

OncLive[®]

BREAST CANCER
JANUARY 11, 2023
VIRTUAL WORKSHOP

SCIENTIFIC INTERCHANGE & WORKSHOP

Updates and Advances in
Early-Stage **Breast Cancer**

The background of the lower half of the image is a dark blue breast cancer scan. A central, glowing green tumor is visible, surrounded by a network of white and light blue geometric lines, including circles and dashed lines, which suggest a scientific or technological theme. Small white plus signs are scattered throughout the scan area.

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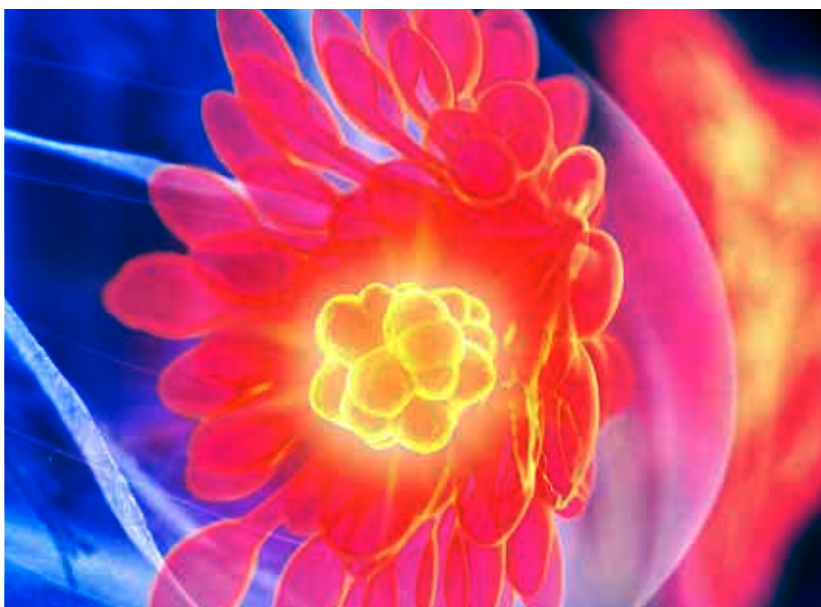
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Breast Cancer



KEY TAKEAWAYS

- ▶ A number of clinical factors are important to consider when identifying patients with hormone receptor (HR)-positive/HER2-negative (HR+/HER2-), early breast cancer (EBC) who have a high risk of recurrence; these include the degree of lymph node involvement, tumor size, Ki-67 index, and genomic signatures assessed with commercial assays.
- ▶ Ki-67 scores offer important insights into guiding treatment selection, particularly among patients with node-positive disease who may benefit from abemaciclib but who may not qualify for treatment solely based upon disease grade or tumor size. In March 2023, the FDA removed the Ki-67 scoring requirement for the use of abemaciclib in patients with HR+/HER- EBC.
- ▶ Subanalyses of results from the TAILORx and RxPONDER trials comparing endocrine treatment with chemoendocrine therapy in treating HR+/HER2- EBC are important for gaining insight regarding disparities in EBC; however, higher recruitment from various racial and ethnic groups is necessary to determine whether modified treatment approaches would benefit specific populations.
- ▶ Inherent differences, including kinase selectivity, among CDK4/6 inhibitors may explain response differences observed in EBC with high-risk features. Abemaciclib appears to have a broader spectrum of activity, and it may offer greater benefit in patients with EBC that features greater genomic instability or clonal heterogeneity.
- ▶ The advent of CDK4/6 inhibitors has played an important role in transforming the treatment landscape for patients with HR+/HER- EBC, including those with high-risk disease. However, treatment-related adverse events (AEs) can limit treatment, highlighting an ongoing need for monitoring and prevention strategies to improve AE management in patients being treated with CDK4/6 inhibitors.
- ▶ Future studies, including those involving intrinsic subtyping and genomic and proteomic characterization, are needed to better identify patients who will likely benefit from treatment with CDK4/6 inhibitors vs those who have a greater potential for disease recurrence. In addition, studies that assess the predictive power of genomic assay results are needed.

Updates and Advances in Early-Stage Breast Cancer

INTRODUCTION

ON JANUARY 11, 2023, the *OncLive*® Scientific Interchange and Workshop: Updates and Advances in Early-Stage Breast Cancer featured a panel of experts who specialize in the treatment of breast cancer. **Joyce O'Shaughnessy, MD**, Celebrating Women Chair in Breast Cancer Research at Baylor Medical Center and director of the Breast Cancer Research Program at Texas Oncology, US Oncology, in Dallas, Texas, served as the moderator.

The goals of the interchange were to evaluate clinical characteristics and biomarkers in assessing recurrence risk in patients with HR+/HER2- EBC and identifying high-risk patients who may benefit from escalated adjuvant endocrine strategies; obtain insight into treatment selection as well as monitoring and management of AEs for patients with HR+/HER2- EBC to optimize outcomes and patient quality of life; discuss racial and ethnic disparities in EBC diagnosis and treatment selection and how they may impact patient care; and describe the shared decision-making process between patients with EBC and their multidisciplinary care team to enhance adherence to the treatment plan.

