Breast Cancer: Targets and Therapy

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REVIEW

Practical Guidance on Abemaciclib in Combination with Adjuvant Endocrine Therapy for Treating Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative High-Risk Early Breast Cancer

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Abstract: The most common subtype of breast cancer is hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer, accounting for 65–70% of all breast cancer cases diagnosed in the United States. Until 2015, single-agent endocrine therapy (ET) was the recommended first-line treatment for metastatic HR-positive, HER2-negative breast cancer. However, the paradigm has since shifted, as targeted therapy is now recommended in combination with ET. The cyclin-dependent kinase (CDK) 4/6 inhibitors have revolutionized the treatment of this breast cancer subtype, and combining either palbociclib, ribociclib, or abemaciclib with ET is now the standard first-line treatment for metastatic disease. Results of clinical trials in the metastatic setting have demonstrated that treatment with the combination of a CDK4/6 inhibitor and ET rather than ET alone is associated with longer overall survival, longer progression-free survival, and better objective response rates. Each of the CDK4/6 inhibitors has been investigated in combination with ET in patients with early-stage HR-positive, HER2-negative breast cancer who are at high risk of relapse. In October 2021, abemaciclib was the first CDK4/6 inhibitor approved in combination with ET by the US Food and Drug Administration for adjuvant treatment of patients with HR-positive, HER2-negative, high-risk early breast cancer. Herein, we provide practical guidance on the use of abemaciclib in combination with ET for HR-positive, HER2-negative, high-risk early breast cancer to assist clinicians in their day-to-day practice, and we review clinically relevant topics of dosing, side effect management, sequencing and optimal timing for initiation, and patient selection.

Keywords: abemaciclib, CDK4/6 inhibitors, high-risk early breast cancer

Introduction

Breast cancer is the most-diagnosed cancer and the second-leading cause of cancer-related deaths among women in the United States; in 2024, an estimated 313,510 new cases are expected to be diagnosed in both women and men and 42,780 estimated deaths from this disease.[1] Hormone receptor (HR)-positive breast cancer accounts for over two-thirds of all breast cancer cases.[2] Endocrine therapy (ET) is the backbone of standard-of-care treatment for HR-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer.[3] However, many patients who initially benefit from ET develop resistance during treatment.[4] Over the last decade, researchers have focused on identifying new treatment options for HR-positive, HER2-negative breast cancer with the goals of prolonging endocrine sensitivity, delaying the use of chemotherapy, extending overall survival (OS), and improving quality of life.[5,6]

For HR-positive, HER2-negative metastatic breast cancer (MBC), cyclin-dependent kinase (CDK) 4/6 inhibitors in combination with ET – either an aromatase inhibitor (AI) or fulvestrant, an estrogen receptor degrader – is now preferred

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over ET alone as first-line therapy, after results from multiple clinical trials consistently showed improved progression-free survival (PFS) and OS.[5] Furthermore, the toxicity profiles of CDK4/6 inhibitors are more acceptable than those of traditional cytotoxic chemotherapy treatments, which were previously recommended after a patient developed endocrine resistance. Taken together, these results have established the combination of CDK4/6 inhibitors and ET as the preferred first-line therapy for HR-positive, HER2-negative MBC.[7–11]

Historically, advances in treating MBC have preceded those in the adjuvant setting. Treatment of early breast cancer involves surgery, radiation, and systemic therapy in the neoadjuvant and/or adjuvant setting.[12] The goal is to minimize recurrence and development of distant metastases. However, up to 30% of patients with HR-positive, HER2-negative early breast cancer will experience a distant relapse even with curative intent multimodality therapy.[13] Increased risk of disease recurrence is driven by several clinical and pathologic factors including presence of nodal involvement, large tumor size, and high histologic grade.[14] There is variability in how high-risk early breast cancer is defined in clinical trials, but common features do exist. For example, the IRIDE (hIGh Risk Definition in breast cancer) working group defines HR-positive, HER2-negative high-risk early breast cancer as tumors with grade 3 histology, tumor size >5 cm and/or metastases in ≥4 lymph nodes (pT3-pT4 and/or pN2-pN3), Ki67 >30%, ER expression level <10% and/or PR expression level <20%, high residual cancer burden after neoadjuvant chemotherapy, and a high genomic signature.[15] In the monarchE adjuvant trial with abemaciclib, HR-positive, HER2-negative, high-risk early breast cancer was defined as tumors ≥4 positive axillary lymph nodes or 1–3 positive axillary lymph nodes with a histologic grade 3 tumor and/or size ≥5 cm, or a Ki67 of at least 20%.[16]

