Review Article

Role of abemaciclib in primary breast cancer: a narrative review of MonarchE

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Abstract: Estrogen affects cyclin signaling which results in proliferation of breast cancer cells. Breast cancers expressing hormone receptors (known as hormone receptor-positive or HR+ breast cancers) are characterized by dysregulation of cyclin-dependent kinase 4 and 6 (CDK4/6) activity due to overexpression and amplification of genes associated with the cell cycle. Inhibition of CDK4/6, in combination with endocrine therapy (ET), have shown significant clinical efficacy in treating HR+, human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer, leading to global approval of this combination. Abemaciclib is a CDK4/6 inhibitor with higher potency and inhibits a wider range of CDKs compared with other CDK4/6 inhibitors. The MonarchE study is a global, open-label, randomized phase III study of the efficacy of 2-year abemaciclib treatment, together with standard adjuvant ET, in patients who underwent surgery for early-stage HR+, HER2– breast cancer with anatomical or pathological high-risk recurrence features. Preplanned interim analysis of the MonarchE study showed significantly improved invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) with the use of abemaciclib-ET combination therapy in comparison with ET alone. This review focuses on the emerging results and limitations of the MonarchE study in determining the way forward from the CDK4/6-ET combination treatment in HR+, HER2– early-stage breast cancer.

Keywords: Abemaciclib; MonarchE; CDK4/6 inhibitors; adjuvant therapy

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Introduction

Abnormal cell proliferation is a hallmark of cancer (1). Cyclins and cyclin-dependent kinases (CDKs) play key roles in cell cycle regulation in proliferating cancer cells. Breast cancers expressing hormone receptors (known as hormone receptor-positive/HR+ cancers) are characterized by dysregulated CDK 4 and 6 (CDK4/6) activity due to overexpression and amplification of genes associated with the cell cycle (such as *CCND1*) (2). Estrogen affects the cyclin-CDK complex via estrogen receptor signaling and results in the proliferation of breast cancer cells. These findings have led to clinical trials and global approval of combination treatment with CDK4/6 inhibitors and endocrine therapy (ET) for patients with metastatic HR+ and human epidermal growth factor receptor 2-negative (HER2–) breast cancer.

Abemaciclib is a CDK4/6 inhibitor with higher potency and inhibits a wider range of CDKs than the two other CDK4/6 inhibitors (palbociclib and ribociclib). It has been approved by the United States Food and Drug

Administration (FDA). These CDK4/6 inhibitors were initially approved for previously treated HR+, HER2– metastatic breast cancers. Subsequent studies showed that the addition of CDK4/6 inhibitors to the ET was also effective for previously untreated patients. The MonarchE study is a global randomized phase III study evaluating the efficacy of adding abemaciclib to ET for early-stage breast cancer. This study has shown promising results in terms of efficacy of the combination treatment. In this narrative review, we discuss the emerging results of the MonarchE study and future prospects of abemaciclib treatment for patients with HR+ early-breast cancer. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-21-27/rc).

Pharmacology of abemaciclib

In mammalian cells, D-type cyclins (CCND1, CCND2, and CCND3) and CDK4/6 play critical roles in entry into the cell cycle and subsequent downstream signaling pathways; these include RAS-ERK, phosphoinositide 3-kinase, and mammalian target of rapamycin signaling networks. One of the major functions of D-type cyclin-CDK4/6 complexes is to phosphorylate and inhibit the expression of retinoblastoma protein 1 (*RB1*), a tumor-suppressor gene required for DNA synthesis, DNA repair, and mitosis. D-type cyclins may also interact with the HR. Cyclin D1 is required for proliferation of progenitors, driven by estrogen and progesterone, in the mammary gland (3).

HR+ human breast cancer cell lines showed increased sensitivity to CDK4/6 inhibitors (4). These preclinical studies led to clinical trials and global approval of three CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) in combination with ET, for patients with metastatic HR+, HER2– breast cancer. Abemaciclib inhibits CDK4 more selectively than the other FDA-approved CDK4/6 inhibitors. This may prevent CDK4 overexpression as a mechanism of CDK4/6 inhibitor resistance (5). Moreover, abemaciclib leads to cell cycle arrest in HR+ breast cancer cells, and induces irreversible induction of senescence and apoptosis in a time- and dose-dependent manner, compared with palbociclib (6).

