (ClinicalTrials.gov identifier NCT00066690) demonstrated a significant reduction in distant recurrence when OFS was added to tamoxifen or exemestane compared with tamoxifen alone. In the SOFT study and the TEXT trial (ClinicalTrials.gov identifier NCT00066703), benefit was also particularly evident in patients with high-risk disease who required chemotherapy, whereas patients with low-risk disease who did not require chemotherapy showed minimal benefit from the addition of OFS.[42] Current NCCN and ESMO guidelines recommend adding OFS to endocrine therapy in premenopausal patients with higher risk disease (eg, young age, high-grade tumors, node-positive).[2,10] OFS can be administered with either tamoxifen or an AI, although tamoxifen may be better tolerated and provides protection in the event that ovarian suppression is insufficient. Data from the SOFT study showed that up to 25% of patients had breakthrough estradiol levels at some point during the first year of OFS therapy.[43] Bilateral oophorectomy can also be considered for very young patients who are many years from natural menopause to obviate the need for long-term OFS.[10]

Optimal duration of adjuvant endocrine therapy

Multiple studies have demonstrated improved DFS when patients received AI therapy for 5 additional years after the completion of 5 years of either tamoxifen, an AI, or sequential tamoxifen-AI therapy.[44] In addition, the ABCSG-16 study (ClinicalTrials.gov identifier NCT00295620) demonstrated a similar benefit from 2 additional years of AI therapy instead of 5 years, suggesting that therapy could be stopped at 7 years without compromising outcomes.[45] A meta-analysis of almost 25,000 patients showed that extending endocrine therapy beyond 5 years significantly reduced recurrences but also reported a differential benefit based on the degree of nodal involvement. Five years of additional AI therapy reduced recurrence by 1.1% in node-negative patients, by 3.8% in those with 1 to 3 positive nodes, and by 7.7% in those with ≥4 positive nodes. The benefit was more pronounced in patients who received 5 years of tamoxifen alone compared with those who received prior adjuvant AI therapy.[46] Taken together, the available data suggest that 5 years of endocrine therapy may be sufficient for patients who have stage I, low-risk breast cancers, whereas those who have higher stage disease and increased nodal involvement should be strongly considered for extended-duration endocrine therapy.

Endocrine therapy safety considerations

Available endocrine therapies differ with regard to safety profile and tolerability, which should be thoroughly discussed with patients when selecting adjuvant

therapy. Tamoxifen is commonly associated with hot flashes, night sweats, and vaginal discharge as well as a small risk for deep-vein thrombosis and uterine cancer. The side effects primarily associated with AIs include increased vaginal dryness, sexual side effects, hair thinning, and arthralgia, with fewer hot flashes and night sweats compared with tamoxifen. AIs are associated with a risk for accelerated osteoporosis, and both tamoxifen and AIs can increase the risk for cognitive impairment, which must be closely monitored. Hot flashes and AI-related musculoskeletal symptoms can be particularly bothersome for patients and may contribute to nonadherence to adjuvant treatment.[1] Patients experiencing tolerability issues with an AI can be considered for a treatment switch to a different AI or to tamoxifen if necessary. Eight-year follow-up data from the BIG 1-98 study suggested a similar reduction in the risk of recurrence for sequential tamoxifen-AI and AI-tamoxifen (DFS, 77.3% vs 77.8%; distant recurrence-free interval, 88.1% vs 88.7%), although the statistical analysis did not directly compare the 2 sequential treatment arms.[47] Data from the phase 3 SOLE trial (ClinicalTrials.gov identifier NCT00553410) also showed a similar benefit for intermittent versus continuous, extended letrozole in postmenopausal patients, suggesting that short treatment breaks after the initial 5 years of AI are feasible and will not compromise long-term benefit.[48]

Adjuvant Chemotherapy for HR-Positive Early Breast Cancer

Recent years have witnessed an evolution in the use of adjuvant chemotherapy for HR-positive disease, with genomic assays allowing the better identification of which patients are unlikely to benefit and reducing unnecessary toxicity. Current ESMO guidelines recommend consideration of adjuvant chemotherapy for patients who have luminal A tumors and a high disease burden (≥4 lymph nodes involved, ≥T3) as well as those who have luminal B, highly proliferative tumors. In contrast, patients who have low-grade luminal A tumors with strong HR expression and low genomic risk likely derive less benefit from adjuvant chemotherapy and can be considered for endocrine therapy alone.[2]