To improve outcomes for patients with node-positive, HR-positive and HER2-negative breast cancer, clinical trials have compared efficacy and safety outcomes in patients treated with ET alone and ET combined with CDK4/6 inhibitors. Studies involving the oral CDK4/6 inhibitors, palbociclib, abemaciclib, and ribociclib have been reported.[16–19] In October 2021, abemaciclib in combination with adjuvant ET received an initial US Food and Drug Administration (FDA) approval for treating node-positive, HR-positive, HER2-negative early breast cancer patients with tumors that have Ki67 (proliferation marker) ≥20%. The approval decision was based on the results of the monarchE trial, which showed longer invasive disease-free survival (iDFS) and distant recurrence-free survival (DRFS) rates with abemaciclib plus ET than with ET alone.[16,20] In March 2023, the FDA expanded approval of abemaciclib and ET for HR-positive, HER2-negative, high-risk early breast cancer, removing the Ki67 requirement.[21,22]

In this review, we will discuss evidence in support of using abemaciclib for treating patients with HR-positive, HER2-negative, high-risk early breast cancer. We will explore recent efforts to define patient and disease characteristics for determining who is likely to benefit most from adjuvant abemaciclib therapy. We will also compare the efficacy outcomes for abemaciclib and other CDK4/6 inhibitors in the adjuvant setting and review the safety and tolerability data for abemaciclib.

Abemaciclib, an Oral CDK4/6 Inhibitor

CDK4/6 inhibitors were initially of interest as novel agents because activation of CDK drives tumor growth in many cancer types.[23] D-cyclins bind and activate CDK4 and CDK6. In many cancers, CDK4 and CDK6 become hyperactivated, which drives uncontrolled tumor proliferation by decreasing dependency on external growth factors and signaling pathways.[24–26] In breast cancer, dysregulation of the cyclin D-CDK4/6-Rb pathway can mediate endocrine resistance; therefore, targeting this pathway with CDK4/6 inhibitors has been considered a promising therapeutic strategy.[27–29]

Abemaciclib is an oral, small-molecule CDK4/6 inhibitor that blocks the phosphorylation of retinoblastoma tumor suppressor protein and prevents progression through the cell cycle, resulting in arrest at the G1 phase.[30] This antitumor activity is specific to Rb-proficient cells. Preclinical studies show that abemaciclib has greater potency against CDK4 than against CDK6.[31] Torres-Guzman et al reported that the specificity of abemaciclib is 14-fold higher for CDK4/cyclinD1 than for CDK6/cyclinD3 complex.[32] The selectivity differences of the oral CDK4/6 inhibitors for their targets may explain their differences in monotherapy efficacy and toxicity profiles. CDK4/cyclin D1 is important for breast cancer proliferation, and CDK6 has a role in hematopoietic stem cell activation.[33,34] Abemaciclib is the only CDK4/6 inhibitor that is approved as a single-agent for the treatment of pretreated metastatic HR-positive, HER2-negative breast cancer, which could be related to its greater potency for CDK4.[35] Its lower inhibitory effect on CDK6 may explain why

myelosuppression incidence is lower with abemaciclib than with other oral CDK4/6 inhibitors.[36] Results of preclinical studies in breast cancer cell lines show that abemaciclib inhibits proliferation with higher potency than palbociclib and ribociclib do.[37] Abemaciclib inhibits other kinases (eg, CDK2/cyclin A/E, CDK1/cyclin B, CDK9/cyclin K/T1) more potently than the other CDK4/6 inhibitors do; however, the clinical impact of this is unknown.[38]

Several studies have evaluated abemaciclib either alone or in combination with ET in patients with MBC.[9,35,39–42] Results of the MONARCH 1 phase II trial demonstrated the efficacy of abemaciclib as a single-agent in patients with HR-positive, HER2-negative MBC who have been pretreated.[35] Additionally, abemaciclib with fulvestrant or AIs proved beneficial to patients with HR-positive, HER2-negative MBC in the MONARCH 2[41,42] and MONARCH 3[9,39,40] phase III trials. Treatment with abemaciclib plus fulvestrant in MONARCH 2 resulted in a statistically significant and clinically meaningful median OS improvement of 9.4 months for patients with HR-positive, HER2-negative advanced breast cancer who progressed during prior ET, including pre-/perimenopausal women and postmenopausal women. Median OS was 46.7 months for the abemaciclib plus fulvestrant arm and 37.3 months for the placebo plus fulvestrant arm (hazard ratio (HR), 0.757; 95% CI, 0.606–0.945; $P = 0.01$).[41]