Abemaciclib is continuously administered twice daily at a dosage of 150 mg when used in combination with ET. Abemaciclib is associated with more gastrointestinal (GI) adverse effects, such as diarrhea, but less hematological toxicities (particularly neutropenia) compared with the other FDA-approved CDK4/6 inhibitors. GI adverse effects are generally well-controlled by routine antiemetics, such as metoclopramide, and prophylactic administration of loperamide is often recommended. Approximately 81% of the dose of abemaciclib is eliminated in feces as metabolites; its elimination half-life is 18.3 hours, which is consistent with the twice-daily dosing schedule (7). Abemaciclib is extensively metabolized by CYP3A4 to form equipotent, active metabolites. Therefore, caution should be exercised when co-administering abemaciclib with other CYP3A4 inhibitors or inducers, and dose adjustment of abemaciclib should be considered, if necessary (7). Abemaciclib demonstrates good central nervous system penetration, with concentrations of the parent drug and active metabolites in cerebrospinal fluid comparable to unbound plasma concentrations (8). Promising intracranial antitumor efficacy is observed in patients with metastatic HR+, HER2– breast cancer (9).

Clinical evidence for the efficacy of abemaciclib in metastatic HR+, HER2– breast cancer

Abemaciclib has shown clinically significant benefits in different settings for patients with metastatic HR+ breast cancer (*Table 1*). A randomized double-blind phase III study (Monarch 3) showed significantly greater progression-free survival (PFS), which was its primary endpoint, with the combination of abemaciclib and aromatase inhibitors (AIs), compared with AIs alone [median PFS: not reached *vs.* 14.7 months; hazard ratio (HR): 0.54; 95% confidence interval (CI): 0.41–0.72]. In addition, the objective response rate (ORR) was higher with the combination than with AIs alone (48.2% *vs.* 34.5%, P=0.002) (10). In an ET-pretreated setting, a global double-blind randomized phase III study (Monarch 2) investigated the efficacy of a combination of fulvestrant and abemaciclib in patients with metastatic HR+, HER2– breast cancer. The combination group experienced an improved PFS [median PFS: 16.4 *vs.* 9.3 months; HR: 0.55; 95% CI: 0.45–0.68), ORR (48% *vs.* 21%), and OS (median OS: 46.7 *vs.* 37.3 months; HR: 0.76; 95% CI: 0.61–0.95], compared with the group receiving fulvestrant alone (11,12). Another phase III study conducted in China, Brazil, India, and South Africa showed similar PFS and ORR benefits with the combination of abemaciclib and ET compared with ET alone (median PFS: 11.5 *vs.* 5.6 months; HR: 0.55; 95% CI: 0.45–0.68; ORR: 50.0% *vs.* 10.5%) (13). Single-agent abemaciclib also has substantial antitumor activity in patients with metastatic HR+ breast cancer who showed disease progression on or after ET and chemotherapy. In a single-arm phase

Table 1 Results of clinical trials examining abemaciclib for advanced breast cancer