Similarly, the NCCN guidelines include several factors in adjuvant therapy decision-making, including menopausal status, tumor size, nodal involvement, and genomic risk.[10] As mentioned above, gene expression analysis should be strongly considered for patients who have 0 to 3 positive lymph nodes. Current NCCN guidelines list the Oncotype DX 21-gene assay as the preferred testing option for lymph node-negative disease and for postmenopausal patients with node-positive disease, strongly recommending adjuvant chemotherapy for all patients with stage I or II disease and an RS ≥26. On the basis of data from the TAILORx and RxPONDER trials in node-negative and node-positive disease, respectively, adjuvant chemotherapy does not provide a significant benefit in postmenopausal patients who have ≤3 positive nodes and an RS <26 or in node-negative, premenopausal patients with an RS ≤15. In premenopausal patients with either node-negative disease and an intermediate RS (range, 16-25) or pN1 disease and an RS <26, chemotherapy provides a small benefit. The chemotherapy benefit in younger patients could be related primarily to ovarian suppression, reinforcing the importance of discussing the benefits and risks for each adjuvant approach with patients and their families.[10]

Regimen selection

The optimal selection of chemotherapy in the adjuvant setting is an ongoing area of debate. Data from a joint efficacy analysis of docetaxel plus cyclophosphamide (TC) versus a taxane plus doxorubicin/cyclophosphamide in patients with early breast cancer demonstrated important differences in benefit based on HR expression and nodal involvement. In patients with HR-positive, node-negative disease, iDFS analysis strongly favored TC over a taxane plus doxorubicin/cyclophosphamide (hazard ratio, 0.69). Although patients with HR-positive breast cancer and a high tumor burden showed benefit from the addition of anthracyclines, patients with only 1 to 3 positive nodes showed minimal benefit from the addition of an anthracycline (2% gain in 4-year iDFS compared with TC: hazard ratio, 1.14).[49] In contrast, the West German Study PLAN-B study showed similar benefit for 4 cycles of epirubicin/cyclophosphamide followed by docetaxel versus 6 cycles of TC in patients with early breast cancer regardless of HR status.[50]

There are considerable regional differences regarding the preferred chemotherapy regimens for HR-positive early breast cancers. In the United States and Germany, there has been a general shift away from using anthracyclines in patients who have HR-positive tumors with minimal or no nodal involvement, although practice varies between institutions. In southern Europe and the United Kingdom, anthracyclines are still commonly used, including in patients with node-negative disease.

Tolerability of adjuvant chemotherapy

Adverse events (AEs) associated with chemotherapy are another important consideration when selecting adjuvant

