AXIS Medical Education

Community Practice Perspectives:

Exploring Treatment Intensification with CDK 4/6 Inhibitors in Adjuvant HR+, HER2-, High-Risk Early Breast Cancer

CME/CPE/CNE/AAPA-Certified

Provided by AXIS Medical Education.

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PRE-ASSESSMENT QUESTIONS

ACTIVITY INFORMATION

FACULTY

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Utilize consensus-based guidelines to identify patients at high risk of recurrence
- Apply guidelines and evidence for CDK4/6 inhibitors in combination with ET to reduce recurrence in patients with high-risk HR+/HER2- early breast cancer
- Develop team-based mitigation and management strategies for CDK 4/6 inhibitor-related and ET-related adverse events to reduce toxicities and treatment discontinuation
- Employ collaborative team-based communication strategies to foster patient engagement, adherence, and persistence of therapy

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Activity Accreditation Information

SECTION 1:
WHAT CONSTITUTES HIGH-RISK IN HR+/HER2- EARLY BREAST CANCER?

Early Breast Cancer

Introduction and Rationale for Determining Risk of Recurrence as Early as Possible

Early breast cancer (EBC) refers to disease confined within the breast and/or neighboring lymph nodes (National Cancer Institute). Approximately 90% of breast cancer diagnoses are EBC, with about 70% of EBC patients having hormone receptor (HR)-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative (HER2-) disease (Howlander et al, 2014). Around 20% of EBC patients experience disease recurrence within 10 years after diagnosis, often with incurable distant metastases (Early Breast Cancer Trialists' Collaborative Group, 2015). The risk of recurrence is highest in the first 2 years following diagnosis. Patients with high-risk clinical and/or pathologic features are more likely to experience recurrence or distant metastases, particularly in the initial years of adjuvant endocrine therapy (Mamounas, 2018). Patients who experience disease recurrence have poorer prognosis and worse overall outcomes (Sheffield, 2021).

The goal of HR+, HER2- EBC treatment is to eradicate cancer and prevent disease recurrence (Gradishar et al, 2024). The standard of care for HR+, HER2- EBC includes locoregional therapies (surgery, radiation therapy) and adjuvant/neoadjuvant systemic therapies (chemotherapy, endocrine therapy, and targeted therapy; Gradishar et al, 2024). Unmet needs include understanding who does/does not need adjuvant chemotherapy, identifying those with primary endocrine resistant HR+ BC, and preventing or delaying recurrence with additional therapy. Preventing early recurrence and metastasis is crucial. Novel therapies have been shown to reduce the risk of distant relapse in patients with HR+/HER2- EBC, improving overall outcomes. CDK4/6 (cyclin-dependent kinases 4 and 6) inhibitors represent a major breakthrough in the treatment of HR+/HER2- advanced breast cancer. These agents markedly improve outcomes in the metastatic setting and have demonstrated significant benefits in progression-free survival (PFS), objective response rate (ORR), and overall survival (OS) (Gil-Gil, 2021) They are now standard-of-care in the advanced breast cancer treatment. Naturally, these same agents have and continue to be explored in the adjuvant setting for EBC. The purpose of this review is to look at CDK4/6 inhibitors in the adjuvant treatment of early-stage HR+/ HER2- breast cancer.

Risk Assessment

When, and in Whom, is Treatment Intensification Needed to Reduce the Risk of Recurrence?

Various factors contribute to the risk of breast cancer recurrence, including age at diagnosis, tumor size, nodal status, lymphovascular invasion, histologic tumor grade, ER/HER2 status, and proliferation rate as measured by Ki-67 protein levels (Gyorffy, 2015; Sheffield, 2021). Factors that affect risk of recurrence

in patients with EBC are summarized in **Figure 1**. Understanding and recognizing these factors allows for personalized treatment plans and improved outcomes for patients with early-stage breast cancer in the community setting.

View Figure 1

Community-based clinicians play a vital role in identifying patients at high risk of recurrence, based on clinicopathologic features. There are several ways to determine which patients with EBC are at high risk of recurrence. One prognostic factor is tumor grade. When examining the relationship between histological grade and breast cancer-specific survival, it is evident that patients with high-grade tumors are at greater risk of early recurrence, metastasis, and death, while low-grade tumors tend to be associated with very good outcomes with few, if any, events occurring (Rakha et al, 2010).

Another prognostic factor in identifying high-risk EBC recurrence is Ki-67 expression, a marker of cellular proliferation (Viale et al, 2008; Fasching et al, 2019). Ki-67 is a nuclear protein expressed in proliferative cells, usually during the mitotic cell division stage of the cell cycle. Patients with a higher proportion of Ki-67-expressing tumor cells tend to have lower 5-year disease-free survivals than those with fewer Ki-67-expressing tumor cells. The SOFT and TEXT trials of premenopausal women with HR+/HER2- breast cancer who received adjuvant LHRH agonist therapy plus antihormonal therapies following chemotherapy, showed an improvement in freedom from recurrence (Pagani et al, 2020). Secondary analyses of prognostic factors in these trials identified that higher Ki-67 expression was associated with worse prognosis. There was an 8-year freedom from distant recurrence rate of 96% for a Ki-67 expression level of ≤14, 87% for a Ki-67 expression level of 20-25, and 82% for a Ki-67 expression level ≥26. There is, however, a lack of standardization and consistency among different institutions and even within the same institution in Ki-67 staining and interpretation (OncoLetter, 2023; Polley et al, 2013).

Other tools, including genomic tests, help to determine recurrence risk in estrogen receptor (ER)-positive (ER+) early-stage breast cancer. PREDICT Plus is an online prognostic tool developed from clinical data from breast cancer patients and is endorsed by the American Joint Committee on Cancer (AJCC). This tool helps patients and clinicians see how different treatments for early invasive breast cancer might improve survival rates following surgery. Once patient and disease details such as age, menopausal status, Ki-67 expression, ER status, PR status, HER2 status, tumor size, tumor grade, and types of therapies the patient is scheduled to receive have been entered, the tool provides 5-year and 10-year overall survival projections and quantifies the benefits of chemotherapy and hormonal therapy (https://breast.predict.cam/tool), similar to the previously employed prognostic tool *Adjuvant! Online*.