Study and reference	ET	Setting	Participants	Primary endpoint	ORR	PFS	OS
Monarch3 (NCT02246621) (10)	Anastrozole Letrozole	• Treatment-naïve ABC • Relapse >1 year after adjuvant ET	Post-menopausal HR+, HER2–	PFS	48.2% *vs.* 34.5%, P=0.002	NR *vs.* 14.7 months HR (95% CI): 0.54 (0.41–0.72) P=0.00021	Not reported
Monarch2 (NCT02107703) (11,12)	Fulvestrant	• PD while or ≤12 months after neoadjuvant or adjuvant ET • Chemotherapy-naive	Pre-/post-menopausal HR+, HER2–	PFS	48.1% *vs.* 21.3%	16.4 *vs.* 9.3 months HR (95% CI): 0.55 (0.45–0.68) P<0.001	46.7 *vs.* 37.3 months HR (95% CI): 0.76 (0.61–0.95) P=0.01
Monarchplus cohort A (NCT02763566) (13)	Anastrozole Letrozole	• Treatment-naïve ABC • Relapse >1 year after adjuvant ET • Relapse <1 year after adjuvant ET except anastrozole or letrozole	Post-menopausal HR+, HER2–	PFS	65.9% *vs.* 36.1%, P<0.0001	NR *vs.* 14.7 months HR (95% CI): 0.50 (0.35–0.72) P=0.0001	Not reported
Monarchplus cohort B (NCT02763566) (13)	Fulvestrant	• ≤1 line of ET and no chemotherapy for ABC • PD while or ≤12 months after adjuvant ET	Post-menopausal HR+, HER2–	PFS	50.0% *vs.* 10.5%, P<0.0001	11.5 *vs.* 5.6 months HR (95% CI): 0.38 (0.24–0.59) P<0.0001	Not reported
Monarch1 (NCT02102490) (14)	None	• PD on ET and ≥ two chemotherapy	Pre-/post-menopausal HR+, HER2–	ORR	19.7%	6.0 months	17.7 months

ET, endocrine therapy; ABC, advanced breast cancer; PD, progressive disease; HR+, hormonal receptor positive; HER2, Human Epidermal Growth Factor Receptor 2; ORR, objective response rate; PFS, progression free survival; NR, not reached; HR, hazard ratio; CI, confidence interval; OS, overall survival.

II open-label study, Monarch 1, abemaciclib showed an ORR of 20% with a median PFS of 6.0 months (14). Most abemaciclib trials have been limited to postmenopausal women or included premenopausal women with ovarian function suppression (OFS) as a small subset population. Preliminary analysis of the pre- and perimenopausal subset of patients enrolled in the Monarch 2 study showed that the addition of abemaciclib to fulvestrant and a gonadotropin-releasing hormone agonist (GnRHa) improved both PFS (not reached *vs.* 10.5 months; HR: 0.45; 95% CI: 0.26–0.75) and ORR (61% *vs.* 29%), compared with those receiving fulvestrant and a GnRHa only (6).

Adjuvant abemaciclib with ET: results and limitations of the MonarchE study

As described above, abemaciclib has shown clinical benefits in metastatic HR+, HER2– breast cancer. However, more than 90% of breast cancers are diagnosed at an early stage and 70% of these cancers are HR+ (15). Adjuvant ET is associated with a significant reduction in the risk of recurrence and death (16,17). However, subsets of these patients, especially those with high-risk clinical and pathological features, experience disease recurrence, often with distant metastases (18).

Recently, a preplanned interim analysis of the results of MonarchE was published (19). MonarchE is a global, open-label, randomized phase III study evaluating the efficacy of 2-year abemaciclib treatment, in addition to standard ET, in patients who underwent surgery for early-stage breast cancer and who were categorized as having a high risk of recurrence. Adjuvant radiation and/or adjuvant or neoadjuvant chemotherapy were allowed but not required. High-risk clinical and/or pathological features were defined

