Beyond Standard Endocrine Therapy: A New Adjuvant Treatment in High-Risk Early Breast Cancer

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

The standard adjuvant treatment of estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (EBC) is endocrine therapy (ET). Despite this treatment, 20% of patients will have their disease recur. Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors with ET have shown overall survival (OS) benefit in ER-positive, HER2-negative breast cancer in the metastatic setting. Clinical trials are studying the role of oral CDK4/6 inhibitors in the adjuvant treatment of ER-positive, HER2-negative EBC patients who are clinically and pathologically at high risk for recurrence while on standard ET. The monarchE phase III, randomized, controlled trial, looked at one arm of high-risk ER-positive, HER2-negative EBC patients receiving standard ET and the second arm receiving standard ET with a CDK4/6 inhibitor, abemaciclib. Primary endpoint data showed improvement in invasive disease-free survival of 92.2% in the ET and abemaciclib arm vs. 88.7% in the ET arm at 2 years. At 5 years, a preplanned interim analysis showed continued absolute improvement in invasive disease-free survival. Secondary endpoint data for OS have not yet matured. Abemaciclib is approved for use with ET in patients with high-risk, ER-positive, HER2-negative EBC. This article aims to review a case study and the rationale for using oral CDK4/6 inhibitors as adjuvant treatment for this high-risk subset of patients.

CASE STUDY

Mrs. J is a 29-year-old premenopausal female who palpated a lump in her right breast. A right breast ultrasound revealed two irregular masses and an abnormal right axillary lymph node. A diagnostic mammogram showed two adjacent, spiculated right breast masses measuring 1.2 cm and 1.1 cm at 12 o'clock and 4 cm from the nipple (Figure 1). The biopsy-derived pathology from both masses showed intermediate-grade invasive ductal carcinoma, estrogen receptor (ER)-positive 100%, progesterone receptor (PR)-positive 2%, and human epidermal growth factor receptor