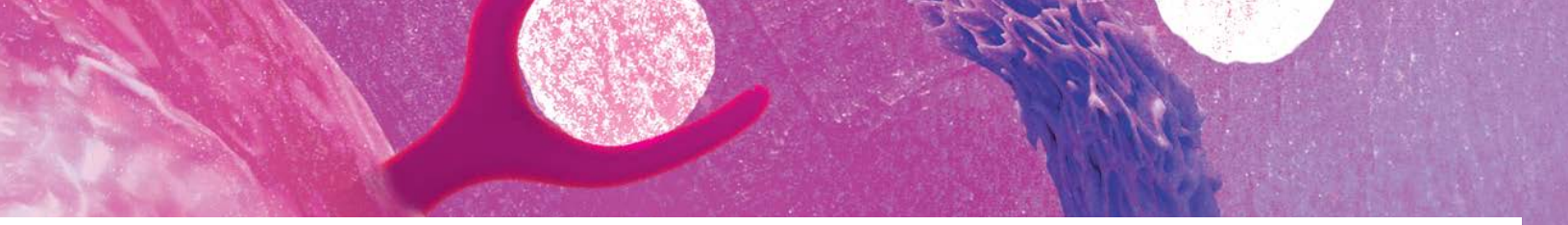
Multigene assays can help identify patients with EBC who have a higher risk of recurrence, and may also predict whether patients can benefit from adjuvant systemic therapy. Multiparametric genomic tests include the 21-gene assay, the 70-gene assay, and the 12-gene assay. The 21-gene assay, or Oncotype DX, is both prognostic and predictive of chemotherapy benefit and is the tool preferred by NCCN® Guidelines (Gradishar et al, 2024). It has been clinically validated for predicting the benefit of adjuvant chemotherapy in reducing the risk of recurrence for patients with HR+/HER2- EBC with 0-3 positive lymph nodes. Oncotype DX includes 16 cancer genes that are most prognostic of recurrence and 5 reference genes (McVeigh et al, 2017). The test generates a recurrence score between 0 and 100, which correlates with probability of distant disease recurrence. Patients with low-risk recurrence

scores (0–17) are unlikely to derive a significant survival benefit from the addition of adjuvant chemotherapy to hormonal agents. Conversely, adjuvant chemotherapy has been shown to significantly improve survival in patients with high recurrence risk scores (≥31). In the TAILORx trial of over 10,000 women with HR+/HER2- axillary node–negative breast cancer, adjuvant endocrine therapy and chemoendocrine therapy had similar efficacy in women who had midrange (11-25) 21-gene recurrence scores, indicating that chemotherapy is not needed in the vast majority of patients with recurrence score under 25 (Sparano et al, 2018). However, patients with recurrence scores >26 had a 13.6% distant recurrence rate, despite use of chemoendocrine therapy, signifying a need for other treatment options in addition to chemo and endocrine therapy. In the RxPONDER trial, women with node-positive disease and recurrence scores of 0-25 were randomized to chemotherapy followed by endocrine therapy vs endocrine therapy alone (Kalinsky et al, 2021). In postmenopausal patients at 5 years, there was no statistically significant difference in invasive disease-free survival (92% in both arms), However, in premenopausal patients, there was an absolute benefit with chemotherapy of 4.9% as well as a 5-year IDFS of 94% in the chemoendocrine arm versus 89% in the endocrine-only arm. In otherwords, post-menopausal women did not benefit from the addition of chemotherapy while pre-menopausal women did.

Another genetic tool is the 70-gene assay, or MammaPrint. In the MINDACT study, approximately 6,600 women with early-stage breast cancer had their genomic risk determined using the 70-gene signature and their clinical risk determined using a modified version of Adjuvant! Online (Cardoso et al, 2016). Women at low clinical and genomic risk (about 41%) did not receive chemotherapy; women at high clinical and genomic risk (about 27%) received chemotherapy. In women at high clinical risk but low genomic risk for recurrence (about 23%), there was no statistical difference between the chemotherapy and no-chemotherapy arms, with a 5-year distant metastasis-free survival rate of 94.7% among those not receiving chemotherapy, which was 1.5 percentage points lower those who received chemotherapy. Long-term follow-up results with an exploratory analysis by age for clinically–high, genomically–low-risk patients with HR+/HER2- disease, recorded an 8-year distant metastasis-free survival of 93.6% with chemotherapy versus 88.6% without chemotherapy in women ≤ 50 years (absolute difference 5.0 percentage points), and 90.2% versus 90.0% in women > 50 years (absolute difference 0.2 percentage points; Piccart et al, 2021).

A third genomic assay, EndoPredict, is a 12-gene molecular tool that predicts for early and late recurrence. The molecular score is combined with tumor size and nodal status to determine the EPclin risk score (scale of 1-6), a prognostic test validated to inform decisions on adjuvant chemotherapy vs endocrine therapy alone for patients with ER+/HER2- breast cancer (Dubsky et al, 2013; Filipits et al, 2011; Sestak et al, 2019). In a combined analysis of two large trials, the TransATAC trial (that treated women with endocrine therapy alone) and the GEICAM/2003-02/9906 trial (that treated women with endocrine therapy and chemotherapy), the rate of increase in distant recurrence with increasing EPclin score was significantly reduced in women who received ET + chemotherapy versus ET alone (Sestak et al, 2019). Specifically, an EPclin score >3 is associated with a modest 1.9% absolute benefit from the addition of chemotherapy while a 33% absolute benefit is associated with an EPclin score of 6.

“ Updated data presented at ASCO 2024 examined DFS in RxPONDER in woman with low Oncotype scores less than 25 based on levels of anti-Müllerian hormone (Kalinsky et al, 2024). Anti-Müllerian hormone is a measurement of ovarian reserve. In the women



under 50, who were presumably premenopausal, the only women who had a chemotherapy benefit were those with premenopausal level of anti-Müllerian hormone greater than 10 picograms per mil (pg/mL), suggesting that maybe the chemo benefit here is actually ovarian suppression. The OFSET study (NCT05879926) takes women with Oncotype scores of 16 or greater with node-negative disease, or, any Oncotype score with node-positive disease, and randomizes these patients to ovarian function suppression plus endocrine therapy with or without adjuvant chemotherapy. We encourage people to enroll in the OFSET trial to answer this question once and for all in randomized data."

– *Adam Brufsky, MD, PhD*

Professor of Medicine, UPMC Hillman Cancer Center

So, there are numerous ways to predict who has high-risk disease and would benefit from adjuvant therapy to reduce the risk of disease recurrence. The patients that experience recurrence or distant metastases in EBC are more likely to have high-risk clinical and/or pathologic features (Stuart-Harris et al, 2019). In addition to high tumor grade and high Ki-67 levels, high recurrence rates in patients with HR+/HER2- EBC include negative PR status, lymphovascular invasion, large tumor size, and luminal B subtype. Higher mortality rates have been observed in patients with HR+/HER2- EBC who have ≥4 positive lymph nodes, grade 3 tumors, and greater tumor size (Brown et al, 2019). In patients at high enough risk, adding an adjuvant CDK4/6 inhibitor has been shown to improve distant disease-free survival. In the monarchE trial, which led to the FDA approval of abemaciclib in EBC, node-positive, high-risk EBC was defined as 4+ positive nodes, or 1-3 positive nodes and at least one of the following: tumor size ≥ 5cm or grade 3 (Johnston et al, 2023).