RISK STRATIFICATION OF PATIENTS WITH HIGH-RISK EBC

BC remains the most common malignancy diagnosed among women in the United States, accounting for approximately 31% of all cancer cases.¹ HR+/HER2- BC is the most frequently reported subtype; it is associated with approximately 68% of all BC cases in women.² Most patients with HR+/HER2- BC are diagnosed in early stages of the disease, contributing to higher rates of survival.^{2,3} However, approximately 20% of patients with HR+/HER2- EBC

will experience disease recurrence within 10 years, highlighting the need for biomarkers and other clinical factors to identify patients who are at high risk for recurrence and determine treatment strategies to help manage recurrent disease.^{4,5}

Defining High-Risk EBC

Criteria established in major clinical trials, such as OlympiA (NCT02032823) and monarchE (NCT03155997), have played a major role in defining high-risk disease among patients with HR+/HER2- EBC.^{6,7} In the OlympiA trial, assessment was based on prior adjuvant or neoadjuvant therapy. Patients with prior adjuvant therapy needed to have at least 4 pathologically confirmed positive lymph nodes. For patients with prior neoadjuvant therapy, a pathological complete response was not required; however, all eligible patients had a pretreatment clinical and posttreatment pathological stage, estrogen receptor (ER) status, and histological grade (CPS+EG) score of 3 or greater.⁶ In the monarchE trial, high risk was defined by the presence of 4 or more pathologically confirmed positive lymph nodes or 1-3 positive lymph nodes and 1 of the following: grade 3 histology, tumor size of 5 cm or greater, or Ki-67 score of 20% or greater.⁷

Assessing Risk for Recurrent Disease in EBC

Data from the International Breast Cancer Study Group (IBCSG) trial showed that the risk for recurrence in EBC was greatest during the first 5 years after surgery (10.4%); it typically peaked between the first 2 years (15.2%) and then decreased between years 5 and 10 (4.5%), with an approximate 1% to 2% risk of recurrence.⁸ Among patients with ER-positive (ER+) EBC, the risk for recurrence was lower during the first 5 years compared with patients with

ER-negative (ER-) EBC (9.9% vs 11.5%, respectively). At 5 years, the risk for recurrence became continuously greater in patients with ER+ disease versus those having ER- disease.⁸ There was also a positive correlation between the number of positive lymph nodes and the risk for recurrence, with the greatest risk observed among patients with at least 4 positive nodes.⁸ Tumor size and menopausal status did not influence the risk of recurrence.

Patient age and tumor size are both well-established predictors for BC recurrence, with a younger age (< 50 years) and larger tumor size (diameter, > 2 cm) associated with a greater risk for distant return of disease.⁹ Tumor grade may also contribute to the risk for recurrence, with the highest risk found for poorly differentiated tumors and the lowest risk noted for tumors that were well- or moderately differentiated.⁹ Other clinical factors (eg, Ki-67 score, residual cancer burden, and genomic factors assessed via gene assays) have also been identified as important prognostic factors for disease relapse.¹⁰

Biomarker Testing in Patients With HR+/HER2- EBC

Along with recurrence score algorithms, assays that evaluate expression of specific genes and proteins involved in tumor proliferation and invasion have been developed to better assess the risk for recurrent disease in patients with EBC.⁹ Updated guidelines from the National Comprehensive Cancer Network (NCCN) published in 2023 and American Society of Clinical Oncology (ASCO) published in 2022 provide recommendations surrounding biomarker testing with specific genomic assays, including Oncotype DX, MammaPrint, EndoPredict, Prosigna, and Breast Cancer Index.^{10,11}

In premenopausal patients with ER+/HER2- EBC, ASCO guidelines

recommend biomarker testing to guide adjuvant endocrine treatment and chemotherapy with Oncotype DX in node-negative disease. In postmenopausal patients who have 3 or fewer positive nodes, biomarker testing using gene assays, Ki-67 index, and immunohistochemistry (IHC) platforms is recommended.¹¹

NCCN guidelines indicate that biomarker assessment using the 21-gene Oncotype DX panel has prognostic value; this panel can also be used to predict outcomes of chemotherapy treatment in lymph node-negative disease for both pre- and postmenopausal patients, including postmenopausal patients with fewer than 3 identified nodes. The 70-gene MammaPrint, 50-gene Prosigna, and 12-gene EndoPredict are also listed by NCCN guidelines, but they are only recommended as useful prognostic tools.¹²

Ki-67 Index: A Prognostic Factor for BC

First described in 1983, Ki-67 is a nuclear protein expressed in cycling cells during the G1, S, G2, and M phases and established as an indicator of tumor proliferation.^{13,14} Assessment of Ki-67 expression in tumor cells is a useful prognostic marker in clinical trials, with higher levels of Ki-67 being associated with lower disease-free survival and a higher risk for disease recurrence.^{14,15} Among patients with HR+/HER2- EBC, a high Ki-67 index (> 20%) has a positive correlation with larger tumor size and high grade. Patients with higher levels of Ki-67 expression in tumor cells have lower 5-year disease-free survival than do those with lower levels of Ki-67 expression, with a stronger association noted among younger patients and those with more advanced stage disease.^{15,16}

Several clinical trials have also investigated the potential role of Ki-67 as a predictive marker for adjuvant therapy, with an underlying rationale

that higher sensitivity to chemotherapy in patients with ER- tumors may be associated with higher rates of tumor proliferation. However, study results have been inconclusive, with some data demonstrating a high Ki-67 score to be predictive of benefit for adjuvant chemotherapy, whereas other data have shown no observed benefit.¹⁷⁻¹⁹

IHC is an established method for measuring Ki-67 levels, and it is widely considered the assay of choice for Ki-67 assessment. However, a substantial degree of variability in testing methodologies and data interpretation remains, highlighting the need for standardization.^{17,20}