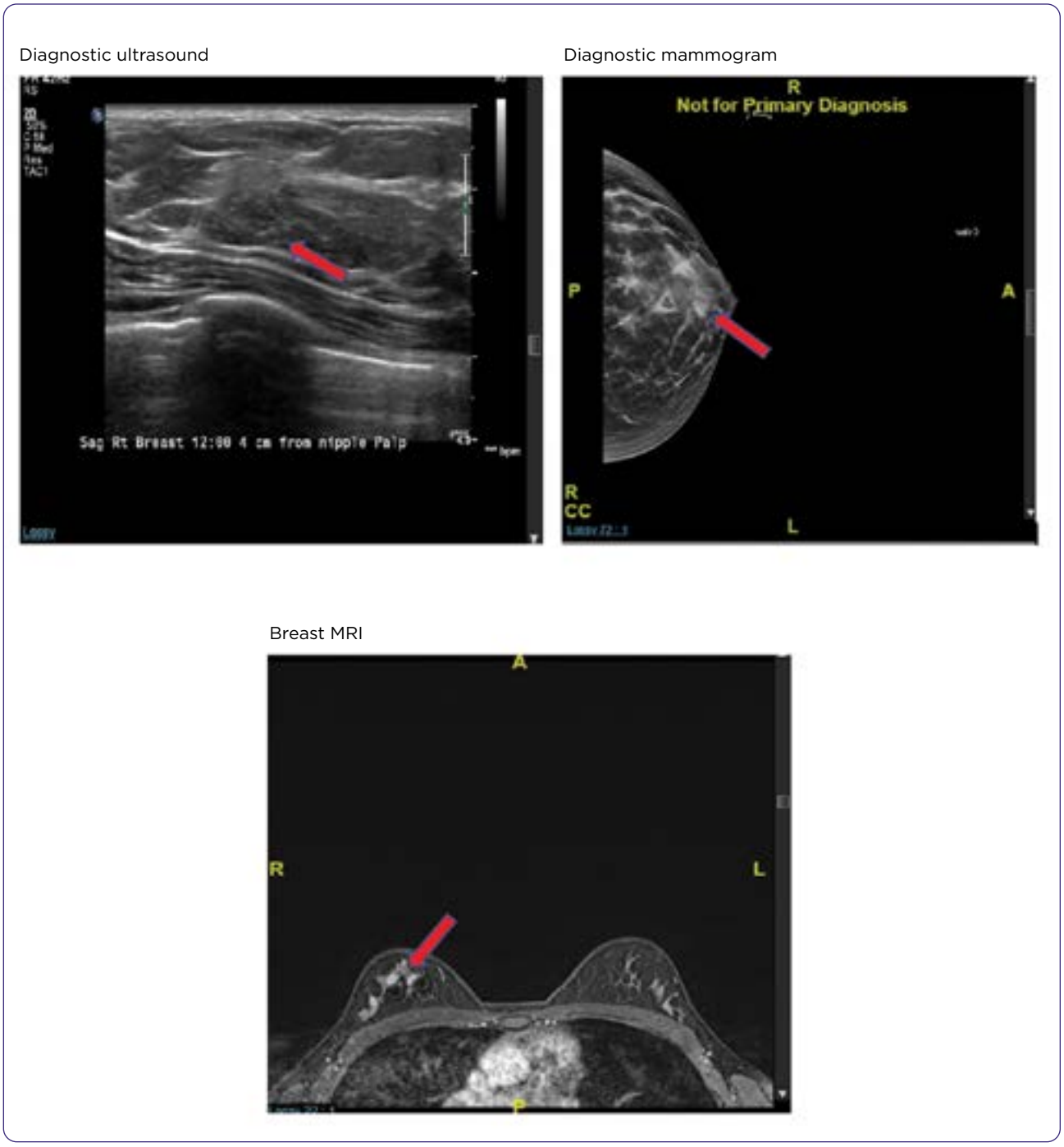

Figure 1. Initial imaging findings after self-palpating right breast mass. Arrows indicate the right breast mass in each image type.

2 (HER2)-equivocal by immunohistochemistry (IHC) and not overexpressed on fluorescence in situ hybridization (FISH). The right axillary lymph node biopsy was benign.

An MRI of the breasts confirmed the two right breast masses, measuring 2 cm and 1.8 cm. These masses were part of a contiguous abnormal area of multifocal and multicentric disease estimated at 5 × 6 cm. After a discussion with her surgeon about her options, Mrs. J elected to proceed with a bilateral mastectomy, with a sentinel lymph node biopsy on the right and

immediate initiation of reconstruction. The final pathology from the right mastectomy revealed multifocal, moderately differentiated invasive ductal carcinoma with the largest masses 14 mm and 17 mm, Ki-67 of 19%, and clear final margins. In addition, there were minimal scattered foci of intermediate nuclear grade cribriform ductal carcinoma in situ (DCIS). Two total lymph nodes had invasive cancer involvement. Staging CT scans and a bone scan showed no evidence of metastatic disease. Her final stage was IIA (pT1cN1aM0).

Mrs. J received adjuvant chemotherapy with docetaxel and cyclophosphamide given every 3 weeks for six cycles, followed by adjuvant radiation. She had monthly leuprolide injections for ovarian suppression during chemotherapy and radiation due to her premenopausal status. After completing radiation, she returned for a discussion about starting adjuvant endocrine therapy (ET). Her germline genetic testing results showed a variant of uncertain significance (VUS) for the *BRCA2* gene but no actionable pathogenic mutations. A baseline bone density test showed normal bone density. Factors to consider for recommending adjuvant ET for Mrs. J were age, menopausal status, surgical pathology results, germline genetic testing results, baseline bone density measurements, current performance status, and overall risk of disease recurrence.

Endocrine therapy (ET) has been the standard of care for treating patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (EBC) dating back to 1985 with the initial approval of tamoxifen in the adjuvant setting (Early Breast Cancer Trialists' Collaborative Group, 1998; Midatech Pharma, 2018). Aromatase inhibitors (AIs) were introduced as the standard of care in postmenopausal ET for HR-positive EBC after the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial results in 2002 (Baum et al., 2003). Despite treatment with tamoxifen or an AI for at least 5 years, one fifth of ER-positive and HER2-negative EBC patients will recur locally or with distant metastatic disease (Abdel-Razeq & Sharaf, 2022).