The MONARCH 3 trial compared the combination of abemaciclib and a non-steroidal AI to a non-steroidal AI alone as front-line therapy for HR-positive, HER2-negative MBC.[9,40] The primary endpoint was PFS. Johnston et al reported the preplanned final analysis of PFS, which showed that the addition of abemaciclib to AI treatment improved PFS by 13.4 months; median PFS was 28.2 months with the combination and 14.8 months with AI alone (HR, 0.540; 95% CI, 0.418–0.698; $P = 0.000002$).[40] At the 2023 San Antonio Breast Cancer Symposium (SABCS) meeting, final OS analysis was reported.[39] Updated results with 8 years of follow-up data showed that abemaciclib plus AI resulted in an overall 13.1 month increase in OS over AI alone; 66.8 months vs 53.7 months with AI alone, which was not considered statistically significant (HR, 0.804; 95% CI, 0.637–1.015; $P = 0.0664$). However, with regard to the primary endpoint of PFS, with the updated analysis, the addition of abemaciclib to AI therapy showed a 14.3-month improvement in median PFS (29 months vs 14 months; HR, 0.535; 95% CI, 0.429–0.668; $P < 0.0001$) and the 6-year PFS rate was 23.3% for participants treated with the combination vs 4.3% for those treated with AI alone. These data support the role of CDK4/6 inhibitors in treating HR-positive, HER2-negative MBC. The cumulative data show improved efficacy for abemaciclib with ET in the metastatic setting, laying the groundwork for the evaluation of abemaciclib for the adjuvant treatment of HR-positive, HER2-negative, high-risk early breast cancer.

Abemaciclib in the Adjuvant Setting

In monarchE, the international, randomized, open-label, phase III trial, the addition of abemaciclib to ET was compared to ET alone in the adjuvant setting.[16] The primary endpoint was iDFS. Key secondary endpoints included DRFS, OS, safety, and in the subgroup of patients with Ki-67 ≥20%, iDFS. Eligible patients were enrolled between July 2017 and August 2019 and had HR-positive, HER2-negative breast cancer and ≥N1 disease with at least one of the following features: histologic grade 3, tumor size ≥5 cm, or Ki-67 ≥20% (per centralized testing). Cohort one included those with either ≥4 positive axillary lymph nodes or 1–3 positive axillary nodes with histological grade 3 and/or tumors ≥5 cm (T3 disease); cohort two included those with 1–3 positive axillary nodes, Ki-67 ≥20% histological grade ≤2, and tumor size <5 cm. In the intention-to-treat (ITT) population, nearly 60% of participants were eligible on the basis of four or more positive lymph nodes, 95.4% had received prior neoadjuvant chemotherapy or adjuvant chemotherapy, 38% had histological grade 3 disease, and 60% had Ki-67 ≥20%.

One unique inclusion criterion in monarchE was the centrally-assessed Ki-67 ≥20%.[43] Fresh-frozen, paraffin-embedded tissue samples from participants were submitted for immunohistochemistry testing to measure Ki-67 expression levels. Accordingly, patients were risk stratified in the cohorts; those with a Ki67 ≥20% were considered higher risk, in accordance with the St. Gallen International Expert and International Ki-67 Working Group Consensus.[44]

The trial enrolled 5637 participants. For each cohort, those in the experimental arm (n = 2808) were assigned to receive abemaciclib 150 mg twice daily continuously for two years plus ET for 5–10 years as clinically indicated per standard-of-care physician's choice. Patients started abemaciclib within 12 weeks of beginning adjuvant ET. The control arm (ET alone) had 2829 participants. The median duration of ET was approximately 15 months in each arm. The median duration of abemaciclib was 14 months. At a median follow-up of 27 months in the ITT population, 136 iDFS events

(4.8%) had been reported in the abemaciclib plus ET arm and 187 in the ET arm (6.6%). Those who received abemaciclib plus ET had significantly longer iDFS, with 2-year iDFS rates at 92.2% versus 88.7% for those who received ET only (HR, 0.75; 95% CI, 0.60–0.93; P =0.01). Most iDFS events were distant recurrences (abemaciclib plus ET arm, 87; control arm, 138). Participants in the abemaciclib plus ET arm also had longer DRFS (HR, 0.72; 95% CI, 0.56–0.92; nominal P =0.01).

Results for the estimated 2-year iDFS rate in the control arm indicated that 11.3% of patients with high-risk clinicopathologic features were expected to develop an invasive disease event within two years. Treating with abemaciclib and ET reduced the risk for an iDFS event by 25% and improved 2-year iDFS rates by 3.5% in absolute terms. This reduction, which was observed across all prespecified subgroups, is considered clinically meaningful.