Circulating Tumor DNA: A Potential Predictor for Relapse-Free Survival

More recently, circulating tumor DNA (ctDNA) has emerged as a potential predictive marker for disease relapse across various cancer types, including EBC. The multicenter, prospective EBLIS study evaluated the utility of ctDNA in early detection of overt metastatic and/or recurrent disease.²¹ Plasma ctDNA was detected in 89% of patients with disease relapse, with differing sensitivity noted according to disease subtype (HR+/HER2-, 82%; HR+/HER2-positive, 100%; triple-negative BC, 100%). All ctDNA-positive patients experienced disease relapse within 50 months after surgery, with molecular relapse detected up to 2 years prior to patient relapse (median, 8.9 months). The results suggested that ctDNA is a promising tool in predicting relapse. Investigators concluded that further studies are needed to validate these findings.²¹

STAKEHOLDER INSIGHTS

To identify patients with HR+/HER2- EBC at high risk of recurrence, the faculty consider a number of clinical factors (eg, degree of lymph node involvement, tumor size, Ki-67 index, and

genomic signatures assessed with Oncotype DX or MammaPrint assays). Some faculty offer germline mutation testing to all patients when appropriate according to guidelines, whereas others reserve germline testing for young patients with ER+ BC.

Generally, premenopausal women with multiple positive nodes are treated with chemotherapy, whereas genomic signatures are typically used to guide treatment for women with little to no nodal involvement. Patients at low risk of recurrence are typically treated with ovarian function suppression rather than chemotherapy.

The faculty expressed that identifying patients who are at high risk of recurrence before surgery can influence surgical decisions depending on whether the patient receives neoadjuvant therapy; this often involves consultations between surgeons and medical oncologists.

Some faculty noted that Ki-67 testing is typically performed on all patients at their practice sites to determine which patients should have assessment of genomic signatures. However, experts acknowledged that the practice of omitting genomic signature testing for patients with low Ki-67 scores may need more supporting data.

The duration of endocrine therapy for patients with high-risk EBC depends on cancer stage and patient age. The Breast Cancer Index test is often used in patients with disease at lower stages to predict which patients will likely benefit from extending endocrine therapy beyond 5 years. The faculty agreed that nuance and discretion are important in determining an optimal duration of treatment of 7 years compared with 10 years.

RACIAL AND ETHNIC DISPARITIES IN PATIENTS WITH HIGH-RISK EBC

Racial and ethnic disparities in EBC outcomes continue to be a major health care challenge. The 21-gene recurrence score assay is an important tool for guiding treatment decisions for women with EBC.^{22,23} Poststudy analyses have been conducted on several prospective trials to detect racial and ethnic disparities among patients with a similar recurrence score.^{24,25}

TAILORx Trial

The TAILORx trial (NCT00310180) was a prospective study that compared endocrine therapy and chemoendocrine therapy in 10,253 women with HR+/HER2-, node-negative EBC. Patients were assigned to 1 of 4 treatment groups on the basis of a 21-gene recurrence score. Investigators sought to assess invasive disease-free survival (iDFS), the rate of recurrence at distant or local tumor sites, and overall survival (OS).²²

Following publication of the initial study results, a subanalysis was conducted to evaluate the presence of racial and ethnic disparities in locoregional recurrence (LRR, defined as ipsilateral invasive in-breast, chest wall, or regional nodal recurrence without distant recurrence) in trial participants who had similar access to care. Among the 8782 patients eligible for analysis, reported race and ethnicity were non-Hispanic White (78.9%), non-Hispanic Black (7.2%), Hispanic (9.3%), and Asian (4.6%). With a median follow-up of 8 years, the reported overall LRR rates were lowest among non-Hispanic White patients (1.9%), followed by Hispanic patients (3.2%), Asian patients (3.9%), and non-Hispanic Black patients (4.2%). The adjusted analysis also showed that compared with non-Hispanic White patients, non-Hispanic Black and Asian patients were more likely to experience locoregional recurrence (HR, 1.94 and 2.04, respectively; $P < .05$).²⁴

RxPONDER Trial

The prospective, randomized RxPONDER trial (NCT01272037) compared endocrine therapy with chemoendocrine therapy in 5083 patients with HR+/HER2-, nodal stage N1 BC.²³ Investigators assessed iDFS, distant relapse-free survival (DRFS), time to distant recurrence or death, and OS.

Following the publication of the initial study results, a subanalysis was conducted to evaluate the presence of racial and ethnic disparities with regard to iDFS and DRFS.²⁵ Among the 4048 patients eligible for analysis, 70% identified themselves as non-Hispanic White, 6.1% as non-Hispanic Black, 15.1% as Hispanic, 8.0% as Asian, and 0.8% as Native American or Pacific Islander. Overall, 5-year iDFS was the lowest for non-Hispanic Black patients (87.0%) when compared with Asian (93.9%), non-Hispanic White (91.5%), and Hispanic (91.4%) patients. Compared with non-Hispanic White patients, non-Hispanic Black patients demonstrated a less favorable DRFS among both postmenopausal and premenopausal women.²⁵

STAKEHOLDER INSIGHTS

Results of the TAILORx and RxPONDER trial subanalyses are important to gain insight regarding disparities in EBC, and generated hypotheses tease out observed outcome disparities among patients of different racial and ethnic groups. However, higher recruitment in clinical trials from various races and ethnic groups is necessary to determine whether modified treatment approaches would benefit specific populations.