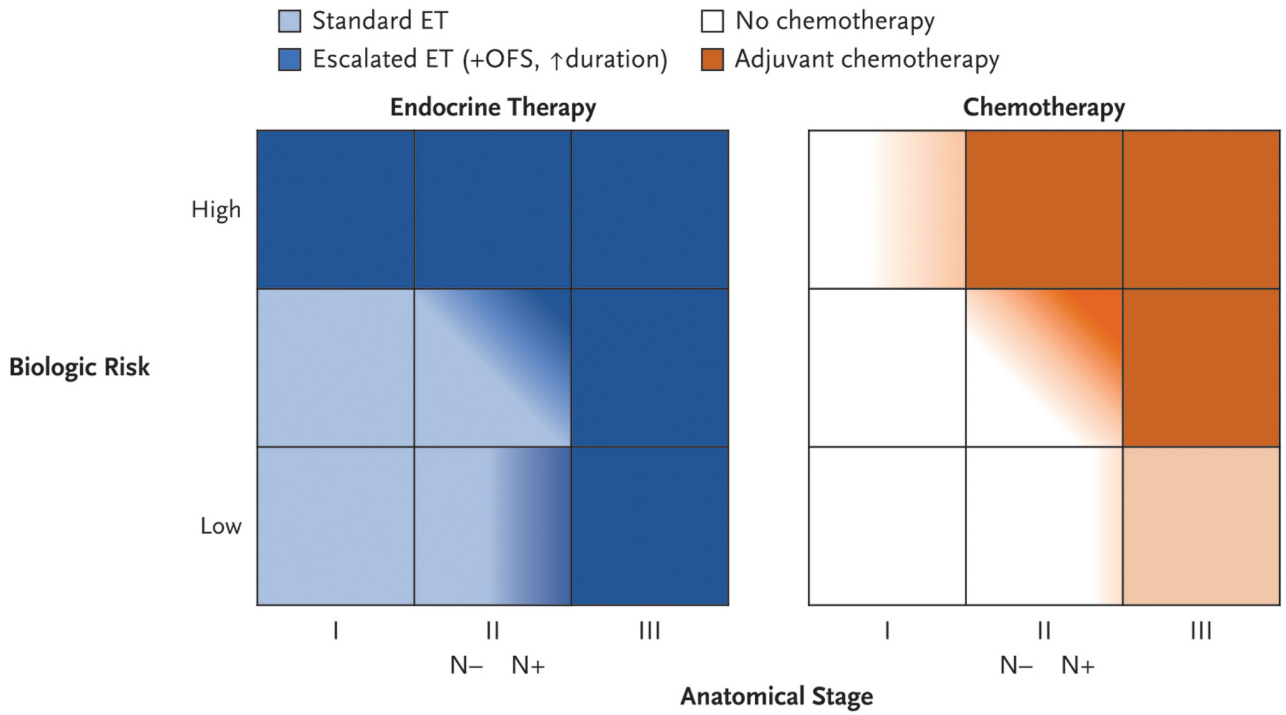

FIGURE 1. This is a model of treatment decision-making in patients with hormone receptor (HR)-positive early breast cancer. ET indicates endocrine therapy; N–, negative nodal status; N+, positive nodal status; OFS, ovarian function suppression. Reprinted from: Burstein H. Systemic therapy for estrogen receptor-positive, HER2-negative breast cancer. *N Engl J Med*. 2020;383:2557-2570,[1] with permission from the Massachusetts Medical Society. Copyright © 2020 Massachusetts Medical Society.

therapy. Anthracyclines may have a slightly more predictable safety profile with regard to the more common AEs, allowing effective patient education on the incidence and timing of side effects as well as optimal implementation of supportive care. Taxane-based TC regimens appear to have a less predictable AE profile, with some patients doing very well and some experiencing significant toxicity. Both anthracyclines and taxanes are commonly associated with alopecia, and anthracyclines have a smaller risk for serious events, such as cardiac damage and leukemia.[51]

GUIDELINE-BASED RECOMMENDATIONS FOR ADJUVANT THERAPY

Numerous guidelines are available to inform the treatment of early breast cancer, including the NCCN and ESMO guidelines and recommendations from individual countries. There are important similarities and differences between these recommendations regarding risk assessment and adjuvant therapy selection. Guidelines from both the NCCN and the ESMO include consideration for clinical characteristics, axillary nodal status, and careful review of disease pathology in the initial evaluation of patients with early breast cancer.[2,10] The NCCN guidelines strongly emphasize the role for gene expression assays, allowing a more refined estimation of the risk of recurrence as it relates to treatment selection.[10] However, the availability and access to gene expression assays varies widely around the world, contributing to differences in breast cancer guidelines. As a result, the ESMO guidelines emphasize intrinsic tumor subtypes (luminal A-like vs luminal B-like tumors) based on IHC biomarker analysis and tumor burden as the basis for recommending systemic therapy for patients with early breast cancer.[2]

Ultimately, adjuvant therapy decisions should be guided by accurate assessment of recurrence risk, tolerability of available therapies, and patient preferences. As Figure 1 illustrates, between the 2 extremes of low-risk and high-risk disease, there is considerable heterogeneity and ambiguity regarding optimal treatment approaches.[1] Although patients with lower recurrence risk can be adequately treated with endocrine therapy alone, escalation of therapy with the addition of OFS or extended adjuvant endocrine therapy can be beneficial in patients at increased risk. The addition of adjuvant chemotherapy should also be considered in patients with high-risk disease.

ADDRESSING UNMET NEEDS IN PATIENTS WITH HIGH-RISK, HR-POSITIVE EARLY BREAST CANCER

Despite the efficacy of current locoregional and adjuvant therapy approaches, approximately 20% of patients with HR-positive, HER2-negative early breast cancer will still experience disease recurrence within the first 10 years.[39] Factors that increase this risk include larger tumor size, nodal involvement, and highly proliferative disease (eg, high tumor grade, high Ki67 index), signaling more aggressive tumor behavior.[2,52] Persistent risk for recurrence creates a need for more effective adjuvant treatment approaches, particularly for this high-risk, HR-positive patient population. To address this unmet need, ongoing studies continue to investigate novel adjuvant therapy strategies, including the addition of targeted agents to endocrine therapy.