Specific clinical and pathologic features are identified as high risk within the one fifth of patients who recur with standard adjuvant ET. The National Comprehensive Cancer Network (NCCN) defines high risk as having ≥ 4 lymph nodes involved with cancer, or 1 to 3 lymph nodes involved, and a tumor size ≥ 5 cm or grade 3 disease (NCCN, 2023). The 5-year survival rates for patients with stage II and III breast cancer are 93% and 72%, respectively (Alkabban & Ferguson, 2023).

For the adjuvant treatment of ER-positive, HER2-negative EBC patients, new groundbreaking studies propose adding oral cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors to ET for a subset of these patients with a higher risk of recurrence. Until recently, standard ET was the only recommended treatment choice for this subset of high-risk patients. New data thus far has led to one oral CDK4/6 inhibitor being approved for use in these patients.

MECHANISMS OF ACTION OF ADJUVANT TREATMENTS

Tamoxifen binds with estrogen receptors, competing with endogenous estrogen. Receptor-bound estrogen promotes the proliferation of ER-positive cancer cells (Midatech Pharma, 2018). In postmenopausal women, AIs disrupt the pathway of the enzyme aromatase that typically converts androgens into estrogen at the level of the skin, adipose tissue, muscle, and adrenal glands. Aromatase inhibitors, therefore, suppress estrogen levels. With the lack of circulating estrogen, it cannot bind to the estrogen receptors inside the cancer cell, thus inhibiting malignant cellular growth (Peters & Tadi, 2023).

Oral CDK4/6 inhibitors block the phosphorylation mechanism of the retinoblastoma protein by selective inhibition at the time of the first gap (G_1) phase inside the cell. This inhibitory process stops the cell cycle, interrupting deoxyribonucleic acid (DNA) synthesis and its normal progression to the synthesis (S) phase, which results in the cessation of malignant cellular proliferation (Eli Lilly, 2023; Lukasik et al., 2021). For reasons not entirely

clear at this time, but thought to be related to ET resistance, there appears to be a synergistic effect when CDK4/6 inhibitors combine with ET (Watt & Goel, 2022).

METASTATIC BREAST CANCER DATA

Oral CDK4/6 inhibitors in combination with ET exhibit a clinically meaningful and statistically significant progression-free survival (PFS) and overall survival (OS) benefit in the ER-positive, HER2-negative metastatic breast cancer (MBC) setting (Cristofanilli et al., 2022; Hortobagyi et al., 2022; Sledge et al., 2020). The MONARCH 2 trial (Sledge et al., 2020) studied the CDK4/6 inhibitor abemaciclib (Verzenio) plus fulvestrant (Faslodex) vs. fulvestrant alone in *ERBB2* (HER2)-negative MBC in 669 patients. At a preplanned interim analysis, there was an improvement in PFS of 16.4 months vs. 9.3 months (hazard ratio [HR], 0.553; 95% confidence interval [CI] = 0.449–0.681; $p < .001$) and an improvement in OS (HR, 0.757; 95% CI = 0.606–0.945; $p = .01$) of 46.7 months vs. 37.3 months. Patients can continue the trial until discontinuation criteria are met, with data collection planned for 10 years or until 2024.

After more than 6 years, an updated analysis of the PALOMA-3 study (Cristofanilli et al., 2022) in 521 HR-positive, HER2-negative patients with MBC proved that the use of the CDK4/6 inhibitor palbociclib (Ibrance) with fulvestrant vs. placebo and fulvestrant alone demonstrated a continued OS benefit of 34.8 months and 28.0 months, respectively. The median PFS was 11.3 months in the palbociclib arm vs. 3.6 months with ET alone. The trial reached completion in September 2022.

The CDK4/6 inhibitor, ribociclib (Kisqali), via the MONALEESA-3 trial (Hortobagyi et al., 2022) with 721 patients, showed an OS benefit after 6.6 years when used in combination with letrozole (Femara) vs. placebo with letrozole in the HR-positive, *ERBB2* (HER2)-negative MCB setting. The OS of the ribociclib arm was 63.9 months vs. the placebo arm of 51.4 months, and PFS was 25.3 months vs. 16.0 months. The trial reached completion in January 2023.