CLINICAL THOUGHT

Are you comfortable assessing and determining which patients are at high-risk of recurrence?

a. Yes

b. No

c. I need more information

d. Unsure

Post-Assessment Question 1

In the monarchE trial, which of the following early-stage breast cancer patients are at high risk of recurrence and could receive adjuvant abemaciclib?

a. Node negative tumor with recurrence score 30

b. 3+ positive nodes, any tumor size, any tumor grade

c. 1-3 positive nodes, tumor size <3 cm and grade 2

d. 1-3 positive nodes, tumor size ≥5 cm or grade 3

e. Unsure

SECTION 2
HOW CAN WE DRIVE RECURRENCE RISK DOWN WITH INTENSIFIED ADJUVANT THERAPY?

Adjuvant ET for 5 years results in a substantial reduction in the risk of local recurrence, contralateral BC, distant recurrence, and risk of death (Pan et al, 2017; Sheffield et al, 2022; Johnston et al, 2023; Gradishar et al, 2024). The addition of chemotherapy to adjuvant ET is recommended in certain patients with HR+/HER2- breast cancer based on recurrence risk (Oncotype Dx 21-gene assay). We know that the risk of recurrence in patients with early-stage disease is greatest within the first 2 to 4 years after diagnosis. Clinical trials of adjuvant CDK4/6 inhibitors in high-risk HR+ EBC aim to prevent recurrences during the expected peak timeframe for earlier recurrences, as show in **Figure 2**. Three CDK4/6 inhibitors and one PARP inhibitor have been studied as adjuvant treatment for EBC, and are reviewed below.

View Figure 2

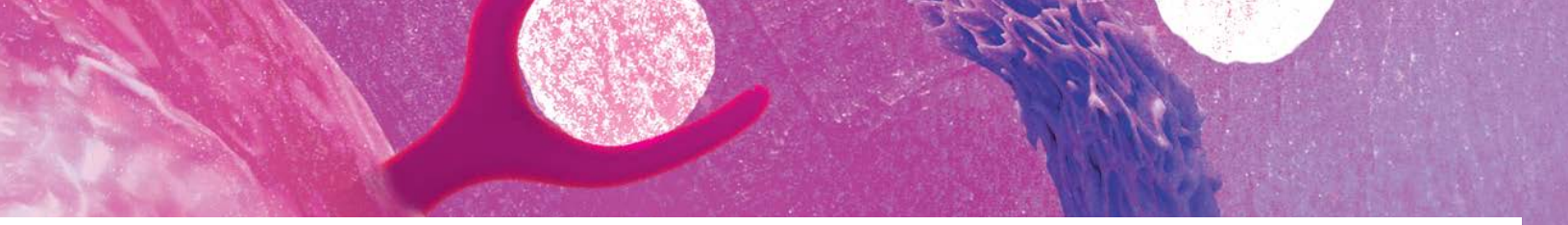
monarchE
Abemaciclib + ET

The phase III monarchE study included patients with HR+, HER2-, node-positive, high-risk EBC, who had undergone surgery, radiotherapy and/or adjuvant/ neoadjuvant chemotherapy (Johnston et al, 2020). Patients with 4 or more positive nodes, or 1 to 3 nodes and either tumor size ≥5 cm, histologic grade 3, or central Ki-67 expression ≥20% were deemed eligible and randomly assigned 1:1 to standard-of-care adjuvant ET (AI or tamoxifen) with or without abemaciclib (150 mg twice daily) for 2 years **(Figure 3)**. The primary endpoint was invasive disease-free survival (IDFS).

View Figure 3

The 4-year IDFS absolute improvement with abemaciclib + ET was 6.4%, with a 34% reduction in the risk of developing an IDFS event (**Table 1**; Johnston et al, 2022, 2023; Hamilton et al, 2023). The 4-year distant relapse-free survival (DRFS) absolute difference with abemaciclib + ET was 5.9%, associated with a 34% reduction in the risk of developing a DRFS event. The IDFS and DRFS benefits persist and deepen beyond completion of the 2-year abemaciclib treatment period. Results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy outcomes, were presented at the 2023 European Society for Medical Oncology (ESMO) Annual Meeting (**Table 1**; Harbeck et al, 2023; Rastogi et al, 2024). After the on-study treatment period of 2 years, ET was continued for an additional 3-8 years as clinically indicated. In this analysis, all patients were off abemaciclib and more than 80% of patients have been followed for at least 2 years since completing abemaciclib. Results show a sustained IDFS benefit in the ITT population, with a 32% reduction in the risk of developing an IDFS event. The Kaplan-Meier curves continue to separate and the absolute difference in IDFS rates between arms was 7.6% at 5 years. The IDFS benefit of abemaciclib + ET was consistent and observed in all subgroups, including patients with grade 1 and 2 disease, patients with 10 or more lymph nodes, and in both premenopausal and postmenopausal patients. The 5-year DRFS benefit was also sustained, with a 32.5% reduction in the risk of developing a DRFS event, and an absolute difference in DRFS rates between arms of 6.7% at 5 years.

View Table 1



FDA Approval and Guideline Recommendations

In 2021, the U.S. Food and Drug Administration (FDA) approved abemaciclib with ET (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR+/HER2-, node-positive EBC at high risk of recurrence, defined as those having either ≥4 pALN (pathologic axillary lymph nodes) or 1-3 pALN and either tumor grade 3 or a tumor size ≥50 mm (FDA.gov, 2021). In 2023, the original requirement of having a Ki-67 score ≥20% was removed as more deaths were observed with abemaciclib plus standard endocrine therapy compared to standard endocrine therapy alone in the cohort that included tumor Ki-67 score ≥20% (FDA.gov, 2023). The National Comprehensive Cancer Network (NCCN) Guidelines® now recommends the consideration of 2 years of adjuvant abemaciclib incombination with ET in patients with HR+/HER2- high-risk breast cancer (category 1, preferred; Gradishar et al, 2024).

At the third interim analysis, fewer deaths were observed in the abemaciclib + ET arm (208) versus the ET arm (234, HR 0.903), but a statistical overall survival (OS) significance was not reached (*P* = 0.284; Harbeck et al, 2023). However, there were also fewer patients with metastatic disease in the abemaciclib + ET arm (138 versus 269).

A smaller group of patients were enrolled in Cohort 2 with 1-3+ ALN, grade 1-2, tumor size <5 cm, and central Ki-67 ≥20%.