Faculty noted that the higher locoregional recurrence among high-risk patients in the TAILORx trial may have been influenced by an observed reluctance among Asian patients to receive chemotherapy and high rates of

insulin resistance among patients in the Hispanic population. They noted that high rates of obesity and diabetes among different racial and ethnic populations may also contribute to cancers with more aggressive biology and worse outcomes.

Factors contributing to lower enrollment in clinical trials among different racial and ethnic groups may include hesitation on patients' parts as well as physician biases to not encourage some patient populations to enroll in clinical trials. Faculty noted that access issues regarding payer coverage for oral therapies, lack of insurance, and transportation or logistical challenges are common among different racial and ethnic groups.

Faculty also highlighted that breast surgeons may have a more positive influence on patient choices regarding treatment and adherence than do general surgeons due to their more extensive education concerning BC treatment.

OPTIMAL TREATMENT OF HIGH-RISK, HR+/HER2- EBC

According to NCCN guidelines, adjuvant treatment of both premenopausal and postmenopausal patients with HR+ EBC often involves endocrine therapy with tamoxifen or aromatase inhibitors (AIs).¹² In premenopausal patients, endocrine therapy may be combined with either ovarian ablation or ovarian suppression using luteinizing hormone-releasing hormone analogs.¹² In patients with HR+/HER2- EBC that harbors germline *BRCA1/2* mutations with a CPS+EG score of at least 3 and residual disease following surgery, olaparib may be added to endocrine therapy.¹² The CPS+EG score takes into consideration the pretreatment clinical and posttreatment pathological stage, ER status, and disease grade. The addition of CDK4/6 inhibitors

to endocrine therapy may also improve outcomes in patients with high-risk, HR+/HER2- EBC.

CDK4/6 Inhibitors in High-Risk EBC

The protein kinases CDK4 and CDK6 play a crucial role in signaling pathways involved in cellular proliferation and cell cycle progression.²⁶ The first CDK4/6 inhibitor to receive FDA-approved indications for the treatment of HR+/HER2-, advanced or metastatic BC was palbociclib in 2015, followed by ribociclib and abemaciclib in 2017.²⁶⁻²⁸ Abemaciclib received FDA approval as monotherapy for HR+/HER2-, metastatic BC in patients who had disease progression following endocrine therapy and chemotherapy. In October 2021, based on the results of the monarchE trial, abemaciclib plus endocrine therapy was granted approval for adjuvant therapy in patients with HR+/HER2-, node-positive EBC with a high risk of recurrence and a Ki-67 score of 20% or greater; approval of the companion Ki-67 IHC MIB-1 pharmDx assay accompanied this newly granted indication.²⁸⁻³¹ In March 2023, the FDA removed the Ki-67 requirement for the

use of abemaciclib in patients with HR+/HER2- EBC.³²

Trials evaluating the addition of CDK4/6 inhibitors to endocrine therapy in patients with HR+/HER2-, high-risk BC are shown in **TABLE 1**.^{7,33-37} Current NCCN and ASCO guidelines recommend use of CDK4/6 inhibitors in combination with endocrine therapy as a preferred first-line approach for systemic therapy in patients with HR+/HER2- EBC, with abemaciclib specifically recommended for the treatment of node-positive EBC with a high risk of recurrence (defined as having ≥ 4 positive nodes or 1-3 positive nodes and 1 of the following: Ki-67 score $\geq 20\%$, histologic grade 3 disease, or tumor size ≥ 5 cm).^{12,38}

monarchE TRIAL

The randomized, open-label, phase 3 monarchE study evaluated endocrine therapy with or without the addition of abemaciclib treatment in patients with HR+/HER2-, node-positive EBC and a high risk for disease recurrence.³⁹ Among the 5637 patients in the intention-to-treat (ITT) population, the addition of abemaciclib reduced the risk of invasive disease when compared

with placebo (estimated 4-year iDFS, 85.8% vs 79.4%, respectively).³⁹ The risk of disease recurrence was also lower in the abemaciclib group than in the placebo group (estimated 4-year DRFS, 88.4% vs 82.5%).³⁹

The most frequently reported any-grade AEs among patients receiving abemaciclib plus endocrine therapy included diarrhea, neutropenia, and fatigue; arthralgia, hot flush, and fatigue were most common in the placebo group. AEs of grade 3 or greater were more common in the abemaciclib group and included neutropenia (19.6%), leukopenia (11.4%), and diarrhea (7.8%).³⁹ In the abemaciclib group, 6.4% of patients discontinued treatment due to AEs (eg, diarrhea and fatigue); treatment interruption and dose reductions were necessary for 61.7% and 43.6%, respectively, of patients given abemaciclib.³⁹

PALLAS TRIAL

The prospective, randomized, phase 3 PALLAS trial (NCT02513394) evaluated the addition of palbociclib to endocrine therapy in patients with HR+/HER2- EBC.^{34,35} In all, 5761 patients received endocrine therapy for 5 years and

TABLE 1.
CLINICAL TRIAL DATA FOR ADJUVANT CDK4/6 INHIBITORS IN COMBINATION WITH ENDOCRINE THERAPY IN EBC^{7,33-37}

Trial (NCT number)	CDK4/6 inhibitor	3-year iDFS (T vs C), %	DRFS (T vs C), %	Most common AEs (any grade), %
monarchE (NCT03155997)	Abemaciclib	89 vs 83	90 vs 86	Diarrhea, 82 Neutropenia, 45 Fatigue, 38
PALLAS (NCT02513394)	Palbociclib	88 vs 89	86 vs 88	Fatigue, 38 Arthralgia, 37 URTI, 28
PENELOPE-B (NCT01864746)	Palbociclib	81 vs 78	No difference	Leukopenia, 99 Neutropenia, 96 Anemia, 74
NATALEE ^a (NCT03701334)	Ribociclib	NR	NR	NR

AE, adverse event; C, control; DRFS, distant relapse-free survival; iDFS, invasive disease-free survival; NCT, National Controlled Trial; NR, not reported; T, treatment; URTI, upper respiratory tract infection.