Rationale for Cyclin-Dependent Kinase 4 and 6 Inhibitors in Breast Cancer

In HR-positive breast cancers, ER signaling is responsible for the upregulation and downregulation of hundreds of genes involved in normal and pathologic cell function, including the cyclins and downstream cyclin-dependent kinases (CDKs) involved in cell cycle regulation. Promitotic signaling early in the G1 phase of the cell cycle leads to the expression of D-type cyclins and subsequent activation of CDK4 and CDK6. These cyclin/CDK complexes phosphorylate retinoblastoma-associated protein 1 (Rb1), a protein that normally represses cell cycle progression in its unphosphorylated state. Phosphorylation of Rb1 leads to release of E2F transcription factors and progression of cells from G1 phase to S phase of the cell cycle.[53]

Inhibitors of CDK4/CDK6 bind to the adenosine triphosphate-binding pocket of these CDKs and prevent the phosphorylation of Rb, downregulating the proteins required for cell cycle progression. This results in cell cycle arrest in the G1 phase and, ultimately, apoptosis.[53] Preclinical studies demonstrated that CDK4/CDK6 inhibitors were active in ER-positive cell lines and xenograft models, including breast cancer cell lines that were resistant to standard endocrine therapies.[54-56] Those data led to the investigation of 3 CDK4/CDK6 inhibitors—palbociclib, abemaciclib, and ribociclib—in patients with HR-positive, HER2-negative breast cancer. All 3 of these agents are administered orally and are highly potent and specific for CDK4 and CDK6 (Table 3).[53]

TABLE 3. Potency of Currently Available Cyclin-Dependent Kinase 4 and 6 Inhibitors[a]

IC_{50}	Abemaciclib	Palbociclib	Ribociclib
CDK1	>1 μM	>10 μM	>100 μM
CDK2	500 nM	>10 μM	>50 μM
CDK4	2 nM	9-11 nM	10 nM
CDK5	NR	>10 μM	ND
CDK6	5 nM	15 nM	39 nM
CDK7	300 nM	NR	NR
CDK9	57 nM	NR	NR

Abbreviations: CDK, cyclin-dependent kinase; IC_{50}, half-maximal inhibitory concentration; ND, not determined; NR, not reported.
[a]Reprinted from: O'Leary B, Finn RS, Turner NC. Treating cancer with selective CDK4/6 inhibitors. *Nat Rev Clin Oncol*. 2016;13:417-430,[53] with permission from Springer Nature. Copyright © 2016 Springer Nature.

EFFICACY AND SAFETY OF CDK4/CDK6 INHIBITORS IN EARLY BREAST CANCER

CDK4/CDK6 inhibitors were initially investigated in patients with HR-positive advanced breast cancer, demonstrating significant efficacy in combination with endocrine therapy in the first-line and second-line settings.[57] Palbociclib, ribociclib, and abemaciclib are now approved in combination with either an AI or fulvestrant and have become an established part of the standard of care for patients with advanced, HR-positive, HER2-negative disease.[2,10,58-60] On the basis of efficacy demonstrated in the metastatic setting, CDK4/CDK6 inhibitors are now under investigation in patients with early stage disease and are expanding treatment options in the adjuvant setting.

Palbociclib

Palbociclib was investigated in the adjuvant setting in the phase 3 PALLAS study (ClinicalTrials.gov identifier NCT02513394), which evaluated the addition of 2 years of palbociclib to tamoxifen or an AI versus endocrine therapy alone in patients with HR-positive, HER2-negative early breast cancer. Eligibility criteria included stage II or III disease, an Eastern Cooperative Oncology Group performance status of 0 or 1, and enrollment within 12 months of initial diagnosis. Premenopausal patients also received concurrent luteinizing hormone-releasing hormone agonist therapy.[61]

With a median follow-up of 23.7 months, the PALLAS study failed to meet the primary end point of improved iDFS (3-year iDFS, 88.2% vs 88.5% for endocrine therapy alone; hazard ratio, 0.93; $P = .51$) (Table 4).[61-64] Post-hoc subgroup analyses did not identify a specific patient subgroup that demonstrated benefit from adjuvant palbociclib therapy. In total, 42.2% of patients discontinued palbociclib prematurely