The successful use of CDK4/6 inhibitors in the MBC setting led to clinical trial development to assess the benefit of CDK4/6 inhibitors with standard ET in the adjuvant setting in high-risk, ER-positive, and HER2-negative EBC (Abdel-Razeq & Sharaf, 2022; Sledge et al., 2020).

ADJUVANT APPLICATION

The monarchE phase III trial (Johnston et al., 2020) is an open-label randomized trial of 5,637 patients studying 2 years of abemaciclib dosed at 150 mg twice daily to standard ET for HR-positive, HER2-negative high-risk EBC in the adjuvant setting. Patients enrolled completed standard treatment with neoadjuvant or adjuvant chemotherapy, surgery, and radiation as indicated. Patients could be men or pre/postmenopausal women. The trial's high-risk definition included participants with ≥ 4 involved axillary lymph nodes, or 1 to 3 involved axillary lymph nodes with either a tumor size ≥ 5 cm, a grade 3 histology, or a Ki-67 mitotic index ≥ 20%. Patients with node-negative disease, inflammatory breast cancer, and metastatic disease were excluded. There could be no prior use of a CDK4/6 inhibitor or preventative ET. Patients who met the inclusion criteria were randomized to either the control arm with standard ET or to standard ET with oral abemaciclib.

The 2-year duration for using adjuvant abemaciclib in the monarchE trial was chosen based on recurrence data from past studies (Johnston et al., 2020). In EBC patients on ET, recurrent malignancy occurs most commonly within 2 years of starting ET and is thought to be related to primary endocrine resistance (Cardoso et al., 2018).

The monarchE phase III trial's (Johnston et al., 2020) primary endpoint was invasive disease-free survival (IDFS). A preplanned analysis of the trial at 2 years showed abemaciclib with ET to be superior with a statistically significant IDFS (HR, 0.75; 95% CI = 0.60–0.933; $p = .01$) of 92.2% vs. 88.7% with ET alone. In the control arm with ET alone, 11.3% of patients developed recurrent invasive disease, 75% of which were distant recurrences. In adding abemaciclib to ET for 2 years, there was a 3.5% absolute improvement in IDFS, reducing the risk of invasive disease from 11.3% to 7.8%. At 3 and 4 years, the absolute improvement in IDFS was 4.8% and 6%, respectively (Johnston et al., 2023). Rastogi and colleagues (2024) reviewed the preplanned interim analysis of the monarchE trial at 5 years, which showed an absolute improvement in IDFS of 7.6% in the

Table 1. Safety Results From the monarchE Trial

	Abemaciclib + ET (*n* = 2,791)			ET alone (*n* = 2,800)		
≥ 10% in either arm	**Any grade**	**Grade 3**	**Grade 4**	**Any grade**	**Grade 3**	**Grade 4**
Any adverse event	2,731 (97.9)	1,200 (43.0)	70 (2.5)	2,410 (86.1)	335 (12.0)	19 (0.7)
Diarrhea	2,294 (82.2)	212 (7.6)	0	199 (7.1)	3 (0.1)	0
Neutropenia	1,246 (44.6)	501 (18.0)	18 (0.6)	141 (5.0)	16 (0.6)	3 (0.1)
Fatigue	1,073 (38.4)	78 (2.8)	0	433 (15.5)	4 (0.1)	0
Leukopenia	1,027 (36.8)	301 (10.8)	4 (0.1)	171 (6.1)	10 (0.4)	0
Abdominal pain	948 (34.0)	37 (1.3)	0	227 (8.1)	9 (0.3)	0
Nausea	779 (27.9)	13 (0.5)	0	223 (8.0)	1 (0.0)	0
Anemia	638 (22.9)	47 (1.7)	1 (0.0)	90 (3.2)	9 (0.3)	1 (0.0)
Arthralgia	571 (20.5)	6 (0.2)	0	876 (31.3)	18 (0.6)	0
Hot flush	393 (14.1)	3 (0.1)	0	587 (21.0)	8 (0.3)	0
Lymphopenia	372 (13.3)	140 (5.0)	2 (0.1)	94 (3.4)	13 (0.5)	0
Thrombocytopenia	341 (12.2)	25 (0.9)	6 (0.2)	40 (1.4)	1 (0.0)	2 (0.1)
Vomiting	455 (16.3)	13 (0.5)	0	117 (4.2)	2 (0.1)	0
Constipation	288 (10.3)	1 (0.0)	0	142 (5.1)	0	0
Upper respiratory infection	285 (10.2)	6 (0.2)	0	214 (7.6)	0	0
Urinary tract infection	284 (10.2)	13 (0.5)	0	170 (6.1)	6 (0.2)	0
Decreased appetite	312 (11.2)	15 (0.5)	0	54 (1.9)	1 (0.0)	0
Headache	482 (17.3)	6 (0.2)	0	359 (12.8)	3 (0.1)	0
Cough	337 (12.1)	1 (0.0)	0	193 (6.9)	0	0
Lymphedema	285 (10.2)	2 (0.1)	0	208 (7.4)	0	0
Additional adverse events of interest[a]						
Aspartate aminotransferase increase	257 (9.2)	43 (1.5)	3 (0.1)	106 (3.8)	13 (0.5)	0
Alanine aminotransferase increase	265 (9.5)	59 (2.1)	5 (0.2)	119 (4.3)	16 (0.6)	0
Alopecia	254 (9.1)	0	0	53 (1.9)	0	0
Venous thromboembolic event	63 (2.3)	27 (1.0)	6 (0.2)	14 (0.5)	4 (0.1)	0
Interstitial lung disease[b]	75 (2.7)	9 (0.3)	0	33 (1.2)	1 (0.0)	0