^aTrial in progress is active but not recruiting; anticipated first-analysis results expected in 2023

palbociclib for 2 years. At a median follow-up of 31 months, invasive disease occurred in 8.8% of patients receiving palbociclib plus endocrine therapy compared with 9.1% of patients in the endocrine monotherapy group. Four-year iDFS was also similar among the treatment groups, and subgroup analysis did not find any differences between the treatment arms. The investigators of this trial concluded that adding palbociclib to endocrine therapy was not superior to endocrine therapy alone in patients with HR+ EBC. Compared with the endocrine monotherapy group, those receiving palbociclib plus endocrine therapy reported more AEs, including neutropenia, leukopenia, anemia, thrombocytopenia, and fatigue.³⁵

PENELOPE-B TRIAL

The PENELOPE-B trial (NCT01864746) was a double-blind, placebo-controlled, phase 3 study of palbociclib plus endocrine therapy in patients with HR+/HER2- BC.³⁶ In all, 1250 patients had a high risk of relapse and had residual disease after treatment with neoadjuvant chemotherapy. After a median follow-up of 42.8 months, palbociclib plus endocrine therapy did not improve iDFS compared with endocrine therapy alone, and no differences between the subgroups were noted.

Several AEs of any grade and of at least grade 3 noted in the palbociclib group were neutropenia and leukopenia; AEs of any grade that were more commonly seen in the palbociclib group included thrombocytopenia, anemia, fatigue, hypocalcemia, stomatitis, constipation, cough, and infection. Common serious AEs included infections and vascular AEs, which did not differ among the groups.³⁶

STAKEHOLDER INSIGHTS

Inherent differences including kinase selectivity were noted among the CDK4/6 inhibitors;

this may explain response differences observed in EBC with high-risk features. Abemaciclib, in particular, appears to have a broader spectrum of activity, and it may offer greater benefit in EBC with more extensive genomic instability or clonal heterogeneity. Conversely, experts agree these inherent differences seem to play a lesser role among patients with endocrine-sensitive EBC, with use of CDK4/6 inhibitors producing similar observed responses among patients in this population.

Participants expressed that the monarchE treatment regimen is generally used for most patients who qualify; however, factors used to identify candidates for treatment varied among clinicians. Some experts only use trial inclusion criteria associated with FDA approval to determine eligibility; others use NCCN and ASCO guidelines, although they may also consider patient age and comorbidities, tumor stage and size, and Ki-67 score.

Although many patients experience some degree of diarrhea with abemaciclib therapy, experts noted AEs are generally manageable, and most patients are able to tolerate treatment. However, a number of older patients with multiple comorbidities choose to forego treatment with abemaciclib due to its associated AEs.

Although elevated creatinine levels are often observed in patients receiving abemaciclib, this effect is not toxicity related; rather, it is a result of abemaciclib competing for a transport protein necessary for creatinine excretion, and there is no clinical consequence. Faculty noted the need to provide reassurance to patients and to educate primary care physicians regarding this phenomenon.

STRATEGIES FOR PROMOTING ADHERENCE AND PERSISTENCE TO ORAL CDK4/6 INHIBITORS IN EBC

The advent of CDK4/6 inhibitors has played an important role in transforming the treatment landscape for HR+/HER- EBC, including therapy for patients with high-risk disease. However, treatment-related AEs (eg, diarrhea, hepatobiliary toxicity, QT prolongation, neutropenia, venous thromboembolism, and interstitial lung disease) remain a limiting factor for CDK4/6 therapy, with many patients needing dose reductions or eventual treatment discontinuation (TABLE 2).^{7,33,34} Consequently, monitoring and prevention strategies are needed to improve AE management in patients given CDK4/6 inhibitors.

Monitoring and Prevention Strategies for CDK4/6 Inhibitor-Related AEs

Diarrhea is one of the most frequently reported nonhematologic AEs among patients receiving treatment with CDK4/6 inhibitors. Overall incidence varies among agents, with reported frequency (any grade) greatest among patients receiving abemaciclib (84%), followed by those using ribociclib (30%) and patients treated with palbociclib (25%).⁴⁰⁻⁴² Generally, diarrhea is observed most commonly during the early treatment period, with incidence decreasing over time. Management of AEs is generally achieved with use of antidiarrheal medications, although dose reductions may be necessary for some patients.