TABLE 4. Key Efficacy Data for Cyclin-Dependent Kinase 4 and 6 Inhibition in the Adjuvant Setting

	PALLAS (Mayer 2021[61])	PENELOPE-B (Loibl 2021[62])	monarchE (O'Shaughnessy 2021[63,64])
CDK4/6 inhibitor	Palbociclib	Palbociclib	Abemaciclib
Duration of therapy, y	2	1	2
Median follow-up, mo	23.7	42.8	27.1
2-y iDFS, %	NR	88.3 vs 84.0	92.7 vs 90.0
3-y iDFS, %: HR	88.2 vs 88.5: 0.93 (P = NS)	81.2 vs 77.7: 0.93 (P = NS)	88.8 vs 83.4: 0.696 (P < .0001)
Distant RFS: HR	1.00 (P = NS)	NR	0.687 (P < .0001)
Discontinuation rate due to any reason, %	42.2	17.5	27.7

Abbreviations: CDK, cyclin-dependent kinase; HR, hazard ratio; iDFS, invasive disease-free survival; NR, not reported; NS, not significant; RFS, recurrence-free survival.

TABLE 5. Key Safety Data for Cyclin-Dependent Kinase 4 and 6 Inhibition in the Adjuvant Setting

	All Grade (Grade 3/4), %					
	PALLAS (Mayer 2021[61])		PENELOPE-B (Loibl 2021[62])		monarchE (O'Shaughnessy 2021, Rugo 2021[64,65])	
Event	Palbo-ET	ET Alone	Palbo-ET	Placebo-ET	Abema-ET	ET Alone
Neutropenia	82.8 (61.3)	4.7 (0.4)	95.7 (70.0)	23.4 (1.0)	45.2 (19.1)	5.2 (0.7)
Leukopenia	54.6 (30.2)	7.3 (0.1)	99.2 (56.1)	69.9 (0.7)	37.2 (10.9)	6.3 (0.4)
Lymphopenia	12.8 (3.5)	4.1 (0.3)	NR	NR	NR	NR
Anemia	23.4 (0.5)	5.4 (0.1)	73.9 (0.3)	30.3 (0.2)	23.5 (1.8)	3.4 (0.3)
Thrombocytopenia	21.4 (0.9)	1.7 (0.0)	56.6 (0.8)	16.2 (0.3)	NR	NR
Fatigue	40.5 (2.1)	18.7 (0.3)	66.4 (2.7)	51.1 (1.5)	39.2 (2.8)	16.6 (0.1)
Diarrhea	16.4 (0.7)	5.0 (0.2)	18.3 (0.2)	15.7 (0.5)	82.6 (7.7)	7.8 (0.2)
Nausea	19.1 (0.3)	8.2 (0.1)	23.7 (0.3)	20.6 (0.3)	28.5 (0.5)	8.3 (<0.1)
Constipation	13.6 (0.0)	5.6 (0.0)	22.1 (0.0)	13.7 (0.0)	NR	NR
Arthralgia	34.9 (1.1)	41.6 (1.1)	41.2 (0.8)	46.8 (1.5)	22.0 (0.3)	33.1 (0.7)
Hot flushes	24.2 (0.2)	28.8 (0.2)	43.8 (0.8)	50.9 (1.0)	14.5 (0.1)	21.8 (0.4)
Headache	15.2 (0.2)	11.1 (0.2)	23.2 (0.5)	23.1 (0.5)	NR	NR
Infection	NR	NR	59.9 (3.2)	51.1 (3.9)	NR	NR
Cough	13.7 (0.0)	7.2 (0.0)	20.9 (0.0)	16.2 (0.0)	NR	NR

Abbreviations: Abema, abemaciclib; ET, endocrine therapy; NR, not reported; Palbo, palbociclib.