> *"Cohort 2 did not seem to have as much benefit. There were many fewer events. In these patients with lower risk disease, really stage 2 with grade 1 disease with a Ki-67 of 20% or greater, there were too few events to make any conclusions. We do not use the Ki-67 cutoff in our practice. In my practice, I will give a CDK4/6 inhibitor to women with a stage II grade 3 cancer and potentially a stage II grade 2 cancer with high-risk features. But generally I reserve CDK46i for anatomic grade 3. However if someone younger (under 50) presents with a 4 cm tumor with 1 lymph node involved and grade 3, I think a lot of us may consider adjuvant CDK4/6i in that patient. But again, for me, it's usually T3N1 or N2 and above that tend to be the ones that I offer abemaciclib to in my practice. And again, Ki-67 really was not a predictor of benefit. Patients had benefit regardless of Ki-67 expression."*
>
> — *Adam Brufsky, MD, PhD*
> *Professor of Medicine, UPMC Hillman Cancer Center*

In looking at a biomarker subset to predict who would benefit from the addition of abemaciclib to ET in the monarchE trial, a consistent abemaciclib treatment benefit was noted across all intrinsic molecular subtypes as measured by RNA sequencing, including patients with luminal A, luminal B, HER2-enriched, and basal-like cancers (Turner et al, 2023). Luminal A cancers had the lowest risk of recurrence, while HER2-enriched and basal-like subtypes had the highest. A treatment benefit with abemaciclib + ET was also observed across inferred 21-gene expression signature scores, both with an inferred Oncotype-RNA score of less than 25 (HR 0.59) and over 25 (HR 0.73), so this score was not predictive of benefit from the use of the adjuvant CDK4/6 inhibitor. Finally, a consistent treatment benefit of abemaciclib was also observed across the most prevalent genomic alterations, with a

lower benefit from abemaciclib seen in the subset of focal high-level MYC-amplified tumors compared to MYC non-amplified tumors. So at least for now, there are very few, if any, biomarkers that predict benefit from abemaciclib in the adjuvant setting.

CLINICAL THOUGHT

Based on the findings from the monarchE trial, will you offer adjuvant abemaciclib + ET to your patients with HR+/HER2- high-risk EBC?

a. Yes

b. No

c. I need more information to make a decision

d. Unsure at this time

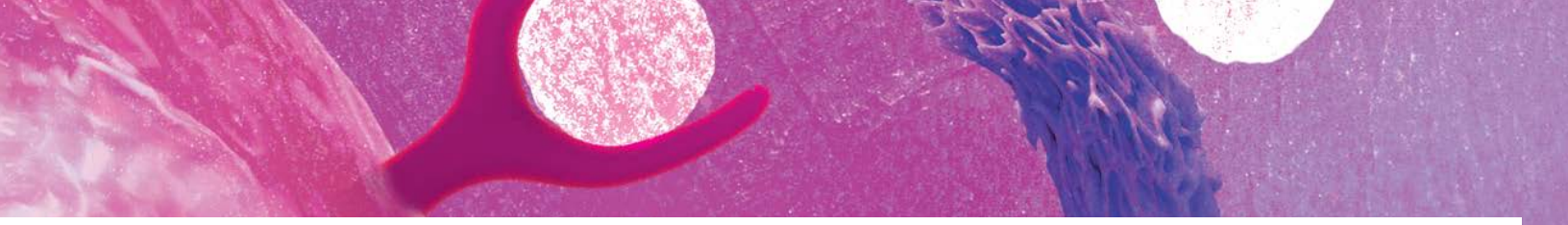
NATALEE
Ribociclib + ET

The phase III NATALEE trial evaluated adjuvant ribociclib + ET in a broad population of HR+/HER2- EBC patients at risk for recurrence, including those with stage II or III disease and those with no nodal involvement (N0; Slamon et al, 2023). Men and pre- or postmenopausal women were randomized 1:1 to ribociclib (400 mg/day; 3 weeks on/1 week off for 3 years) + ET (letrozole 2.5 mg/day or anastrozole 1 mg/day, for ≥5 years) or ET alone. Men and premenopausal women also received goserelin **(Figure 4a)**. Patients with anatomic stage IIA (either N0 with additional risk factors or 1-3 axillary lymph nodes [N1]), stage IIB, or stage III disease were eligible. Since patients with stage II and III HR+/HER2- EBC, including those with no nodal involvement, are at risk of disease recurrence for decades after initial diagnosis, an extended treatment duration of 3 years was chosen to prolong cell cycle arrest and drive more tumor cells into irreversible senescence or death. A dose of 400 mg/day, lower than the 600 mg/day starting dose approved for treatment in metastatic breast cancer, was chosen to improve tolerability while maintaining efficacy **(Figure 4b)**. The primary endpoint was IDFS.

View Figure 4a *View Figure 4b*

Overall, there was an absolute IDFS benefit of 3.3% at 3 years with ribociclib + ET (**Table 2**; Slamon et al, 2023). With a statistically significant hazard ratio of roughly .75, the risk of invasive disease was reduced by 25.2% with ribociclib + ET vs ET alone. The IDFS benefit with ribociclib + ET was consistent across prespecified key subgroups, including a benefit in stage II and stage III patients, as well as N0 patients. A consistent improvement in distant disease-free survival (DDFS) with ribociclib was also observed. DDFS is defined as the time from date of randomization to date of first event of distant recurrences, death (any cause), or second primary non-breast invasive cancer. The absolute DDFS benefit with ribociclib + ET at 3 years was 2.2%. The risk of distant disease was reduced by 26.1% with ribociclib + ET vs ET alone. Results from the final IDFS analysis were presented at the 2023 San Antonio Breast Cancer Symposium (SABCS; **Table 2**; Hortobagyi et al, 2023). The absolute IDFS benefit with ribociclib + ET was 3.1% at 3 years. The risk of invasive disease was reduced by 25.1% with ribociclib + ET vs ET alone. The absolute DDFS benefit with ribociclib + ET was 2.7% at 3 years. The risk of distant disease was reduced by 25.1% with ribociclib + ET vs ET alone at the final analysis. Overall survival was still very immature, but there was a trend for improved OS with ribociclib + ET.

View Table 2



Conference Callout: ASCO 2024

A subgroup analysis presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting of patients with high-risk, node-negative (N0) HR+/HER2- EBC from the NATALEE trial showed an improvement in rates of IDFS, DRFS, and DDFS with ribociclib + ET compared to ET alone (**Table 2**; Yardley et al, 2024). The 3-year IDFS rate was 90.6% with ET alone versus 93.2% with ribociclib + ET, with a 28% risk reduction in IDFS in the subgroup of patients with node-negative (N0) disease at high risk of recurrence. The 3-year DDFS rate was 91.5% versus 94.3%, with a hazard ratio of 0.70, and the 3-year DRFS rate was 92.5% versus 96.3%, with a hazard ratio of 0.58, in patients with high-risk N0 disease. These results outline the benefits of adjuvant ribociclib in node-negative disease.