as involvement of four or more lymph nodes, involvement of 1–3 lymph nodes as well as tumor size of ≥5 cm, histological grade 3, or centrally evaluated Ki-67 of ≥20%. Exclusion criteria included patients who had previously received ET for breast cancer prevention and/or a CDK4/6 inhibitor. Those diagnosed with inflammatory breast cancer and those with a history of venous thromboembolic events (VTEs) were also excluded concerning a potential risk of VTEs with abemaciclib (20). Patients who met the inclusion criteria and unmet exclusion criteria were randomly assigned (1:1) to receive either abemaciclib (150 mg twice daily on a continuous dosing schedule) and ET, or ET alone. Stratification factors of randomization included previous chemotherapy (neoadjuvant, adjuvant, or none), menopausal status at the time of breast cancer diagnosis (premenopausal *vs.* postmenopausal), and region (North America/Europe, Asia, or others). Patients received the assigned treatment for 2 years, followed by ET alone for 5 to 10 years as clinically indicated. The primary endpoint was invasive disease-free survival (IDFS) in the intent-to-treat population. From July 2017 to August 2019, 5,637 patients from 603 sites in 38 countries were enrolled in the study. Patients were predominantly postmenopausal (56.5%) and were eligible based on ≥4 lymph node involvement (59.6%). AIs were prescribed as the first ET on study treatment in 68.3% of patients (including 14.2% treated with OFS in addition) and tamoxifen in 31.4% (including 7.6% treated with OFS in addition). In the median follow-up time of 15.5 months, abemaciclib together with ET demonstrated a significant improvement in IDFS compared with that in ET alone (HR, 0.75; 95% CI: 0.60–0.93) with a 2-year IDFS of 92.2% *vs.* 88.7%. Distant relapse-free survival (DRFS) also improved with the combination (HR: 0.72; 95% CI, 0.56–0.92), with a 2-year DRFS of 93.6% *vs.* 90.3%. These clinically insightful IDFS and DRFS results were also seen in multiple subgroups of patients who received neoadjuvant chemotherapy (21); whose high-risk feature were defined by Ki-67 of ≥20% (22); and in Asian population (23,24). OS data were immature. Grade ≥3 adverse events (AEs) were observed in 45.9% of patients in the abemaciclib arm and in 12.9% of patients in the control arm. The most frequent grade 3 or 4 AEs in the abemaciclib arm were diarrhea (7.6%), neutropenia (18.6%), and fatigue (2.8%). Abemaciclib dose adjustments due to AEs occurred in 68.1% of patients; 16.6% of patients discontinued abemaciclib because of AEs; and 6.2% of patients discontinued both. These discontinuation rates were higher than in the control arm, in which 0.8% of patients discontinued ET. Higher incidences of VTEs and interstitial lung disease (ILD) occurred in the abemaciclib arm than in the control arm (2.7% *vs.* 0.3%; 1.2% *vs.* one patient, respectively). The risk of VTE was even higher in patients who received tamoxifen and in patients who had a body mass index >25 (6). ILD was observed more frequently in the Asian population (6.6%) (6).

As described above, preplanned analysis of the MonarchE study showed significantly greater IDFS and DRFS with the use of abemaciclib-ET combination treatment than with ET alone. Despite these promising results, several limitations must be considered. The results obtained for the combination of abemaciclib and ET are inconsistent with the results of two studies in which a combination of palbociclib and ET was evaluated. The PALLAS study was an open-label randomized phase III trial to determine if the addition of 2-year palbociclib treatment (125 mg once daily on days 1–21 of a 28-day cycle) to standard adjuvant ET improves IDFS in patients with early-stage HR+, HER2– breast cancer. Patients with stage II to III breast cancers were eligible, in contrast with the high-risk inclusion criteria of the MonarchE study described above. In the follow-up period of 23.7 months, pre-specified interim analysis did not show significant improvement in 3-year IDFS (88.2% in the palbociclib group *vs.* 88.5% in the control group; HR: 0.93; 95% CI: 0.76–1.15) as well as in 3-year DRFS (89.3% in the palbociclib group *vs.* 90.7% in the control group; HR: 1.00; 95% CI: 0.79–1.27) (25). The discrepancy in efficacies of combination CDK4/6 inhibitor-ET treatment between the MonarchE and PALLAS studies may be due to several reasons. First, the MonarchE study included patients with a higher risk of recurrence than the PALLAS study, especially those with ≥4 lymph node involvement. These patients may be better candidates for CDK4/6 inhibitor-ET combination treatment, and this contributed to the substantially greater efficacy observed in the MonarchE study. Second, AE profiles differ between abemaciclib and palbociclib (26). In the two studies, the discontinuation rate due to AEs was lower with abemaciclib than with palbociclib (16.6% and 27.1%, respectively). In the PALLAS study, only 32.3% of patients completed treatment and 25.5% received planned protocol therapy, suggesting a lack of adequate drug exposure. The majority of patients enrolled in the MonarchE study had continued to receive abemaciclib at the cutoff date: 12.5% completed and 72.8% continued to receive planned protocol therapy. A longer follow-up of the MonarchE study is warranted. Third, abemaciclib is more potent than palbociclib, and

can inhibit other CDKs in addition to CDK4/6. This eventually results in the inhibition of G1 to S and G2 to M phase transitions in the cell cycle (27). Further clinical and preclinical studies directly comparing different CDK4/6 inhibitors are needed to reveal the discrepancies between the results of the two trials.