(27.1% because of an AE), with 55.4% and 34.3% of patients requiring palbociclib dose reductions to 100 and 75 mg, respectively, within 24 months of starting therapy. Grade 3 and 4 AEs observed most often in the palbociclib arm included neutropenia (61.3%), leukopenia (30.2%), lymphopenia (3.5%), and fatigue (2.1%) (Table 5).[61,62,64,65] Interstitial lung disease and thromboembolic events occurred in 0.5% and 1.7% of patients in the palbociclib arm, respectively.[61]

Adjuvant palbociclib was also evaluated in the phase 3 placebo-controlled PENELOPE-B study (ClinicalTrials.gov identifier NCT01864746) in combination with endocrine therapy in patients with high-risk early breast cancer who had residual, invasive disease after completion of neoadjuvant taxane-based chemotherapy. High-risk disease was defined as a clinical pathologic staging-ER grading (CPS-EG) score ≥3 or a CPS-EG score of 2 and pathologically positive nodes after neoadjuvant chemotherapy (ypN+). Patients received 13 cycles of either palbociclib (125 mg daily) or placebo in combination with endocrine therapy.[62]

Similar to the PALLAS study, the PENELOPE-B study failed to meet its primary end point, and the addition of palbociclib to adjuvant endocrine therapy did not improve iDFS (hazard ratio, 0.93; P = .525) or OS (hazard ratio, 0.87; P = .420) compared with endocrine therapy alone (Table 4). With a median follow-up of 42.8 months, the iDFS curves showed promising separation early in the study, but the 2 treatment arms converged over time. In total, 17.5% of patients discontinued therapy, 3% because of toxicity. Also similar to the PALLAS study, palbociclib was associated with increases in cytopenias, fatigue, and gastrointestinal events (Table 5).[62]

Abemaciclib

Abemaciclib is under investigation in combination with adjuvant endocrine therapy in the phase 3 monarchE study (ClinicalTrials.gov identifier NCT03155997), which enrolled patients with HR-positive,

TABLE 6. Ongoing Phase 3 Trials of Adjuvant Cyclin-Dependent Kinase 4 and 6 Inhibitors in Hormone Receptor-Positive, HER2-Negative Early Breast Cancer

Trial Name (Reference)	CDK Inhibitor Arm	Comparator Arm	Eligibility	Primary End Point	ClinicalTrials.gov Identifier
NATALEE (Novartis Pharmaceuticals 2021[68])	Ribociclib (for 3 y) plus ET	Nonsteroidal AI (with goserelin for premenopausal patients)	HR-positive, HER2-negative EBC, stage III or high-risk stage II	iDFS	NCT03701334
ADAPTcycle (Harbeck et al 2020[69])	Ribociclib (for 2 y) plus ET	Adjuvant chemotherapy plus ET	Intermediate-risk, HR-positive, HER2-negative EBC after 3-wk induction ET	iDFS	NCT04055493
ADAPTlate (Gluz et al 2021[70])	Abemaciclib (for 2 y) plus ET 2-6 y after diagnosis	Standard ET	HR-positive, HER2-negative EBC with clinical or genomic high risk	iDFS	NCT04565054
POETIC-A (Institute of Cancer Research, United Kingdom 2020[9])	Abemaciclib (for 2 y) plus ET	Standard ET	HR-positive, HER2-negative EBC with high risk after 2 wk of neoadjuvant AI therapy	Time to tumor recurrence	NCT04584853

Abbreviations: AI, aromatase inhibitor; CDK, cyclin-dependent kinase; EBC, early breast cancer; ET, endocrine therapy; HR, hormone receptor; iDFS, invasive disease-free survival; NCT, National Clinical Trials.

HER2-negative, node-positive, high-risk early breast cancer. High-risk disease was defined as ≥4 positive nodes or 1 to 3 positive nodes with either a grade 3 tumor, a tumor ≥5 cm in size, or a high proliferation rate (Ki67 level ≥20%). Patients received standard endocrine therapy with or without 2 years of abemaciclib at a dose of 150 mg twice daily.[63]

After a median follow-up of 27.1 months, the addition of abemaciclib significantly increased 3-year iDFS (88.8% vs 83.4% for endocrine therapy alone; hazard ratio, 0.696; $P < .0001$) (Table 4). The benefit was consistent across patient subgroups, and abemaciclib reduced the risk of distant RFS by 31.3% (hazard ratio, 0.687; $P < .0001$). The magnitude of iDFS and distant RFS benefit continued to increase during the second year of treatment, with benefit maintained beyond the 2-year study treatment period. A high Ki67 level (≥20%) was prognostic for a worse outcome, although the benefit of adjuvant abemaciclib was consistent regardless of the Ki67 index (Ki67-high cohort: hazard ratio, 0.663; $P = .0006$).[63] In addition, a numerically higher iDFS and a distant RFS benefit were observed in patients who received prior neoadjuvant chemotherapy—a subgroup with a particularly high risk of disease recurrence.[66]