With additional follow-up data, the magnitude of effect size for iDFS and DRFS rates increased, and the treatment benefit was maintained in the ITT population and within subgroups. An absolute improvement in 3-year iDFS rate of 5.4% (abemaciclib + ET, 88.8%; ET alone, 83.4%) and 3-year DRFS rate of 4.2% (abemaciclib + ET, 90.3%; ET alone, 86.1%) was observed. Generally, treatment benefit in iDFS and DRFS was consistent across prespecified subgroups.[45] In conclusion, monarchE met its primary endpoint and iDFS improved with longer follow-up.

On October 21, 2021, on the basis of results from monarchE, the FDA approved abemaciclib in combination with ET (tamoxifen or AI) for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive, early breast cancer who are at high risk for recurrence with Ki-67 ≥20%. In the monarchE trial, high-risk was defined as subjects with ≥4 positive axillary lymph nodes or 1–3 positive axillary nodes and either a tumor size ≥5 cm, histologic grade 3, or a Ki-67 ≥20% assessed centrally. In 2023, Johnston et al published additional follow-up results showing that the absolute benefits of adjuvant abemaciclib for iDFS and DRFS were more substantial at 4-year follow-up than at 2- and 3-year follow-up and that the benefits were consistent across all prespecified subgroups.[21] At four years, Ki-67 remained prognostic; however, the benefit of abemaciclib was independent of Ki-67 index status. At a median follow-up of 42 months, the estimated iDFS rates were 85.8% (95% CI, 84.2–87.3) in the abemaciclib plus ET arm and 79.4% (95% CI, 77.5–81.1) in the ET arm, reflecting an absolute difference of 6.4%; a 2.8% difference was observed at 2 years of follow-up and a 4.8% difference at 3 years.[21]

The addition of abemaciclib to ET reduced the risk of developing a DRFS event (HR, 0.659; 95% CI, 0.567–0.767; nominal $P < 0.0001$). The estimated 4-year DRFS rates were 88.4% (95% CI, 86.9–89.7) in the abemaciclib plus ET arm and 82.5% (95% CI, 80.7–84.1) in the ET arm, reflecting an absolute difference of 5.9%; a 2.5% difference was observed at 2 years of follow-up and a 4.1% difference at 3 years. For both iDFS and DRFS, the magnitude of the effective benefit of adding abemaciclib to ET increases over time. The OS data remained immature.[21]

On March 3, 2023, on the basis of the updated results from monarchE with 42 months of follow-up data, the FDA removed the Ki-67 testing requirement from the indication and expanded the indication to adult patients with HR-positive, HER2-negative, node-positive, early breast cancer who are at high risk for recurrence, defined as those with either ≥4 pathologic axillary lymph nodes or 1–3 pathologic axillary lymph nodes and either tumor grade 3 or a tumor ≥5 cm, regardless of Ki-67 levels.[22]

Abemaciclib has become a globally approved, standard adjuvant treatment for high-risk, early-stage HR-positive, HER2-negative breast cancer, with consistent treatment benefit demonstrated across various subgroups and clinically meaningful absolute risk reduction in iDFS and DRFS rates observed in both younger and older patients.[46] In subgroup analyses, adverse events were similar between age groups, although dose reductions and treatment discontinuations were higher among older participants (aged ≥65), who had more pre-existing comorbidities and higher performance status scores before starting protocol therapy than younger patients did. In monarchE, dose adjustments including dose omissions, dose reductions, and early cessation of therapy (median duration of abemaciclib, 14 months vs planned, 24 months) were common, which suggests that dose reductions were triggered by adverse events in the ITT population. Across all patients treated with abemaciclib, iDFS outcomes were similar among those who underwent dose modification and those who did not. Most discontinuations occurred within the first 6 months of treatment.[47] Abemaciclib benefits can be maintained despite dose modifications, as the 4-year iDFS rate from the lowest relative dose intensity group to the highest was 87.1% vs 86.4% vs 83.7%.[46]

In October 2023, Harbeck and co-authors presented results from a preplanned OS interim analysis of the monarchE trial data including 5-year efficacy outcomes at the European Society of Medical Oncology (ESMO) Congress.[48] In the ITT population after 5 years (median follow-up of 54 months), the iDFS rate was 83.6% with abemaciclib plus ET and 76% with ET alone (HR, 0.680; 95% CI, 0.599–0.772; $P < 0.001$). With an absolute difference of 7.6%, this demonstrated the sustained benefit of abemaciclib, which was consistent across all prespecified subgroups (age, menopausal status, type or setting of chemotherapy, and lymph node involvement). After the completion of treatment, the DRFS benefit persisted; 86% with abemaciclib plus ET and 79.2% with ET alone (HR, 0.675; 95% CI, 0.588–0.774; $P < 0.001$). This 6.7% difference, representing a 32.5% reduction in risk, was 2.5% at 2 years of follow-up, 4.1% at 3 years, and 5.9% at 4 years.[16] After 5 years of follow-up, no statistically significant difference in OS was detected between the two arms. Of note, in the Kaplan–Meier curve, a visible separation can be observed after 2 years of adjuvant abemaciclib, which suggests a beneficial carry-over effect of earlier abemaciclib treatment. No new safety signals emerged. Safety data were consistent with previous reports.[49] In 2024, the 5-year efficacy outcomes for monarchE were reported as a Clinical Trial Update by Rastogi et al.[50]