CLINICAL THOUGHT

Would you offer adjuvant ribociclib + ET to your patients with node-negative EBC?

a. Yes

b. No

c. I need more information to make a decision

d. Unsure at this time

PALLAS and Penelope-B
Palbociclib + ET

The last set of CDK4/6 inhibitor trials, PALLAS and Penelope-B, examined palbociclib, the first CDK4/6 inhibitor that was approved in metastatic breast cancer. The PALLAS trial included patients with stage II and III HR+/HER2- breast cancer within 12 months of diagnosis, and within 6 months of starting adjuvant ET (Gnant et al, 2021, 2022). Patients were randomized to ET (tamoxifen or AI) or 2 years of palbociclib (125 mg orally once daily, 3 weeks on/1 week off) plus standard ET. The trial showed no benefit from combination palbociclib + ET in the adjuvant breast cancer setting, and no significant difference in IDFS at 4 years was observed (84.2% with palbociclib + ET versus 84.5% with ET alone, [HR 0.96]). The Penelope-B trial included patients with HR+/HER2- EBC who had no pathological complete response (pCR) after neoadjuvant chemotherapy, and were thus at high risk of relapse with a clinical pathological staging-estrogen receptor grading (CPS-EG) score of greater than 3, or 2 with node-positive disease (ypN+; Loibl et al, 2021). Patients were randomized to palbociclib + ET or placebo + ET. Palbociclib added to ET did not improve IDFS versus ET + placebo (HR 0.93).

A biomarker analysis in the PALLAS trial was presented at SABCS 2023 (Stover et al, 2023). As part of PALLAS trial eligibility, all patient provided a tumor tissue block prior to randomization for translational analyses (TRANS-PALLAS). Genomic subtype (PAM50 intrinsic subtype) measured from whole-transcriptome RNA sequencing data was defined in the protocol of the PALLAS trial as the primary biomarker for analysis of prediction and prognosis. There were 2,370 unique patients with intrinsic subtype defined from their untreated primary tumor: 65.6% luminal A, 12.1% luminal B, 7.0% HER2-enriched, 13.1% basal-like, and 2.2% normal-like. The proportion of luminal A cancers was unexpectedly high, indicating a lower-risk distribution of cancers in this population. When looking at the intrinsic subtype, there is essentially no differentiation in terms of benefit from the addition of the CDK4/6 inhibitor. The potential interaction between PAM50 metrics and palbociclib treatment benefit was not significant. Ultimately, PALLAS did not identify any biomarkers predicting benefit to palbociclib in the adjuvant setting.

Why Do PALLAS/Peneople-B and monarchE Findings Differ?

PALLAS and Penelope-B did not show a benefit with palbociclib in the adjuvant setting, in contrast to monarchE, which was positive for abemaciclib. Why are these results different? Michael Gnant, MD of the Medical University of Vienna proposed: *"There is one clear difference between how we use CDK inhibitors in these large trials, however, both palbociclib and ribociclib are given in a 3-week-on, 1-week off schedule, whereas abemaciclib is given continuously. Particularly in the early breast cancer setting, when we are not targeting proliferating disease but [inhibiting the] awakening of dormant cells, this could be an explanation for the observed differences in outcomes. At this point, however, this remains scientific speculation"* (ASCO Post, 2022). Other reasons have been postulated, but discounted by Dr. Gnant: (1) rates of early discontinuation of palbociclib were substantial, however, now inadequate exposure to palbociclib has been ruled out based on the competing risk analysis, (2) differences in patient selection are also "definitely not" the cause of the differences in outcomes Penelope-B evaluated a high-risk population with residual tumor after surgery and also showed no benefit for palbociclib; this trial also had a "markedly lower" treatment discontinuation rate than PALLAS but was still negative, and (3) differences in the molecules is also not likely the cause since these two CDK4/6 inhibitors produced almost identical progression-free survival benefits in the first-line and second-line settings of advanced breast cancer. More recent data from "real world studies" that reflect current practices with respect to how patients react to treatment in terms of tolerance and efficacy have suggested that there may actually be a benefit from the addition of adjuvant palbociclib to ET (Palmieri et al, 2023).

" Like any newer therapies, there is a learning curve with CDK4/6 inhibitors. Physicians need to conduct risk assessments on their patients following surgery, chemotherapy and radiation using the many tools currently available in order to determine who would benefit from the addition of these drugs. And then it is important to match potential adverse risks from these drugs to pre-existing patient comorbidities in order to minimize the risk of side effects. "

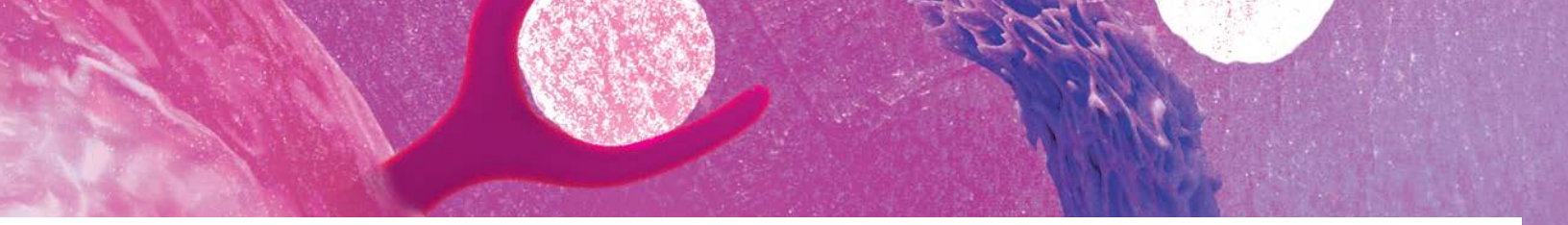
– Robert Mocharnuk, MD

Emeritus Professor of Clinical Medicine

View Expert Commentary

1. *Can you contextualize this evidence and summarize how to integrate adjuvant CDK4/6 inhibitors into treatment planning for community clinical care teams?*

2. *Assuming that ribociclib receives FDA approval for use in early breast cancer in addition to already approved abemaciclib, are there any special patient groups for whom you recommend one therapy over another?*



OlympiA

Olaparib, A PARP Inhibitor

What other therapies besides CDK4/6 inhibitors are available for women with HER2- breast cancer? The phase III OlympiA trial examined the PARP inhibitor olaparib as adjuvant therapy in HER2- (HR+ or TNBC) patients with high-risk stage II-III EBC who have germline *BRCA1/2* mutations after (neo)adjuvant chemotherapy [N]ACT (Tutt et al, 2021). Patients were randomized 1:1 to one year of continuous oral olaparib at 300 mg BID or placebo (**Figure 5**).

View Figure 5

Olaparib significantly improved the primary endpoint of IDFS and secondary endpoint of DDFS compared with placebo at the first event-driven interim analysis, with a median follow up of 2.5 years. OS did not cross the pre-specified boundary. In the second pre-specified analysis of OS and updated IDFS and DDFS with a median follow-up of 3.5 years, adjuvant olaparib significantly improved OS versus placebo, as well as IDFS and DDFS (Tutt et al, 2022). The 4-year OS rate was 89.8% for olaparib versus 86.4% for placebo, a difference of 3.4% (HR 0.68). The IDFS difference was substantial, at 7.3%, with a 4-year IDFS rate of 82.7% with olaparib versus 75.4% with placebo (HR 0.63). The 4-year DDFS rate was 86.5% vs 79.1%, a difference of 7.4% (HR 0.61). The olaparib benefit was consistent across all subgroups, including HR+. In 2022, the FDA approved olaparib for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2- high-risk EBC who have been treated with neoadjuvant or adjuvant chemotherapy based on the OlympiA trial (FDA.gov, 2022).

