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Clinical Challenges in the Management of Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: A Literature Review

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ABSTRACT

Endocrine therapy (ET) is integral to the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC). Aromatase inhibitors (AIs; e.g., anastrozole, letrozole, exemestane), selective estrogen receptor modulators (e.g., tamoxifen), and the selective estrogen receptor degrader, fulvestrant, inhibit tumor cell proliferation by targeting ER signaling. However, the efficacy of ET could be limited by intrinsic and acquired resistance mechanisms, which has prompted the development of targeted agents and combination strategies. In recent years, the treatment landscape for HR+, HER2- MBC has evolved rapidly. AIs, historically the first-line treatment for postmenopausal patients with HR+, HER2- MBC, have been challenged by more effective ET, such as fulvestrant alone or in combination with an AI, and the cyclin-dependent kinase (CDK)4/6 inhibitors, which have increasingly become the new standard of

care. For endocrine-resistant disease (\geq second-line), clinical trials demonstrated that the mammalian target of rapamycin inhibitor, everolimus, enhanced the efficacy of exemestane or fulvestrant after progression on an AI. CDK4/6 inhibitors in combination with fulvestrant have demonstrated superior progression-free survival and overall survival versus fulvestrant alone. Recently, the combination of fulvestrant with alpelisib in phosphatidylinositol-4,5-bisphosphate 3-kinase (*PIK3CA*) mutated HR+, HER2- MBC following progression on or after ET was approved, based on the SOLAR-1 study. However, the optimal sequencing of treatments is unknown, especially following disease progression on a CDK4/6 inhibitor. This review aims to provide practical guidance for the management of HR+, HER2- MBC based on available data and the utility of genomic biomarkers, including germline breast cancer genes 1 and 2 (*BRCA1/2*) mutations, and somatic estrogen receptor alpha gene (*ESR1*), *HER2*, and *PIK3CA* mutations.

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Key Summary Points

Significant progress has been made in recent years for the treatment of postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC).

In the first-line setting, fulvestrant alone or in combination with an aromatase inhibitor (AI) has been shown to be superior to an AI alone, whereas combinations of endocrine therapy (ET) plus a cyclin-dependent kinase (CDK)4/6 inhibitor has increasingly become the new standard of care.

Combinations of ET plus CDK4/6 or mammalian target of rapamycin inhibitors have been approved in the ET-resistant setting.

Recent approval of alpelisib with fulvestrant in phosphatidylinositol-4,5-bisphosphate 3-kinase (*PIK3CA*) mutated HR+, HER2- MBC following progression on or after ET marks the first combination therapy approved based on somatic mutations in MBC.

The role for genomic biomarkers in guiding individualized treatment of HR+, HER2- MBC is expanding.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13134812>.

INTRODUCTION

Breast cancer (BC) is commonly categorized into three major subtypes, based on the presence or absence of molecular markers for estrogen or progesterone receptors and human epidermal growth factor 2 (HER2): hormone receptor-positive (HR+), HER2-positive, and triple-negative (tumors lacking estrogen or progesterone receptors and HER2) [1]. Based on gene expression profiling, the molecular classification of BC includes luminal A and luminal B, HER2-enriched, and basal subtypes. The luminal subtypes make up the majority of HR+ BC [2]. Approximately 75% of BCs are HR+ [3, 4]. Endocrine therapy (ET) inhibits estrogen receptor (ER) signaling [5] and plays a fundamental role in the management of HR+ disease by reducing relapse risk and improving survival [6]. Compared with tamoxifen, aromatase inhibitors (AIs) have shown superior efficacy across all stages of BC in both postmenopausal and premenopausal women (in combination with ovarian suppression) and have emerged as key agents for the treatment of HR+ BC in the last two decades [6, 7]. AIs used to be the first-line treatment of choice for postmenopausal women with HR+, HER2-negative (HER2-) metastatic BC (MBC). However, cyclin-dependent kinase (CDK)4/6 inhibitors (palbociclib, ribociclib, abemaciclib) in combination with ET [8–10] and more effective ET approaches, such as fulvestrant [11] or fulvestrant in combination with an AI, have now demonstrated improved efficacy [12, 13].