Safety and Tolerability of Abemaciclib in the Adjuvant Setting

In monarchE, most patients in the abemaciclib plus ET arm experienced at least one treatment-emergent adverse events (AE) (97.9%),[21] and their most frequent AEs of any grade and any attribution were diarrhea, neutropenia, and fatigue. For many patients, abemaciclib treatment was modified because of AEs; 61.7% needed treatment interruptions and 43.6% needed dose reductions, most commonly due to diarrhea, neutropenia, or fatigue. Diarrhea was the most common AE of any grade, reported in 83.5% of patients in the abemaciclib plus ET arm. Importantly, diarrhea improved over time and early interventions of supportive care and dose adjustments improved tolerability. Overall, the toxicity profile of abemaciclib in the adjuvant setting as described in monarchE was consistent with that observed in the metastatic setting.[40,42]

In the adjuvant setting, assessing the impact of a new treatment on quality of life is important. An analysis of patient-reported outcomes in the adjuvant monarchE trial showed maintenance of health-related quality of life with the addition of abemaciclib to endocrine therapy in the treatment of HR-positive, HER2-negative early breast cancer patients. Scores on a variety of measures, such as fatigue, did not significantly differ from those of patients treated with ET alone.[51]

Practical Guidance for Using Abemaciclib in the Adjuvant Setting

On the basis of the results from monarchE, two years of adjuvant abemaciclib can be considered for combination with ET for treating patients with HR-positive, HER2-negative, high-risk early breast cancer. This approach is designated a category 1 recommendation by the National Comprehensive Cancer Network and is supported by ASCO and ESMO.[11,52–54] To best maintain treatment compliance, all patients should be counseled about symptom management and monitored closely for AEs that would prompt dose modification.

As diarrhea is the most common side effect and can sometimes be severe, patients should be counseled before initiating abemaciclib on its expectant management. Diarrhea is most likely to occur during the first month, with a median time to onset of one week.[49] From the first episode of diarrhea, early intervention with over-the-counter antidiarrheal medications, such as loperamide, should be available to all patients. Patients should remain hydrated, make appropriate dietary modifications, and follow-up with their health care provider if symptoms persist beyond 24 hours. If diarrhea does not resolve within 24 hours after antidiarrheal therapy to ≤ grade 1, abemaciclib dosing should be suspended. If grade 2 diarrhea persists or recurs after resuming the same dose despite maximal supportive measures, then it is recommended to suspend the dose until the toxicity resolves to ≤ grade 1 and resume at a lower dose.[55]

Given the frequency at which AEs such as diarrhea, nausea, neutropenia, hepatoxicity, and fatigue have been reported, patients on abemaciclib should be regularly monitored for complete blood counts, electrolytes, and liver function, particularly during the early months of therapy. Neutropenia is a common side effect, and patients should be advised of the possibility of developing neutropenia and to immediately contact their healthcare provider if they develop a fever, especially when any other signs of infection are also present. It is reversible upon discontinuation. Additionally, granulocyte-colony stimulating factors are not needed, as the neutropenia should be managed with dose reduction. Providers are recommended to monitor complete blood counts before initiating abemaciclib therapy, biweekly for the first

2 months, monthly for the next 2 months, and as clinically indicated thereafter. In parallel, increases in serum transaminases have been observed with abemaciclib therapy; therefore, liver function tests should be performed before initiating abemaciclib, biweekly for the first 2 months, monthly for the next 2 months, and as clinically indicated thereafter.

Another practical consideration for using abemaciclib in the adjuvant setting is the timing during a patient's treatment course. The current prescribing information does not specify when to start adjuvant abemaciclib; however, it is reasonable to follow what was stipulated in the monarchE trial, which allowed up to 12 weeks of ET after the last non-ET intervention (eg, chemotherapy, surgery, radiation) before randomization, and patients had to be randomized within 16 months of surgery.[16] Also, (neo)adjuvant chemotherapy and radiation had to be completed before adjuvant abemaciclib. The only therapy that could be given concurrently with adjuvant abemaciclib was ET in the form of tamoxifen or an AI, with or without ovarian function suppression.