In the MonarchE study, the 2-year duration of abemaciclib treatment was chosen based on historical studies, which reported that recurrence events first peaked at 2 years in patients with early breast cancer treated with adjuvant ET (28). However, more than half of recurrences also occurred after 5-year treatment with ET (29). Although results of later follow-ups (median follow-up duration: 19 months) of MonarchE study continuously showed benefits of IDFS and DRFS (30), with a consistent safety profile (30,31), it is important to confirm results at the pre-specified, final cutoff time point (3 years). Results as well as long-term toxicity should be confirmed at an even longer follow-up duration, given the usage of the combination treatment in the adjuvant setting, where many patients will survive for years without any recurrences. Both the MonarchE and PALLAS studies were open-label and unblinded. The different toxicity profiles of abemaciclib and ET may have affected the blindness of the trials. The open-label design of these studies with the primary endpoint of IDFS evaluated by imaging performed by investigators, can cause lead-time bias, as discussed previously (32).

Another randomized, double-blind, placebo-controlled phase III study, Penelope-B, also did not show any benefit from adding palbociclib, as an adjuvant treatment, to ET for patients with HR+, HER2– early breast cancer who received neoadjuvant chemotherapy and had residual high-risk features (33). Patients with residual high-risk features [defined by CPS+EG score (a score integrating clinical and pathological stage, estrogen receptor expression, and nuclear grade) ≥3 or 2 and ypN+] after neoadjuvant chemotherapy and surgery, were randomly assigned to the 1-year treatment with ET and palbociclib group, or to the ET and placebo group. The primary endpoint was IDFS. Results showed that IDFS was not significantly different between the two groups (HR: 0.93; 95% CI: 0.74–1.17) after a median follow-up of 42.8 months. Up to 40% of patients enrolled in the MonarchE study also received neoadjuvant chemotherapy. However, association between response to neoadjuvant chemotherapy (whether patients achieved pathological complete responses or not) and efficacy of adjuvant abemaciclib-ET combination remains to be addressed. Pre-specified subgroup analysis of MonarchE showed that patients who received neoadjuvant chemotherapy demonstrated better improvement of IDFS and DRFS by abemaciclib-ET combination (HR: 0.614; 95% CI: 0.473–0.797 and HR: 0.609; 95% CI: 0.459–0.809, respectively) compared with the intent-to-treat population (21). The discrepancy between results of Penelope-B and MonarchE may also be due to differences in high-risk feature definitions, drugs, and/or treatment durations (34).

In the MonarchE study, high-risk of recurrence was defined by a combination of anatomical (number of lymph nodes involved and tumor size) and pathological features (histologic grade and Ki-67). In the PALLAS study, patients with stage II or III were enrolled. In the Penelope-B study, patients with a CPS+EG score ≥3 or 2 with ypN1+ were defined as having a high risk of recurrence. It is important to include both anatomical and pathological features to define high-risk recurrence, as shown by the MonarchE study. However, in the MonarchE study, the majority of patients were defined as high-risk based on involvement of ≥4 lymph nodes. According to results of the SWOG S1007 (RxPONDER) trial, adjuvant chemotherapy had benefit to postmenopausal patients, regardless of the number of metastatic lymph nodes (35). It is, therefore, necessary to reconsider how high-risk of recurrence is defined.

We also need to consider how the results of MonarchE should be applied to the premenopausal population. In the interim analysis of the MonarchE study, patients were predominantly postmenopausal and were treated with AIs as the adjuvant ET, with only 31% and 14% of enrolled patients being treated with tamoxifen and OFS, respectively. Although a significant 37% risk reduction of IDFS with abemaciclib and ET was reported in premenopausal patients enrolled in the MonarchE study (19), further investigations are needed to confirm these results. A higher incidence of VTEs was observed in the abemaciclib and ET arm, particularly in combination with tamoxifen (6). The choice of ET should be made carefully and is a subject warranting validation in the future.