Post-Assessment Question 2

Five-year data from the monarchE trial showed that abemaciclib + ET reduced the risk of invasive disease (IDFS) in HR+/HER2- early breast cancer compared to ET alone by:

a. 19%

b. 22%

c. 32%

d. 45%

e. Unsure

Post-Assessment Question 3

Which is true of the NATALEE trial of adjuvant ribociclib + ET?

a. Included patients with no nodal involvement

b. Included patients with stage 3 disease only

c. Shortened treatment duration of 1 year

d. Increased ribociclib dose of 800 mg/day

e. Unsure

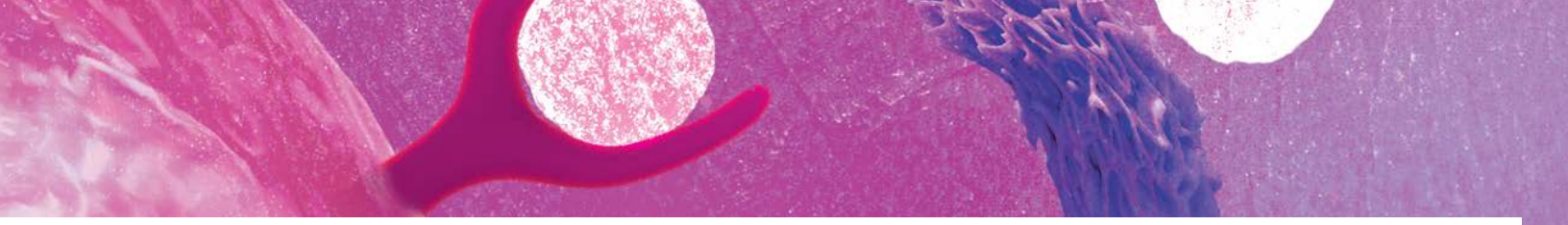
SECTION 3
FROM EVIDENCE TO PRACTICE: CDK4/6 INHIBITOR ADVERSE EVENTS

Adverse events with the CDK4/6 inhibitors abemaciclib and ribociclib in the adjuvant setting include neutropenia, liver function test (LFT) abnormalities, QT interval prolongation, diarrhea, and venous thromboembolism (VTE). The most frequent adverse events of any grade and any attribution in the monarchE trial were diarrhea, neutropenia, and fatigue in the abemaciclib + ET group, and arthralgia, hot flushes, and fatigue in the ET group (Johnston et al, 2022, 2023). Venous thromboembolic events were more frequent with abemaciclib + ET (2.5%) versus ET alone (0.7%). The most common grade 3-4 adverse events in the monarchE trial in the abemaciclib + ET group versus in the ET alone group were neutropenia (19.6% vs 0.9%), leukopenia (11.4% vs 0.4%), and diarrhea (7.8% vs 0.2%; Johnston et al, 2023). The most frequently reported serious adverse events in both groups were infections (5.3% vs 2.9%) and gastrointestinal disorders (2.1% vs 0.6%). Overall, abemaciclib was relatively safe with a manageable toxicity profile. In the abemaciclib + ET arm, 43.6% of patients required dose reductions due to adverse events, 61.7% had a treatment interruption, and 16.6% discontinued treatment. The most frequent causes of abemaciclib + ET discontinuation were diarrhea (2.4%) and fatigue (1.0%; Johnston et al, 2023). Abemaciclib treatment interruption due to adverse events were generally related to diarrhea, neutropenia, or fatigue. In the 5-year outcome update, no new safety concerns were identified, and there were higher rates of serious adverse events regardless of causality observed at long-term follow-up in the ET alone arm (7.3%) compared with abemaciclib + ET (6.5%), predominantly because of more infections and GI disorders (Rastogi et al, 2024). Dose adjustments and treatment discontinuations due to adverse events were more common in older patients, especially those > 75 years of age (Hamilton et al, 2023). More frequent surveillance with early intervention may be needed to manage these patients. However, multiple analyses have demonstrated that the effectiveness of adjuvant abemaciclib was not compromised by dose reductions (Hamilton et al, 2023; O'Shaugnessy et al, 2023; **Figure 6**).

View Figure 6

In the NATALEE trial, ribociclib had a well-tolerated safety profile (Slamon et al, 2023). Adverse events of special interest included neutropenia, liver-related adverse events, QT interval prolongation, and interstitial lung disease or pneumonitis. Ribociclib at a starting dose of 400 mg showed lower rates of dose-dependent toxicities such as neutropenia and QTc prolongation and less need for dose modifications when administered up to 3 years, compared with the standard starting dose of 600 mg in metastatic breast cancer. Treatment discontinuation occurred in 19.5% of patients. The most frequent all-grade adverse events leading to ribociclib + ET discontinuation were liver-related adverse events (8.9%) and arthralgia (1.3%). Grade ≥3 adverse events in the ribociclib + ET vs ET alone group included neutropenia (44.3% vs 0.9%), liver-related AEs (8.6% vs 1.7%), and QT interval prolongation (1.0% vs 0.6%). Most discontinuations of ribociclib occurred early in treatment, with a median time to discontinuation of 4 months. While LFT abnormalities are an issue with ribociclib in the adjuvant setting, these are reversible in the vast majority of patients. In the final analysis, no new safety signals were observed, contributing to the manageable toxicity profile of ribociclib at the 400 mg starting dose (Hortobagyi et al, 2023).

When monitoring for adverse events with CDK4/6 inhibitors, CBC, LFTs, ECGs, and electrolyte testing should be enlisted (KISQALI [ribociclib] prescribing



information, 2024; VERZENIO [abemaciclib] prescribing information, 2024; **Table 3**). For diarrhea typically associated with abemaciclib, at the first sign of loose stools, antidiarrheal therapy should be initiated along with an increase of oral fluids. The CDK4/6 inhibitor can be withheld and potentially dose-reduced for the next cycle. Patients should be monitored for signs and symptoms of thrombosis and pulmonary embolism, such as shortness of breath or limb swelling, usually a lower extremity.

View Table 3

"It is important to consider setting up a system for periodic symptom assessment, laboratory monitoring, and management for these patients knowing that cytopenias and GI symptoms can be a concern for tolerability and adherence to treatment. Additionally, many of these medications have potential for CYP3A4 drug interactions that may require dose adjustments. Utilizing clinical oncology pharmacists (whether that be through collaboration with specialty pharmacies and/or involvement directly in ambulatory care clinics) can be beneficial in reducing the burden on providers by assisting in timely monitoring and management, as well as increasing identification on drug interactions and dose adjustments."