Oncologists must also consider the sequence of abemaciclib and olaparib in the adjuvant setting for HR-positive, HER2-negative, high-risk early breast cancer with germline *BRCA1/2* mutations (g*BRCA1/2*m). Concurrent and sequential therapy with olaparib and abemaciclib were not compared in the monarchE trial. For 1 year of treatment, olaparib, an oral poly(ADP-ribose) polymerase (PARP) inhibitor, is approved by the FDA for adjuvant treatment of patients with high-risk early-stage HER2-negative breast cancer with g*BRCA1/2*m after completion of (neo)adjuvant chemotherapy and local treatment, including radiation. This approval was based on the OlympiA trial results, which showed that, compared to placebo, adjuvant olaparib improved OS.[56,57] Given the OS benefit associated with adjuvant olaparib, this would be the preferred agent to give to patients with ≥4 positive axillary lymph nodes, which was the criteria stipulated in OlympiA, whereas adjuvant abemaciclib in this subset could be considered for those with one to three positive nodes who have a tumor that is either grade 3 or ≥5 cm.[52] No clinical trial data exist to support sequential use of olaparib followed by abemaciclib; however, this approach could be considered in very high-risk patients as adding abemaciclib could still be within the same timeframe stipulated in the monarchE trial if there was a late start to adjuvant radiation therapy. This is purported by the ESMO Clinical Practice Guideline on early breast cancer.[54] It is important to note that because both drugs have overlapping myelosuppression toxicities, their concurrent use is not recommended.

Venous thromboembolism (VTE) is a side effect of CDK4/6 inhibitors. In participants treated with abemaciclib, the incidence of any grade venous thromboembolic event was 4.8% and 6.1% in the MONARCH 2 and MONARCH 3 trials, respectively.[58] These events were primarily treated with anticoagulation therapy. Withholding abemaciclib for 1–2 weeks, and implementing anticoagulation is recommended. If a patient is clinically stable, it is reasonable to resume abemaciclib with no dose reduction and treat with concurrent anticoagulation for the remaining time on abemaciclib. Switching from tamoxifen to an AI is favored in the setting of a venous thromboembolism. The monarchE trial results showed a higher incidence of venous thromboembolism with abemaciclib and tamoxifen than with abemaciclib and AI: 4.3% vs 1.8%.[49] Any pre-existing risk factors for VTE should be evaluated when considering which ET to partner with abemaciclib; if any exist, then the preferred partner would be an AI, given the higher incidence of VTE associated with tamoxifen.

In September 2019, the FDA issued a warning that oral CDK4/6 inhibitors may cause interstitial lung disease (ILD) or pneumonitis.[59] In subjects treated with abemaciclib, the incidence of any grade pneumonitis was 2% and 5.2% in the MONARCH 2 and MONARCH 3 trials, respectively.[58] In monarchE, 3.2% of the abemaciclib-treated subjects experienced ILD or pneumonitis of any grade.[49] Patients on abemaciclib should be monitored for respiratory symptoms, which include cough, dyspnea, and hypoxia. For persistent or recurrent grade 2 ILD or pneumonitis, dose interruption or dose reduction is recommended. For grade 3 ILD or pneumonitis, permanent discontinuation is indicated.[55]

Due to the inhibition of renal transporters, abemaciclib may reversibly increase serum creatinine, but abemaciclib does not reduce renal function.[60] Serum creatinine usually increases after the first treatment cycle, remains increased throughout treatment, and then the creatinine returns to normal values after abemaciclib is discontinued. For severe hepatic impairment, a dose reduction of abemaciclib is required; however, no dose modifications are necessary for mild or moderate renal impairment.[55] Food ingestion has not been shown to affect the bioavailability of abemaciclib, and patients are advised that it can be taken with or without food.

Other CDK4/6 Inhibitors in the Adjuvant Setting

Palbociclib and ribociclib have also been studied in the adjuvant setting for patients with HR-positive, HER2-negative, high-risk early breast cancer.[18,61,62] Palbociclib has been investigated in two phase III trials, PALLAS (PALbociclib CoLlaborative adjuvant study) and PENELOPE-B. The PALLAS trial was a prospective, randomized, phase III trial of participants with stage II or stage III HR-positive, HER2-negative early breast cancer who were randomly assigned to receive either two years of palbociclib (125 mg orally once daily, days 1–21 of a 28-day cycle) plus adjuvant ET or adjuvant ET alone.[18] Study results demonstrated that the addition of two years of palbociclib to adjuvant ET did not significantly improve iDFS, and the trial was closed early for futility.[61] PENELOPE-B was a double-blinded, placebo-controlled, phase III trial in women with HR-positive, HER2-negative primary breast cancer who did not have a pathologic complete response after taxane-based neoadjuvant chemotherapy and who were at high risk for recurrence. Participants were randomly assigned (1:1) to receive ET and either 13 cycles of palbociclib 125 mg once daily or placebo on days 1–21 in a 28-day cycle.[17] After a median follow-up of 42.8 months, those who received palbociclib did not have improved iDFS.[17]