Note. ET = endocrine therapy. Data are presented as No. (%). Adapted from Johnston et al. (2020).
[a]Includes events of clinical significance and/or observed in earlier clinical studies of abemaciclib.
[b]Term is based on the standard MedDRA Query.

abemaciclib arm, lowering the risk of recurrent invasive disease from 11.3% to 3.7%. Adding abemaciclib to standard ET demonstrated sustainability and continuous improvement in IDFS.

The trial's secondary endpoints were safety, distant relapse-free survival (DRFS), and OS. The safety data for the monarchE trial (Table 1) shows the available safety data of abemaciclib. The most common side effect reported was diarrhea (Johnston et al., 2020). There was a statistically significant DRFS in the abemaciclib with ET group vs. the ET alone group (HR, 0.675; nominal $p < .001$) at 5 years. Overall survival data at 5 years was not statistically significant. There is a planned analysis

of OS at the time of the trial completion in 2029 (Rastogi et al, 2024).

Based on the monarchE data, abemaciclib was approved in late 2021 by the United States Food and Drug Administration (FDA) as the first adjuvant treatment of its kind for HR-positive, HER2-negative, high-risk EBC patients in over 16 years (US Food & Drug Administration, 2021; Royce et al., 2022). However, the current approximate retail cost of 30 days of full-dose treatment with abemaciclib is $15,853 (GoodRx, 2023).

CASE STUDY CONTINUED

Mrs. J discussed her options for further adjuvant treatment beyond chemotherapy and radiation therapy with her health-care providers. She had a good performance status, a normal baseline bone density, no significant germline genetic mutations, and her cancer had high-risk clinicopathologic features. Given her premenopausal status, her providers recommended continued leuprolide injections for ovarian suppression and an oral AI for 5 years, followed by tamoxifen for 5 years. They reviewed the monarchE trial findings and felt she was a candidate for adjuvant abemaciclib. She agreed to start abemaciclib 150 mg twice daily for 2 years. She received patient assistance to make the medication affordable for her.

After 3 months on adjuvant abemaciclib and an AI, Mrs. J has tolerated treatment well. She initially had diarrhea as a side effect of abemaciclib, but it resolved with loperamide. She developed gastroesophageal reflux and used famotidine for relief. She has occasional hot flashes due to estrogen suppression while on leuprolide injections. The hot flashes have not changed since starting the oral treatment combination. She plans to pursue breast reconstruction soon.

CONCLUSION

In the ER-positive, HER2-negative MBC setting, oral CDK4/6 inhibitors have shown an OS benefit when used with ET (Peters & Tadi, 2023). The monarchE phase III trial results led to abemaciclib becoming the first FDA-approved oral CDK4/6 inhibitor for use with ET in the adjuvant setting for ER-positive, HER2-negative high-risk EBC patients. The continued improvement in IDFS in the abemaciclib arm over time for these patients is promising, with OS data pending a final analysis upon trial completion planned for 2029 (US Food & Drug Administration, 2021; Johnston et al., 2023; Rastogi et al., 2024; Royce et al., 2022; US National Institutes of Health, 2017).