– Adrienne N. Nedved, PharmD, MPA, BCOP

Hematology/Oncology Pharmacist, Mayo Clinic

Although rare, there is an increased risk of ILD with CDK4/6 inhibitors (FDA.gov, 2019). Patients need to be monitored regularly for pulmonary symptoms indicative of ILD and/or pneumonitis, including hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Patients should notify their healthcare professional immediately if they have sudden shortness of breath that is worse than usual, especially when climbing stairs, or develop a sudden cough or fever.

"In my experience, ILD from the CDK4/6 inhibitors is uncommon, but when it does occur, it tends in my experience to be reversible on discontinuation of the drug."

– Adam Brufsky, MD, PhD

Professor of Medicine, UPMC Hillman Cancer Center

View Expert Commentary

1. *Can you summarize/highlight the importance of interprofessional team (MD, RN, PA, pharmacist) collaboration and communication in managing adverse events?*
2. *Do you notice any differences in side effects among the various CDK4/6 inhibitors, depending on the type of endocrine therapy they are paired with?*
3. *When considering adjuvant CDK4/6 inhibitors, how much of a concern/impact do comorbidities have with full dosing?*

CLINICAL THOUGHT

Would you implement dose reductions to mitigate adverse events and keep patients on therapy?

a. Yes

b. No

c. I need more information

d. Unsure

Post-Assessment Question 4

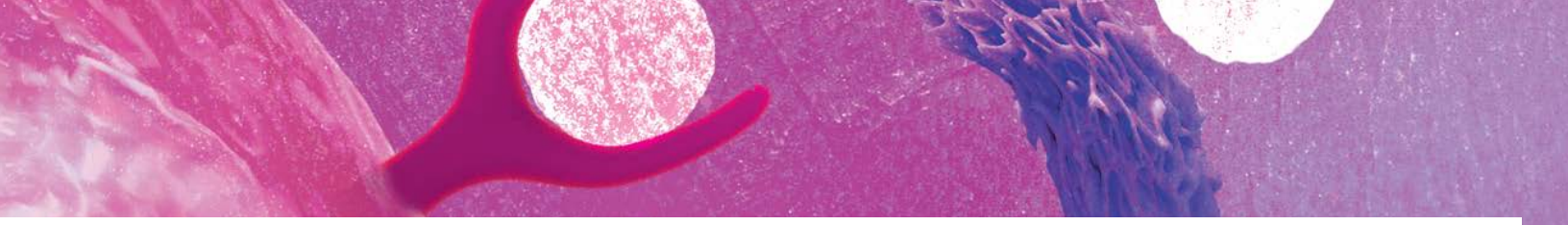
Which is true regarding dose modifications to manage adverse events with adjuvant abemaciclib?

a. Dose modifications were less common in older patients

b. Efficacy is maintained with dose modifications

c. Effectiveness is compromised by dose reductions

d. Unsure



SECTION 4
PROMOTING PATIENT ENGAGEMENT TO MAXIMIZE ADHERENCE, PERSISTENCE, AND OUTCOMES

Adherence to oral adjuvant therapy is challenging, and manageable toxicity profiles are crucial for new treatments. Dose reductions are frequently used to manage treatment-related toxicity and improve treatment adherence. By adjusting the dosage to better align with individual patient tolerability, clinicians can mitigate side effects and enhance the overall adherence to the prescribed treatment regimen.

Maintaining treatment compliance involves medication adherence (degree of medication-taking behavior aligning with physician recommendations, including timing, dosage, and frequency) and persistence (duration of therapy from commencement to discontinuation) (Sella, 2020). Optimal adherence and persistence require an effective and convenient drug regimen with minimal side effects and a positive and supportive approach to treatment, especially through the patient-physician relationship (Cavazza, 2020). Both early discontinuation and nonadherence to adjuvant therapy were associated with increased risk of breast cancer recurrence and mortality (Sella, 2020). Nonadherence is associated with poor outcomes, and can lead to increased physician visits, more frequent or longer hospitalizations, disease progression, development of resistance, and even death.

> *“For oral therapy there is an improved quality of life. There are fewer clinic visits, less travel, you avoid the intravenous infusions, and the patients empower themselves to treat themselves. There is, however, increased patient responsibility.”*
>
> *– Adam Brufsky, MD, PhD*
>
> *Professor of Medicine, UPMC Hillman Cancer Center*

Addressing various patient factors, including patient mental health, disease severity, patient perceptions, effective intervention components such as good communication/shared decision-making (SDM) and patient education, and improved coordination for continued follow-up may improve patient adherence/persistence to therapy (Heiney, 2019; Cavazza, 2020). Shared decision-making can help with adherence to CDK4/6 inhibitors in the adjuvant setting. Treatment decisions should involve shared decision-making (SDM) between patients and healthcare providers, and take into consideration individual preferences, goals, and values (Agency for Healthcare Research and Quality, 2014). Patients desire information and active involvement in the decision-making process for their treatment, leading to higher satisfaction and better outcomes (Josfeld, 2021). Additionally, the Oncology Nursing Society (ONS) has developed evidence-based guidelines for interventions to support patient adherence to oral anticancer medications, including adherence risk assessment, education, ongoing assessments, proactive follow-up, coaching, motivational interviewing, and implementation of a structured program (Belcher, 2022).

“ Shared decision-making – this is where a healthcare provider and patient work together to make sure that the healthcare decision is in the best interest of the patient. I think that it takes into account available options, the provider’s knowledge, and the patient’s values – they are important. In the SHARE approach to shared decision-making, you seek your patient’s participation, help your patient explore and compare treatment options, assess your patient’s values, reach a decision with the patient, and then evaluate your patient’s decision. It is an interactive approach. ”

– Adam Brufsky, MD, PhD

Professor of Medicine, UPMC Hillman Cancer Center

CLINICAL THOUGHT

Do you utilize shared decision-making strategies in your practice to improve patient adherence?

a. Yes

b. No

c. I need more information

d. Unsure

Focused education and follow-up over time are needed to ensure patients are taking their medications properly. One strategy to enhance patient adherence is to make it “simple” by following the mnemonic in **Table 4** (Atreja et al, 2005).