The NATALEE (New Adjuvant TriAl with Ribociclib [LEE011]) trial, a phase III multicenter, randomized, open-label trial, compared the efficacy and safety of the CDK4/6 inhibitor ribociclib plus ET and ET alone for the adjuvant treatment of patients with HR-positive, HER2-negative early breast cancer.[62] Eligible participants had stage II or III HR-positive, HER2-negative breast cancer, and included those with or without node involvement, which represents the broadest patient population of any adjuvant CDK4/6 inhibitor trial to date. Participants were randomized to either ribociclib 400 mg ribociclib daily (3 weeks on/1 week off) for 36 months plus ET or ET alone; in both arms, ET is planned for 60 months. The 3-year treatment duration of ribociclib 400 mg showed a predictable safety profile that was more favorable than the 600 mg dose of ribociclib used in the metastatic setting in terms of improving tolerability while maintaining efficacy.[19] The extended duration of 3-year treatment may also be critical to prolong cell cycle arrest and drive more tumor cells into irreversible senescence.

Primary results of NATALEE, reported for the first time at the 2023 ASCO Annual Meeting, demonstrated that the 3-year iDFS rate of 90.4% for the ribociclib plus ET arm and 87.1% for ET alone arm (HR, 0.748; 95% CI, 0.618–0.906; $P = 0.0014$); therefore, the study met its primary endpoint.[19] At three years, the absolute iDFS benefit for combination therapy was 3.3%. The risk for the development of invasive disease was 25.2% lower with combination therapy than with ET alone. The findings from NATALEE were consistent across subgroups for disease stage, menopausal status, and nodal status. After a median follow-up of 33.3 months, updated results on final iDFS were presented at the 2023 San Antonio Breast Cancer Symposium.[63] Results showed that combination therapy improved 3-year iDFS by 3.1% (HR, 0.749; 95% CI, 0.628–0.892; $P = 0.0006$), corresponding to a 25.1% risk reduction in the risk of recurrence. These results, published in the New England Journal of Medicine in March 2024,[64] are promising and suggest that adjuvant ribociclib could be a future treatment option for patients with high-risk, early-stage breast cancer. However, data on survival are thus far incomplete, and updated results on clinical outcomes after longer follow-up will be important to consider before making final conclusions. In Table 1, we highlight key differences in the design and results of trials that tested the adjuvant use of a CDK4/6 inhibitor with ET in HR-positive, HER2-negative, high-risk early-stage breast cancer.

Table 1 Randomized Controlled Phase III Adjuvant Trials of Oral CDK4/6 Inhibitors with Endocrine Therapy in HR-Positive, HER2-Negative Early Breast Cancer

	MonarchE*[45,50]	PENELOPE-B[17]	PALLAS[18,61]	NATALEE[64]
CDK 4/6i Arm	Abemaciclib + ET	Palbociclib + ET	Palbociclib + ET	Ribociclib + ET
Placebo-Controlled	No	Yes	No	No
Dosing	150 mg twice daily continuous	125 mg once daily, days 1–21, followed by 7 days off, in a 28-day cycle	125 mg once daily, days 1–21, followed by 7 days off, in a 28-day cycle	400 mg once daily, days 1–21, followed by 7 days off, in a 28-day cycle
Duration of CDK 4/6i treatment, years	2	1	2	3

(*Continued*)

Table 1 (Continued).

	MonarchE*[45,50]	PENELOPE-B[17]	PALLAS[18,61]	NATALEE[64]
Key Inclusion Criteria	≥ 4 positive axillary lymph nodes or 1–3 positive lymph nodes and tumor size ≥ 5 cm, grade 3, or Ki67 ≥ 20%	High risk after NAC (defined as RID with CPS-EG score ≥ 3 or score 2 if nodal status at surgery is ypN+)	Stage II or III	Stage II (if N1 or N0 (T2-3, N0) with grade 2–3 and/or Ki67 ≥ 20%) or Stage III
Number of Patients Randomized	5637	1250	5796	5101
3-Year iDFS rate, % (CDK4/6i +ET vs ET alone)	88.1 vs 83.4	81.2 vs 77.7	88.2 vs 88.5	90.4 vs 87.1
HR (95% CI)	0.70 (0.59–0.82)	0.93 (0.74–1.17)	0.93 (0.76–1.15)	0.75 (0.62–0.91)
P value	*P* < 0.0001	*P* = 0.525	*P* = 0.51	*P* = 0.003
3-Year DRFS rate, % (CDK4/6i +ET vs ET alone)	90.3 vs 86.1	Not reported	89.3 vs 90.7	90.8 vs 88.6[a]
HR (95% CI)	0.69 (0.57–0.83)		1.00 (0.79–1.27)	0.74 (0.60–0.91)
P value	*P* < 0.0001		*P* = 0.9997	*P* value not reported
OS Rate (CDK4/6i +ET vs ET Alone)	84 vs 81.4[b]	93.6 vs 90.5[c]	93.8 vs 95.2[d]	Not mature
HR (95% CI)	0.903 (0.749–1.088)	0.87 (0.61–1.23)	1.32 (0.98–1.78)	
P value	*P* = 0.284	*P* = 0.420	*P* value not reported	