There are additional clinical trials with other oral CDK4/6 inhibitors for use in the adjuvant setting in the HR-positive, HER2-negative, high-risk EBC population (Table 2). The New Adjuvant Trial with Ribociclib (LEE011), or NATALEE, has studied ribociclib with ET vs. ET alone in EBC that is node-positive or node-negative in the adjuvant setting, using a lower dose of ribociclib of 400 mg than is used for MBC, and for a duration of 3 years (US National Institutes of Health, 2018). Recent trial data has shown an improved IDFS of 90.4% with ribociclib vs. 87.1%

Table 2. CDK4/6 Inhibitor Trials in the Adjuvant Setting in EBC

Name/Trial ID	Phase	Population characteristics	Intervention	Primary endpoint	Secondary endpoints[a]
monarchE/ NCT03155997	III	HR+/HER2–, high-risk, node-positive EBC	Abemaciclib + ET vs. ET	IDFS	DRFS, OS
PENELOPE-B/ NCT01864746	III	HR+/HER2– EBC	Palbociclib + ET vs. ET	IDFS	DRFS, OS
PALLAS/ NCT02513394	III	HR+/HER2– EBC	Palbociclib + ET vs. ET	IDFS	DRFS, OS
NATALEE/ NCT03701334	III	HR+/HER2– EBC	Ribociclib + ET vs. ET	IDFS	RFS, DDFS, OS

Note. DDFS = distant disease-free survival; DRFS = distant recurrence-free survival; EBC = early breast cancer; ET = endocrine therapy; HR = hormone receptor; IDFS = invasive disease-free survival; OS = overall survival; RFS = recurrence-free survival. Data derived from ClinicalTrials.gov (US National Institutes of Health, 2023).
[a]Not all secondary endpoints are listed.

with ET alone and a reduced risk of invasive disease recurrence by 25% by adding ribociclib to ET. This information has been submitted to the FDA, and the trial is set to be completed in 2026 (Slamon et al., 2023; Novartis, 2024). The trial is set to be completed in 2026 (Slamon et al., 2023). Thus far, adjuvant clinical trials have not shown benefit from adding palbociclib to standard ET (Gnant et al., 2022; Loibl et al., 2021). Given the positive data with palbociclib in OS in the MBC setting, more studies may be warranted (Cristofanilli et al., 2022). To date, there are no planned head-to-head trials in the adjuvant setting looking at CDK4/6 inhibitors.

Implications for Advanced Practitioners

The advanced practitioner (AP) working in oncology will assist patients in managing adverse events (Table 1) related to the use of adjuvant abemaciclib. Advanced practitioners must be aware of the high risk of diarrhea (81% to 90% of patients), particularly in the first month of use of abemaciclib, and advise patients on aggressive intervention with loperamide and oral fluid intake. Persistent grade 3 to 4 diarrhea may require dose reductions and, in some cases, discontinuation of the drug. They should watch for neutropenia, occurring in 37 to 46% of patients. Grade 3 to 4 neutropenia may require dose interruption, reduction of the dose, or a delay in the start of the subsequent treatment cycle. Interstitial lung disease (ILD) occurs in less than 3% of patients, but the AP will need to consider this diagnosis if their patient presents with cough, dyspnea, or hypoxia. For grade 3 or 4 ILD, abemaciclib should be permanently discontinued (Eli Lilly, 2023).

Patients with ER-positive, HER2-negative high-risk EBC comprise much of the 20% of early-stage breast cancers that recur (Abel-Razeq & Sharaf, 2022). In this high-risk subset of EBC patients, clinicians now have an additional adjuvant therapy to consider using for their patients. The data from the monarchE phase III trial supports the practicability of abemaciclib in this population as a new treatment option with trial-proven improved IDFS and safety data (Johnston et al., 2020; Johnston et al., 2023; Rastogi et al, 2024). Advanced practitioners in oncology should aim to help identify appropriate patients who meet the criteria to receive adjuvant abemaciclib. ●

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