View Table 4

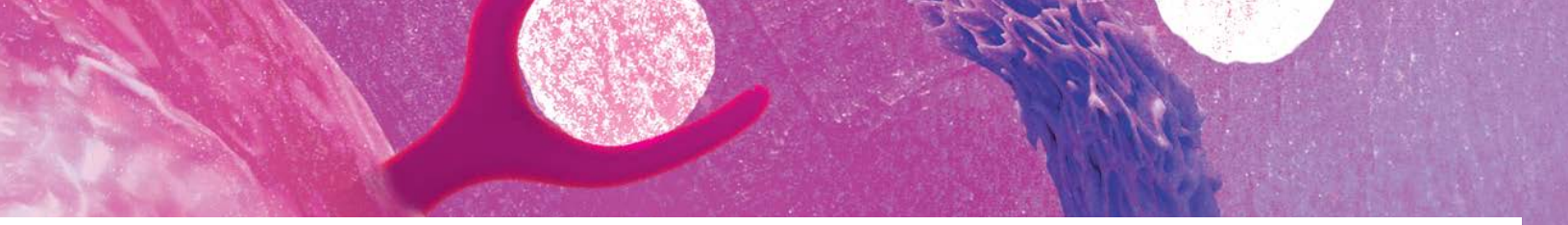
View Expert Commentary

1. *How are you using shared decision-making in your practice?*
2. *How do you monitor compliance to oral therapies in your own practice?*
3. *What are the major obstacles for the interprofessional team and patients to adherence in the community setting?*
4. *Are there any specific tips that your interprofessional team uses to improve compliance to oral therapies?*

“ Healthcare teams must utilize a collaborative approach to improve medication adherence. The involvement of team members such as nurses, pharmacists, advanced practice providers, and physicians is pivotal to ensure patient understanding and compliance. Supportive oncology team members such as dieticians, physical therapists, and psychologists also play an important role in helping patients to mitigate side effects from treatment including but not limited to diarrhea, fatigue, and deconditioning. Team members should be called upon to provide education, monitoring, and continued follow-up starting at the time when medications are initially discussed and prescribed and not just when side effects arise. ”

– Melissa Duffy, MSPAS, PA-C

Physician Assistant, Northwestern Medicine



Post-Assessment Question 5

Which of the following strategies may help to improve patient adherence to medication?

a. Ensure the patient remains on the recommended starting dose without dose reduction to not compromise efficacy

b. Refrain from overwhelming the patient by sending reminders via text, phone, or email

c. Include patients in the treatment decision-making process

d. Make a treatment decision for the patient based on supporting clinical evidence and patient preferences

e. Unsure

View Practical Application Case Review

Downloadable Slide Deck

LINKS TO HELPFUL RESOURCES

- Predict Breast Cancer
- What is Early Breast Cancer?
- Addressing Side Effects – Abemaciclib
- Addressing Side Effects – Ribociclib
- Prescribing and Patient Information – Abemaciclib
- Prescribing and Patient Information – Ribociclib
- Shared Decision-Making
- Adherence
- ONS Guidelines™ to support patient adherence to oral anticancer medications
- NCCN Guidelines® for Breast Cancer

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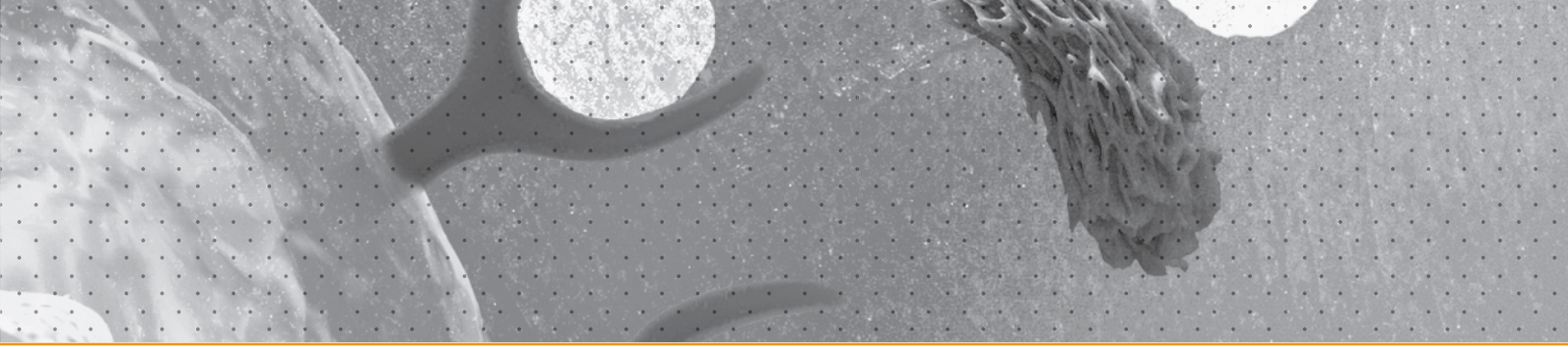

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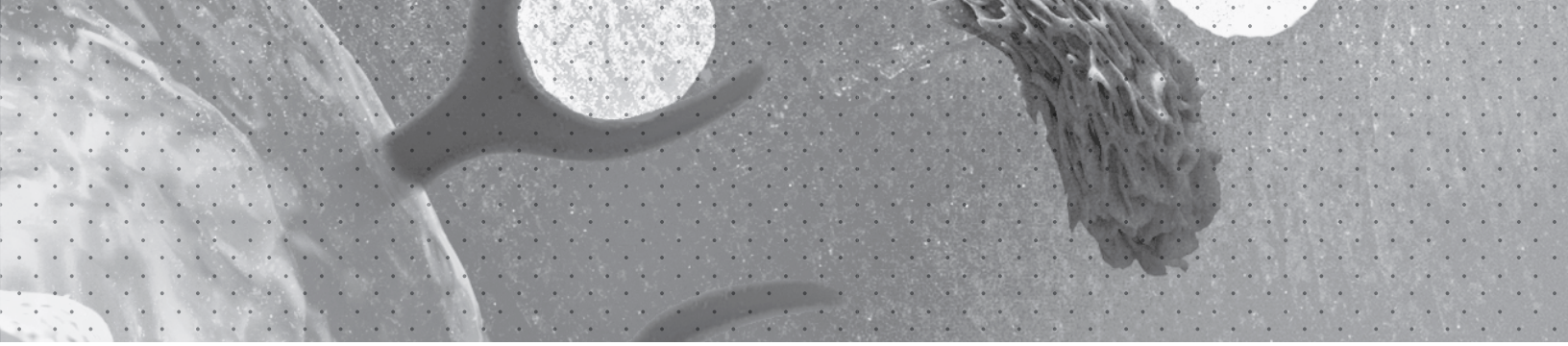

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About AXIS Medical Education, Inc.

AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, web-based, and print-based educational activities for healthcare professionals. AXIS provides convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 75 years of experience in adult learning theory, curriculum design/implementation/assessment, continuing education accreditation standards, and medical meeting planning and logistics. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities. AXIS employs an experienced team of medical and scientific experts, medical writers, project managers, meeting planners, and logistics professionals. This team is dedicated to meeting the unmet educational needs of healthcare professionals, with the goal of improving patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. To that end, AXIS partners with other organizations and accredited providers to offer added expertise and assist in expanding access to our educational interventions. AXIS also partners with numerous patient advocacy organizations to provide recommended patient education and caregiver resources in specific disease areas. AXIS finds value in these partnerships because they complement our core clinical curriculum with validated and relevant supplemental resources for busy clinicians and their patients.

The mission of AXIS is to enhance the knowledge, skills, competence, and performance of the interprofessional healthcare team to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led certified educational activities designed to foster lifelong learning that is applicable to clinical practice and patient-centered care.

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