The most common CDK4/6 inhibitor-related hematologic AE is neutropenia, which frequently presents as grade 3; incidence varies among patients given palbociclib (any grade, 81%; grade 3, 55%), ribociclib (any grade, 74%; grade 3, 52%), or abemaciclib (any grade, 46%; ≥ grade 3, 20%).⁴⁰⁻⁴² Generally, neutropenia is managed with dose modifications and periodic monitoring of complete blood count; however, a

TABLE 2.
SUMMARY OF CDK4/6 INHIBITOR-RELATED ADVERSE EVENTS AND ASSOCIATED MONITORING AND PREVENTION STRATEGIES^{7,33,34}

AE	CDK4/6 inhibitors	Strategies for monitoring and prevention
Diarrhea	Abemaciclib, palbociclib, ribociclib	Administer antidiarrheal therapy and oral hydration; notify primary physician.
Hepatobiliary toxicity	Abemaciclib, ribociclib	Obtain baseline LFT results prior to treatment initiation, then, <i>with abemaciclib</i> , monitor LFTs every 2 weeks for the first 2 months, monthly for the next 2 months, then as indicated; or <i>with ribociclib</i> , monitor LFTs every 2 weeks for the first 2 cycles, then at the beginning of each subsequent 4 cycles.
QT prolongation	Ribociclib	Obtain baseline ECG prior to treatment initiation; repeat ECG on day 14 of cycle 1, at the beginning of cycle 2, then as indicated. Monitor electrolytes at the beginning of each cycle for 6 cycles, then as indicated.
Neutropenia	Abemaciclib, palbociclib, ribociclib	Obtain baseline CBC prior to treatment initiation, then, <i>with abemaciclib</i> , monitor CBC every 2 weeks for 2 months, monthly for the next 2 months, then as indicated; or <i>with palbociclib</i> , monitor CBC on days 1 and 15 of the first 2 cycles, then as indicated; or <i>with ribociclib</i> , monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, then as indicated.
VTE	Abemaciclib	Monitor for signs and symptoms of thrombosis or pulmonary embolism.
ILD/pneumonitis	Abemaciclib, palbociclib, ribociclib	Monitor for pulmonary symptoms indicating ILD or pneumonitis (eg, hypoxia, cough, dyspnea).

AE, adverse event; CBC, complete blood count; ECG, electrocardiogram; ILD, interstitial lung disease; LFTs, liver function tests; VTE, venous thromboembolism.

small number of patients may require treatment discontinuation.⁴⁰⁻⁴²

Interstitial lung disease (ILD) has been observed in a small number of patients treated with CDK4/6 inhibitors, with the highest incidence reported in patients treated with abemaciclib (2.1%) compared with those given palbociclib and ribociclib (0.3% each).⁴³ Among patients treated with abemaciclib, the majority of ILD cases were reported to be low grade and often asymptomatic. Symptomatic ILD is generally managed with steroids and antibiotics, with dose modification or treatment discontinuation rarely needed for most patients.⁴⁰

Increased transaminase levels have also been reported among patients receiving abemaciclib (any grade, 15.5%; grade 3, 3.5%) or ribociclib (any grade, 15%; grade 3, 7%), with the majority of cases reported as low-grade events.^{40,42} Management strategies generally include liver function test monitoring every 2 weeks for the first 2 months or cycles and then as

indicated by manufacturer labeling.^{26,28}

Dosage modification, including dose reductions or holds, are generally used to manage events of grade 3 or greater, and treatment discontinuation is uncommon for most patients.⁴⁰

Cardiovascular-related AEs, including venous thromboembolism (VTE) and QT prolongation, have been observed in a small number of patients; they appear to be specific to use of abemaciclib and ribociclib, respectively.^{39,42} VTEs have been reported in approximately 2.5% of abemaciclib-treated patients, presenting most commonly as grade 3 pulmonary embolism. The majority of these cases are managed with anticoagulant therapy, with about 56% of patients requiring dose holds. QT prolongation has been reported in approximately 6.5% of ribociclib-treated patients, with 1.2% occurring as grade 3 or 4 events.^{26,42} Management strategies include electrocardiographic (ECG) monitoring at baseline and prior to treatment initiation, with subsequent monitoring performed as indicated by

manufacturer labeling. Based on ECG results, treatment interruptions or dose reductions may also be necessary as a part of management strategy.⁴²

STAKEHOLDER INSIGHTS

Diarrhea is by far the most commonly observed AE in patients receiving treatment with abemaciclib. Experts highlighted the importance of discussing the risk of diarrhea with patients prior to treatment initiation and providing instruction for managing AEs with loperamide and diet optimization. They further noted that a significant percentage of patients may require dose reductions to improve the patient's quality of life and allow treatment continuation.

One participant shared that a slow-start abemaciclib treatment strategy was successfully implemented at their practice site to help patients better

tolerate AEs and avoid eventual dose reductions. The slow-start abemaciclib treatment strategy begins with once-daily dosing for several weeks, followed by an increase to twice-daily dosing to allow patients a longer, more gradual adjustment period when starting treatment. Experts noted that in terms of utility, this slow-start strategy would be most appropriate for the adjuvant setting than the metastatic setting, where a more rapid response to treatment is desired.

Although abemaciclib is not associated with renal toxicity, experts noted that it can cause elevated creatinine levels that could potentially mask worsening renal function in patients with prerenal insufficiency. In cases in which worsening renal function is suspected, the faculty advised caution and recommended that patients be referred to a renal specialist.

LOOKING AHEAD

To conclude the panel discussion, experts highlighted the importance of Ki-67 scores, particularly in patients with 1 to 3 positive lymph nodes. They noted that some of these patients may benefit from abemaciclib use, but they may not qualify for treatment solely based on disease grade or tumor size.

Faculty expressed the overall need for future studies to better characterize patients who will likely benefit from abemaciclib. Faculty noted that study designs with intrinsic subtyping and genomic and proteomic characterization may be helpful in identifying patients who may benefit from abemaciclib compared with those who are likely to experience disease recurrence. Panelists also expressed a need for studies to assess the predictive power of genomic signature profiles like Oncotype DX and MammaPrint. ■

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Expert Perspectives: Treatment Decisions in Early-Stage Breast Cancer



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INTRODUCTION

In video interviews with *OncLive*[®], panelists Joyce O'Shaughnessy, MD; and Gregory Vidal, MD, PhD; shared insights about treatment advances in high-risk, hormone receptor-positive (HR+)/HER2-negative (HER2-) early-stage breast cancer and data that impact treatment decisions. They also provided perspectives on racial and ethnic disparities in breast cancer treatment and the role of socioeconomic factors on treatment outcomes.