Abemaciclib had a manageable safety profile, and the most common AEs were gastrointestinal events (diarrhea, nausea, abdominal pain), fatigue, and cytopenias.[64,65] Grade 3 and 4 events included neutropenia (19.1%), leukopenia (10.9%), diarrhea (7.7%), and fatigue (2.8%). Any-grade venous thromboembolic events and any-grade interstitial lung disease occurred in 2.4% and 2.9% of patients treated with abemaciclib, respectively. Most AEs started early, and the majority of patients who required therapy interruption or dose reduction were able to remain on therapy. In total, 27.7% of patients discontinued abemaciclib for any reason, with only 17.2% discontinuing because of an AE.[64,65] Patient-reported outcomes and health-related quality of life were similar between the 2 treatment arms.[67]

On the basis of these data, abemaciclib is now approved by the Food and Drug Administration in the United States in combination with endocrine therapy (either tamoxifen or an AI) for the adjuvant treatment of patients with HR-positive, HER2-negative early breast cancer. Patients are required to have a high risk of recurrence, including node-positive disease, and a Ki67 level ≥20%.[58]

ONGOING TRIALS INVESTIGATING CDK4/CDK6 INHIBITION IN EARLY STAGE BREAST CANCER

Multiple randomized clinical trials are continuing to evaluate the use of CDK4/CDK6 inhibitors in patients with early breast cancer (Table 6).[9,68-70] Ribociclib is being explored as adjuvant therapy in the ongoing phase 3 NATALEE trial (ClinicalTrials.gov identifier NCT03701334), comparing a nonsteroidal AI (plus goserelin for premenopausal patients) with or without 3 years of ribociclib. Eligible patients have HR-positive, HER2-negative breast cancer that is either stage III disease, stage II disease with positive nodes (N1), or stage II N0 disease with grade 2 or 3 tumors and/or a Ki67 level ≥20%.[68] The ongoing phase 3 ADAPTcycle study (ClinicalTrials.gov identifier NCT04055493) is designed to determine whether adding 2 years of ribociclib to adjuvant endocrine therapy is superior to chemoendocrine therapy in patients with luminal A early breast cancer and an increased risk for recurrence.[69] In the ADAPTcycle study, clinically enhanced

risk is defined as intermediate risk according to the original ADAPT trial criteria (N0 or N1 status and an Oncotype RS 12-25) as well as having a high tumor burden (clinical T2 [cT2]-cT4), or a Ki67 level >20%, or grade 3 disease, or clinically positive nodes after 3 weeks of induction endocrine therapy.[69,71] Patients are randomly assigned to receive either ribociclib plus endocrine therapy or chemotherapy followed by endocrine therapy.[69] In both of these studies, the primary end point is superiority of iDFS.[69,71]

For patients who have completed primary therapy and are currently receiving adjuvant endocrine therapy, the phase 3 ADAPTlate study (ClinicalTrials.gov identifier NCT04565054) is examining the iDFS benefit of adding 2 years of abemaciclib to standard endocrine therapy 2 to 6 years after initial diagnosis. Eligibility criteria include either high clinical risk, high genomic risk based on gene expression profiling, or intermediate clinical risk and unknown genomic risk.[70] Similar to the ADAPT study design, the POETIC-A trial is using response (determined by assessing Ki67 levels) to 2 weeks of AI-based preoperative therapy to identify patients at increased risk for recurrence. Patients are then randomly assigned to receive standard endocrine therapy or endocrine therapy plus abemaciclib.[9] The phase 2 CARABELA trial (ClinicalTrials.gov identifier NCT04293393) is directly comparing letrozole plus abemaciclib with chemotherapy in the neoadjuvant setting for patients with HR-positive, HER2-negative early breast cancer who have an intermediate or high risk of relapse.[72]

PERSPECTIVES ON THE POTENTIAL ROLE FOR CDK4/CDK6 INHIBITORS IN THE ADJUVANT SETTING

Although continued long-term follow-up is needed, at a median follow-up of 27 months, the clinical data from the monarchE trial are very promising and have now led to regulatory approval of abemaciclib in the adjuvant setting. Appropriate patient selection for the use of adjuvant CDK4/CDK6 inhibitors in combination with endocrine therapy will be critical and should be done in accordance with the eligibility criteria used in the corresponding clinical trials. The movement of CDK4/CDK6 inhibitors into earlier stages of disease reinforces the significance of shared decision making and careful discussion of recurrence risk with patients. Proactive patient education is also needed on the importance of treatment adherence and how to identify and manage AEs, such as diarrhea, constipation, and fatigue, as well as rarer, yet more serious, complications, including interstitial lung disease and venous thromboembolic events.