Perspective: what is the way forward from MonarchE?

Patients enrolled in MonarchE are conceptually divided into three groups: (I) patients with poor prognosis and inadequate response to the addition of abemaciclib; (II) patients who are highly sensitive to ET and have no benefit with the addition of abemaciclib; and (III) patients having

a high risk of recurrence, for whom the recurrence risk is reduced with the addition of abemaciclib to ET (34). Identification of the third group is necessary to improve the efficacy of abemaciclib-ET combination treatment and to avoid overtreatment of patients who do not need it. There are several potential indicators to identify patients who may benefit from combination treatment. As described above, subgroup analysis of patients who received neoadjuvant chemotherapy showed greater improvement of IDFS and DRFS compared with the intent-to-treat population (21), although these improvements in the outcomes need to be cautiously compared. The high-risk of recurrence feature in the majority of patients enrolled in the MonarchE study was defined as involvement of ≥4 lymph nodes. It is important to evaluate the efficacy with abemaciclib-ET combination particularly in such population. Previous studies have suggested that several genomic characteristics, such as CDK6 amplification and polyclonal *RB1* mutation, can predict CDK4/6 inhibitor resistance (36,37). Currently, these genomic biomarker-based hypotheses have been tested in metastatic breast cancer in multiple studies (NCT03130439, NCT04432454, NCT04256941, and NCT04964934). Exploratory studies using resected tumors are needed to identify these biomarkers to predict which patients will be more likely to benefit from combination treatment in the adjuvant setting. Translational research in MonarchE and PALLAS is ongoing to identify predictive biomarkers. Surgically resected tumors will be suitable for such studies and will guide us in answering these important questions. In addition, the duration of adjuvant CDK4/6 inhibitors should further be discussed.

As the CDK4/6 inhibition alone may not be sufficient to achieve antitumor efficacy, it is also important to predict ET sensitivity. In the Monarch 2 trial, longer OS was observed with an abemaciclib–fulvestrant combination, compared with fulvestrant alone, in both the previously ET-sensitive subgroup (known as the "secondary ET resistance" group; median OS: 48.8 *vs.* 40.7 months) and the ET-resistant subgroup (known as the "primary ET resistance" group; median OS: 38.7 *vs.* 31.5 months) (12). In contrast, according to a subgroup analysis in the PALOMA-3 trial, a double-blind randomized phase III study of palbociclib–fulvestrant combination for metastatic HR+, HER2– breast cancer, the OS was numerically shorter in the palbociclib group than in the placebo group in patients with intrinsic resistance to prior ET (median OS: 20.2 *vs.* 26.2 months). OS was significantly longer, however, in the ET-sensitive population (39.7 *vs.* 29.7 months; HR: 0.72; 95% CI: 0.55–0.94) (38). Several genomic characteristics including *ESR1* alteration and epigenetic changes are associated with ET resistance (39). Resistance mechanisms of ET should be addressed, along with addressing CDK4/6 inhibitors sensitivity for ET-resistant population, in studies exploring results of the MonarchE study.

According to the National Comprehensive Cancer Network guidelines (40), patients with early breast cancer with ≥4 regional lymph nodes involved (pN2 or N3), or 1–3 lymph nodes involved with a high 21-gene reverse transcriptase polymerase chain reaction assay score (≥26), and who have not received neoadjuvant chemotherapy, should consider adjuvant chemotherapy. These patients may also meet the inclusion criteria of the MonarchE study. Future studies must address the role of adjuvant chemotherapy as well as potential additional toxicities of abemaciclib-ET combination treatment when patients have already received adjuvant chemotherapy. Although two-thirds of patients received adjuvant chemotherapy in the MonarchE study, efficacy and toxicities with the abemaciclib-ET combination remain to be addressed within this population.