**Interview transcripts are edited for readability.*

➤ TO WATCH THE VIDEO INTERVIEWS, VISIT [ONCLIVE.COM](https://www.onclive.com)

***OncLive*[®]: What patient characteristics do you consider when deciding between PARP inhibitors and CDK4/6 inhibitors in patients with HR+/HER2- early-stage breast cancer?**

JOYCE O'SHAUGHNESSY, MD: Some patients are eligible to receive adjuvant abemaciclib or adjuvant olaparib, because they have high-risk, HR+/HER2- early-stage breast cancer. [These patients] would have fit the monarchE [trial] eligibility criteria [(ie, ≥ 4 positive nodes, or 1-3 nodes and either tumor size ≥ 5 cm, histologic grade 3, or central Ki-67 score ≥ 20%)].

[In] the OlympiA trial for [patients with HER2- early-stage breast cancer with mutations in *BRCA1* or *BRCA2*], again, patients had to be [at] very high risk. They had to have 4 or more [positive] lymph nodes. If [patients] had surgery first and then [received] chemotherapy, [they were] eligible for randomization to olaparib [or] placebo. [Patients] had to have 4 or more [positive] lymph nodes, or, if they had preoperative chemotherapy, they had to have residual disease and a CPS+EG (clinical stage and posttreatment pathologic stage plus estrogen receptor status and tumor grade) score of 3 or higher. There is an easily accessible algorithm [online that allows you to] plug in the needed parameters to

get the CPS+EG score. So there are patients [who are at] very high risk [who] are eligible for [PARP inhibitors and CDK4/6 inhibitors].

These high-risk patients generally receive chemotherapy. After that, most [doctors] prioritize [use of] the PARP inhibitor olaparib. Germline *BRCA1* or *BRCA2* mutations are such a powerful target [and] lead to such a profound change in the cancer's inability to repair double-strand [DNA] breaks. There is such a high degree of synthetic lethality with the PARP inhibitors in that context—very specific target—that most of us will prioritize olaparib over abemaciclib for those patients, along with endocrine therapy. We never want to combine them, because they would be too toxic [when] combined.

For very high-risk patients [(eg, those with ≥ 4 positive lymph nodes after 1 year of olaparib treatment)], some physicians will [follow up with] 2 years of abemaciclib. I am not doing that, because we do not have any safety or efficacy data. There [are] some early data in the metastatic setting that patients with germline *BRCA1* or *BRCA2* mutations who have HR+/HER2- metastatic breast cancer and are treated with CDK4/6 inhibitors have a considerably shorter progression-free survival with [use of] the CDK4/6 inhibitors than [do patients

with] wild-type [genetic results]. Until we have more data, I am not sequencing abemaciclib after olaparib, but I know some physicians are willing to do that. I prioritize the PARP inhibitor over abemaciclib for [patients with] high-risk, germline *BRCA* mutations.

OncoLive®: Have any additional findings from the monarchE trial influenced your clinical practice?

O'SHAUGHNESSY: At the San Antonio [Breast Cancer Symposium] 2022, Stephen Johnston, [MD, presented an update on the] 4-year, landmark, invasive and distant disease-free survival data [from the monarchE trial]. Patients have all been off adjuvant abemaciclib [treatment] for a while. It was just great to see the curves continuing to pull apart. They are not even paralleling each other with every year of follow-up.

There was a 6.4% absolute improvement in invasive disease-free survival, and a 5.9% absolute improvement in distant relapse-free survival, with 50% fewer patients [in the abemaciclib arm] having developed metastatic disease [compared with endocrine monotherapy]. There are fewer deaths on the abemaciclib arm, as well.

Furthermore, now, with the 4-year landmark analysis, when you look at the high Ki-67 [score of] 20% or [greater] versus less than 20%, the hazard ratio for both groups in favor of abemaciclib is 0.6. [There is] a 40% reduction in the risk of developing an invasive disease-free survival event with abemaciclib, regardless of the Ki-67 [score]. The patients who have the high Ki-67 [score] are recurring much more quickly, but the relative improvement is the same. Patients with a low Ki-67 [score who were not given] abemaciclib had an 82% invasive disease-free survival rate. So that is still a high risk of recurrence for that low Ki-67 population at 4 years. I am applying the monarchE data in my practice and offering adjuvant abemaciclib to all patients who would have been eligible for [the] monarchE [trial].

OncoLive®: What CDK4/6 inhibitors in development for breast cancer are you most excited about?

O'SHAUGHNESSY: The metastatic data with regard to the CDK4/6 inhibitors [have] become quite mature. Three first-line trials with ribociclib have shown [a] statistically significant survival advantage. Unfortunately, first-line palbociclib did not [demonstrate] a significant survival advantage [in the PALOMA-2 trial]. [In] the MONARCH 2 trial, some of the patients had a survival advantage with [first-line] abemaciclib. It was a combined first- and second-line cohort. We are waiting on the results of MONARCH 3, which is [investigating] first-line abemaciclib [combined] with an aromatase inhibitor. The data look very good; [however], we only have interim analysis data [at this time]. It is not yet statistically significant, but there is a very large delta in survival with abemaciclib versus placebo in the first-line setting. We are waiting on the final results, but it looks very promising. The

other data we are waiting for [are results from] the NATALEE trial [looking at patients with] early-stage, high-risk [breast cancer being treated] with 3 years of adjuvant ribociclib.