There are several unanswered questions regarding the role for CDK4/CDK6 inhibitors in the adjuvant setting. Longer follow-up of the monarchE trial and other ongoing studies will be needed to confirm durability of benefit. The optimal duration of therapy also remains unclear, with ongoing trials investigating various durations of adjuvant CKD4/CDK6 inhibitor therapy. Biomarkers predictive for response to adjuvant CDK4/CDK6 inhibitors constitute another area of ongoing investigation, including the role for Ki67-driven adjuvant therapy decisions in the ADAPTcycle, ADAPTlate, and POETIC-A studies. Translational projects are also exploring the potential for genomic assay-based assessment of recurrence risk to assist in the identification of patients who may benefit from the addition of CDK4/CDK6 inhibitors to adjuvant endocrine therapy. As new data emerge, the role for CDK4/CDK6 inhibition will likely continue to expand, improving patient outcomes for those with high-risk, HR-positive, HER2-negative early breast cancer.

FUNDING SUPPORT

This publication was supported by an educational grant from Lilly.

CONFLICT OF INTEREST DISCLOSURES

Nadia Harbeck reports consulting fees from AstraZeneca, Daiichi-Sankyo, Eli Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, and SeaGen; honoraria for lectures, presentations, speakers bureaus, article writing, or educational events from Amgen, AstraZeneca, Daiichi-Sankyo, Exact Sciences, Eli Lilly, Medscape, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, and SeaGen outside the submitted work. Harold J. Burstein reports participation on a Data Safety Monitoring Board for NRG Oncology outside the submitted work. Sara A. Hurvitz reports grants for clinical research (paid to her institution) from Abmrx, Amgen, AstraZeneca, Arvinas, Bayer, Daiichi-Sankyo, Genentech/Roche, Gilead, GlaxoSmithKline, Immunomedics, Eli Lilly, Macrogenics, Novartis, Pfizer, OBI Pharma, Pieris, Puma Biotechnology, Radius, Sanofi, Seattle Genetics/SeaGen, ZymeWorks, Phoenix Molecular Designs, Ltd, and Samumed outside the submitted; and stock ownership in NKMAX. Stephen Johnston reports grants for laboratory/clinical research to his institute from AstraZeneza, Eli Lilly, Novartis, Pfizer, Puma Biotechnology, and Roche/Genentech; personal fees from AstraZeneca, Eli Lilly, Novartis, Pfizer, and Puma Biotechnology; and service as a member of a speakers bureau for AstraZeneca, Eisai, Novartis, Pfizer, and Roche/Genentech, all outside the submitted work. Gregory A. Vidal reports grants for clinical research from Celcuity, GSK, and Puma Biotechnology; personal fees from AstraZeneca, Biotheranautics, Eli Lilly, Genentech, Myriad Genetics, Novartis, Pfizer, and Predicine; service as a speaker or as a member of a speakers bureau for the *American Journal of Managed Care*, Eli Lilly, EPG Health, Medscape; honoraria for writing from Novartis. He owns stock or stock options in Oncodisc.

AUTHOR CONTRIBUTIONS

Nadia Harbeck: Conceptualization, critical review of the original draft, approval of the final version to be published, and accountable for all aspects of the publication. **Harold J. Burstein:** Conceptualization, critical review of

the initial draft, approval of the final version to be published, and accountable for all aspects of the publication. **Sara A. Hurvitz:** Conceptualization, critical review of the initial draft, approval of the final version to be published, and accountable for all aspects of the publication. **Stephen Johnston:** Conceptualization, critical review of the initial draft, approval of the final version to be published, and accountable for all aspects of the publication. **Gregory A. Vidal:** Conceptualization, critical review of the initial draft, approval of the final version to be published, and accountable for all aspects of the publication.

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