Using the abemaciclib-ET combination for treatment in neoadjuvant settings also needs to be investigated by future studies. The NeoMonarch study showed a significant reduction in pathological Ki-67 with the addition of abemaciclib to anastrozole in the neoadjuvant setting, compared with anastrozole alone (41). A similar improvement was also reported with palbociclib in the PALLET study (42). However, the efficacy of ET over chemotherapy in the neoadjuvant setting remains controversial in both premenopausal and postmenopausal patients with HR+, HER2– early breast cancer (43,44). In the era of CDK4/6 inhibitor-ET combination treatment for HR+, HER2– breast cancer, it is important to revisit which treatment option, the CDK4/6 inhibitor-ET combination or standard chemotherapy, has better efficacy in the neoadjuvant or adjuvant setting for patients with HR+, HER2+ early breast cancer. The efficacy of peri-operative abemaciclib against early breast cancer is being tested in several clinical trials (*Table 2*). The questions mentioned above need to be addressed in these studies.

Going forward, the possibility of adding a third agent to the abemaciclib-ET treatment combination needs to be investigated. Numerous preclinical and emerging clinical studies have shown promising synergistic efficacy with CDK4/6 inhibitors by targeting multiple biological pathways. These include agents targeting HER2,

Table 2 Clinical trials of abemaciclib for early breast cancer

NCT identifier trial name	Phase	Setting	Investigational Tx	Comparison	Participants	Primary endpoint	Status
NCT03155997 MonarchE	3	Adjuvant	Abemaciclib and ET (investigator's choice)	ET alone	• Pre-/post-menopausal • HR+, HER2– EBC • >4 axillary LN OR 1-3 LN with tumor size ≥5 cm or histologic grade 3 or Ki67 ≥20%	IDFS	Active not recruiting
NCT04752332 eMonarcHER	3	Adjuvant	Abemaciclib and ET (investigator's choice)	ET alone	• Pre-/post-menopausal • HR+, HER2+ EBC • Neoadjuvant-treated: pathological residual axillary LN involvement • Neoadjuvant-untreated: ≥4 axillary LN involvement OR 1–3 axillary LN involvement and tumor size ≥5 cm or histological grade 3	IDFS	Recruiting
NCT04565054 ADAPTIate	3	Adjuvant	Abemaciclib and ET (investigator's choice)	ET alone	• Pre-/post-menopausal • HR+, HER2– EBC • After completion of 2–6 years of ET Clinical high-risk features (Axillary LN involvement, high recurrence score, high histologic grade, non-pCR with neoadjuvant therapy)	IDFS	Recruiting
NCT04584853 POETIC-A	3	Neoadjuvant	Abemaciclib and ET (investigator's choice)	ET alone	Post-menopausal HR+, HER2– EBC Ki67 ≥20% OR histologic grade 3 OR tumor size >5 cm OR PgR negative OR PgR unknown and vascular invasion	TTR	Recruiting
NCT02441946 neoMonarch	2	Neoadjuvant	Abemaciclib and anastrozole	Anastrozole alone	• Post-menopausal • HR+, HER2– EBC • cStage II–III	Ki67 change	Completed Has results
NCT04293393 CARABELA	2	Neoadjuvant	Abemaciclib and letrozole	ChemoTx (AC->T)	• Pre-/post-menopausal • HR+, HER2– EBC • cStage II-III OR T2N0 with Ki67 >30% OR T2N0 with Ki67 of 20–30% and PgR- and/or histological grade 3	Residual cancer burden 0-I rate	Recruiting
NCT04305236	2	Neoadjuvant	Abemaciclib and fulvestrant	None (single-arm)	• Post-menopausal • HR+ EBC, HER2 irrespective • cStage I–III	pCR rate	Recruiting
NCT02831530 ABC-POP	2	Neoadjuvant	Abemaciclib	None (single-arm)	• Pre-/post-menopausal • HR+ EBC, HER2 irrespective	Ki67 change	Completed no results posted

Table 2 (*continued*)

Table 2 (*continued*)