OncoLive®: Considering disparities in breast cancer care, what is the importance of recognizing the individual needs of each patient depending on their racial and ethnic characteristics and socioeconomic status?

GREGORY VIDAL, MD, PhD: For one, every individual is different. There are some groups of patients who are more likely to be impacted by [socioeconomic] factors than [are] others. In my area in Memphis, patients [belonging to racial or ethnic minority groups] tend to be more under- [or] uninsured. Finance is more of an issue for some [patients in] that population. But, also, biology is very different from one [racial or ethnic] population [to another]. All of these factors have to be taken into consideration when [assessing a patient] for treatment.

From a breast cancer [treatment] perspective, we certainly follow [treatment] guidelines to make sure that every patient gets the appropriate care in terms of mammogram, ultrasound, biomarker receptors, tumor type, when to do surgery, [whether and] when to give neoadjuvant chemotherapy, [and] what type of chemotherapy to use based on histology. It is very important that the [approach is] standardized regardless of the [race, ethnicity, or socioeconomic status of the] patient.

RxPONDER, a large phase 3 trial, recruited both patients [belonging to ethnic or racial minority groups] and White patients. Although there were more White patients, [all patients received] standardized treatment. We now know that patients [belonging to ethnic or racial minority groups], even [when receiving] very similar treatment, actually had worse outcomes [compared with White patients]; so there is a biology aspect that plays a role. We [also] have to consider other social determinants, [such as] whether those patients who are underinsured and, therefore, presenting at a later stage need more aggressive treatment...[or require] more assistance with transportation [to get to appointments]... [and arrive] at the time that you need them to come to get their biopsy.

[We] also [need to consider] other things, like comorbidities. Patients who have diabetes, which is a disease that is very common [in the Black] population, are likely to have more neuropathy; [therefore], the type and dose of chemotherapy matter. Heart health [has] to be taken into consideration. Whether...[a patient has] the support that they need at home and who comes with them [to appointments are] 2 important factors. [Another factor is if a patient is] going to take your recommendation. A lot of folks have some mistrust [of the health care system], and [they] may decide to not take your advice. Even with clinical trials, [some patients belonging



Gregory Vidal, MD, PhD

“We need to stop thinking [there is a] one-size-fits-all [solution] and be able to tailor our drug and treatment [approach] to particular [patient] populations.”

to ethnic or racial minority groups] are more hesitant to participate. And some of those trials are where you get your best care and the newest drugs. These factors need to be considered when [developing a treatment plan].

OncLive®: Does your institution, or other organizations you know of, offer resources that patients can use to optimize their treatment?

VIDAL: There are national advocacy groups and locally available assistance [programs, including] the social work system, that can assist patients [in need]. But at West [Cancer Center & Research Institute], we try to make sure that [every patient] gets equal care. We have navigators who follow up with patients, especially patients who report that they have [an] issue, and try to provide them the best support. There is the West Cancer Foundation, which is within the city, that provides assistance for [patients with] breast cancer, regardless of whether they are treated at West. It has the same name, but it is independent of West. They provide financial and other assistance for patients in need, regardless of [racial or ethnic background] or geographic location.

There are ways in our intake process to identify the social determinants of health based on surveys and patient reports; [we] utilize that data to figure out who needs assistance and then provide [that] assistance the best way we can so that all patients have equal [access to treatment and care.]

OncLive®: What unmet needs remain regarding disparities in breast cancer diagnosis and care?

VIDAL: The biggest [unmet need] is equal outcome based on presentation. We still see, [based on results of the RxPONDER] study, that patients [belonging to racial or ethnic minority groups who are diagnosed with breast cancer tend] to have worse [outcomes]. We need to [ensure] that every

[clinical study] is representative of the population, meaning if [13% of the population of the United States belongs to racial or ethnic minority groups], your study should at least meet that [statistic]. We need to understand how each drug treatment and diagnostic assay behaves in different patients, because we know [that] biology is different. We can then tailor treatment for best outcomes. If there is a drug that [seems to offer a] better [treatment] outcome in White patients compared to Black patients, then we need to investigate what drug would [offer] Black patients an equal outcome.

We need to stop thinking [there is a] one-size-fits-all [solution] and be able to tailor our drug and treatment [approach] to particular [patient] populations. I encourage the decision makers—the pharmaceutical companies and the FDA—to continue [enforcing] equal or at least high-level recruitment [of patients belonging to ethnic or racial minority groups] in [clinical] trials. [We] also [need] to encourage [these] patients to participate in trials to have a [better] understanding of the outcome and tolerability of drugs [being investigated to treat breast cancer in all patient populations]. The good thing is [that] the reason we [are] having this conversation right now is because there is a push and understanding that we need to do better.

Social determinants of health, like insurance and corporate finances, also play a huge role in outcomes. Patients [belonging to racial or ethnic minority groups] tend to [be] underinsured or [have] no insurance. [These patients] tend not to get the same level of care [and] tend to come to clinic later [for treatment], because they [do not have the] insurance [needed] to [access care or be diagnosed] earlier. We have to correct that. I believe everyone should have a basic minimum coverage to allow them [access to] similar care. That is [another] unmet need. ■

NOTES

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