Notes: *5-year efficacy outcomes are available. [a]3-year distant disease-free survival rate. [b]Only 5-year OS rate is shown. [c]3-year OS rate. [d]4-year OS rate.
Abbreviations: CDK4/6i, CDK4/6 inhibitor; CPS+EG, clinical and pathologic stage, estrogen receptor status and histologic grade; DRFS, distant recurrence-free survival; ET, endocrine therapy; HR, hazard ratio; iDFS, invasive disease-free survival; NAC, neoadjuvant chemotherapy; OS, overall survival; RID, residual invasive disease.

Conclusions

The addition of 2 years of abemaciclib to adjuvant ET for HR-positive, HER2-negative high-risk early-stage breast cancer has significantly improved IDFS and DRFS, as demonstrated by the results of the monarchE trial, although no overall survival benefit has been demonstrated thus far.[50] In 2023, abemaciclib was the only oral CDK4/6 inhibitor approved in the adjuvant setting for HR-positive, HER2-negative, high-risk early breast cancer. The goal of intensifying treatment for early breast cancer with the addition of abemaciclib is to maintain remission and prevent disease recurrence. The initial FDA approval of abemaciclib for early breast cancer was practice changing. Now, through the indication expansion that removed the Ki-67 score of ≥20% stipulation, many more patients with high-risk disease have access to adjuvant abemaciclib. The Ki-67 index is prognostic but not predictive of a benefit from abemaciclib, as patients benefitted from abemaciclib regardless of the Ki-67 index. High-risk patients who may be candidates for abemaciclib treatment can now be identified solely on the basis of nodal status, tumor size, and tumor grade (≥4 positive nodes, or 1–3 positive nodes and at least one of the following: tumors that are ≥5 cm or grade 3). Side effects of abemaciclib include diarrhea, neutropenia, ILD, pneumonitis, hepatoxicity, and venous thromboembolism, which are manageable with supportive care, dose modification, and dose reduction.[49] Long-term patient-reported outcomes also showed that quality of life was maintained with the addition of adjuvant abemaciclib to endocrine therapy.[51] The risks and benefits of adjuvant abemaciclib should be thoughtfully discussed with patients.

CDK4/6 inhibitors have been practice-changing in the treatment of HR-positive, HER2-negative breast cancer; however, further investigation is warranted in several emerging areas. Currently, there are no biomarkers other than traditional clinical and pathologic criteria for selecting patients who might benefit from the addition of CDK4/6 inhibitor to adjuvant ET. It would be helpful to identify predictors of efficacy as well as toxicity. Other topics that remain to be explored include the optimal duration of adjuvant CDK4/6 inhibitor treatment, sequencing of therapy after progression on adjuvant CDK4/6 inhibitor, and sequencing adjuvant radiation therapy with CDK4/6 inhibitors. Other emerging areas include economic assessments of CDK4/6 inhibitors in the adjuvant setting and clinical trials investigating the combination of CDK4/6 inhibitors with other ET agents such as oral selective estrogen receptor degraders. Overall, the expanded use of CDK4/6 inhibitors combined with ET in the adjuvant setting is an important advancement for treating HR-positive, HER2-negative high-risk early breast cancer.

Abbreviations

AE, Adverse events; AI, Aromatase inhibitor; ASCO, American Society of Clinical Oncology; CDK, Cyclin-dependent kinase; DRFS, Distant recurrence-free survival; ESMO, European Society of Medical Oncology; ET, Endocrine therapy; FDA, United States Food and Drug Administration; HER2, Human epidermal growth factor receptor 2; HR, Hormone receptor; iDFS, Invasive disease-free survival; ITT, Intention-to-treat; MBC, Metastatic breast cancer; OS, Overall survival; PFS, Progression-free survival.

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