NCT identifier trial name	Phase	Setting	Investigational Tx	Comparison	Participants	Primary endpoint	Status
NCT03979508 BEAUTY	2	Neoadjuvant	Abemaciclib	Surgery alone	• Triple negative breast cancer • Stage I–III	CD8/ FOXP3 change in tumor	Recruiting
NCT04614194	2	Neoadjuvant	Abemaciclib and letrozole	Letrozole alone	• Post-menopausal • HR+, HER2– EBC • cStage I–III	T cell activation change in tumor	Recruiting
NCT04088032	1	Neoadjuvant	Abemaciclib and durvalumab and AI	None (single-arm)	• Post-menopausal • HR+, HER2– EBC • cStage II–III	Safety	Withdrawn (Per sponsor)
NCT04481113	1	Neoadjuvant	Abemaciclib and niraparib	None (single-arm)	• Pre-/post-menopausal • HR+, HER2– EBC • Clinical T1–3, any N, M0	Safety	Recruiting

Status of clinical trials were accessed on 29th September 2021 in clinicaltrial.gov https://clinicaltrials.gov/. NCT, National Clinical Trial; Tx, treatment; ET, endocrine therapy; HR, hormone receptor; HER2, Human Epidermal Growth Factor Receptor 2; EBC, early breast cancer; LN, lymph node; IDFS, invasive disease free survival; pCR, pathological complete response; PgR, progesterone receptor; TTR, time to tumor recurrence; cStage, clinical stage; ChemoTx (AC -> T), chemotherapy with doxorubicin and cyclophosphamide followed by taxane; AI, aromatase inhibitor.

phosphoinositide 3-kinase, mammalian target of rapamycin signaling, protein kinase B, fibroblast growth factor receptor, and poly (ADP-ribose) polymerases (PARP) (45). Recently, the adjuvant PARP inhibitor olaparib showed significant benefits of IDFS and OS for patients with HER2– early breast cancer with *BRCA1* or *BRCA2* germline pathogenic or likely pathogenic variants (46). Looking forward, the way in which these populations can be treated with the abemaciclib-ET combination must be considered.

Conclusions

In conclusion, although pre-specified interim analyses of the MonarchE study have shown the promising results of abemaciclib-ET combination treatment, there are still multiple clinical questions to be addressed. Results of studies addressing these questions as well as exploratory studies of MonarchE will provide guidance on the way forward in the era of CDK4/6 inhibitor-ET combination treatment for patients with HR+, HER2– breast cancer.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-21-27/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-21-27/coif). CS reports that he is a Steering Committee member of MonarchE and receives a research grant from Eli-Lilly. AS reports that he receives research grant from Chugai Pharmaceutical, AstraZeneca, Daiichi Sankyo, Taiho Pharmaceutical, Mochida Pharmaceutical, Eisai, and serves as a lecture honoraria or lecture chair held by Chugai Pharmaceutical, AstraZeneca, Daiichi Sankyo, Eisai, Eli Lilly, Pfizer, Kyowa Kirin, Novartis, Takeda, MSD. MT reports that he receives research grants from Chugai, Takeda, Pfizer, Kyowa-Kirin, Taiho, JBCRG assoc., Eisai, Eli Lilly, Daiichi-Sankyo, AstraZeneca, Astellas, Shimadzu, Yakult, Nippon Kayaku, AFI technology, Luxonus, Shionogi, GL Science, serves as a lecture honoraria or lecture chair held by Chugai, Takeda, Pfizer, Kyowa-Kirin, Taiho, Eisai, Daiichi-Sankyo, AstraZeneca, Eli Lilly, MSD, Exact Science, Novartis, Konica Minolta, Shimadzu,

Yakult, Nippon Kayaku, is an advisory board of Kyowa-Kirin, Daiichi-Sankyo, Eli Lilly, Konica Minolta, BMS, Athenex Oncology, Bertis, Terumo, Kansai Medical Net, is a member of the board of directors (no salary) of JBCRG assoc., KBCRN, OOTR, is an associate editor of *Scientific Reports*, *Breast Cancer Research and Treatment*, *Cancer Science*, *Frontiers in Women's Cancer*, *Asian Journal of Surgery*, *Asian Journal of Breast Surgery*, and is a deputy editor of *International Journal of Oncology*. NT has no conflicts of interest to declare.

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