The selective estrogen receptor degrader (SERD) fulvestrant binds to and induces rapid degradation of the ER. Unlike the selective ER modulator tamoxifen, which exerts agonist activity in some organs, including the uterus, bone, and cardiovascular system [1], fulvestrant lacks agonistic actions [14]. Though initially approved for the treatment of patients with ET-resistant, HR+ advanced BC (ABC), fulvestrant has subsequently been approved for use in the first-line setting after demonstrating improvements in progression-free survival (PFS) versus the AI, anastrozole [11, 15]. Fulvestrant has also been shown to retain relative efficacy in the

presence of some ER alpha gene (*ESR1*) mutations, albeit with efficacy that is reduced versus wild-type *ESR1* [16]. As a result of its unique mechanism of action, fulvestrant has become a common partner for targeted therapy combinations. CDK4/6 inhibitors have been approved in combination with fulvestrant in the first-line (ribociclib) [9] and endocrine-resistant (palbociclib, ribociclib, abemaciclib) settings [8–10]. More recently, fulvestrant has demonstrated efficacy when combined with phosphoinositide 3-kinase (PI3K) inhibitors for the treatment of patients with HR+, HER2–, phosphatidylinositol-4,5-bisphosphate 3-kinase (*PIK3CA*) mutation-positive MBC who have progressed on an AI [17, 18]. The combination of fulvestrant with alpelisib has been approved for use in this setting [19].

As the mechanism of action and clinical utility of various ET agents in HR+ BC have been reviewed extensively [20], this review will focus on recent progress in optimizing ET and the development of targeted agents in the management of HR+ MBC.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

ET IN THE TREATMENT OF HR+, HER2– MBC, MONOTHERAPY VERSUS COMBINATION THERAPY—WHAT DO THE DATA TELL US?

In HR+, HER2– MBC, ET has been used as monotherapy, in dual ER-targeting strategies, and in combination with targeted agents. While AIs have previously demonstrated superiority to tamoxifen in postmenopausal women [21], the SERD fulvestrant, as monotherapy or in combination with an AI, has demonstrated superior efficacy to AIs in ET-naïve patients [13, 15].

Fulvestrant as Monotherapy and in Combination with AIs

Initial studies that led to the approval of fulvestrant by the US Food and Drug

Administration (FDA) in 2002 were based on a 250-mg dose, administered monthly by intramuscular injection [22]. In some studies, a 500-mg loading dose was also administered.

The phase III SWOG S0226 study compared the combination of fulvestrant (initial 500-mg loading dose, followed by a 250-mg dose every 14 days for the first month, and every 28 days thereafter) plus anastrozole versus anastrozole alone in the first-line setting [12, 13]. Improvements in median PFS [15.0 vs. 13.5 months; hazard ratio for progression or death 0.81 (95% confidence interval (CI) 0.69–0.94); $P = 0.007$] and overall survival [OS; 49.8 vs. 42.0 months; hazard ratio 0.82 (95% CI 0.69–0.98); $P = 0.03$] were observed for combination therapy versus anastrozole alone [13]. When data were stratified according to prior tamoxifen therapy, improvements in PFS and OS with combination therapy versus anastrozole alone were limited to patients who had not received prior tamoxifen therapy [13]. Subsequently, the phase III CONFIRM study established the superiority of the 500-mg dose of fulvestrant (500 mg administered on Days 0, 14, and 28, and every 28 days thereafter) versus the previously approved 250-mg dose (250 mg administered on Days 0 and 28, and every 28 days thereafter) in postmenopausal women with HR+ MBC who failed previous hormonal therapy, establishing 500 mg as the recommended dose [11, 23]. In CONFIRM, median PFS was 5.5 and 6.5 months for the 250- and 500-mg doses, respectively [hazard ratio 0.80 (95% CI 0.68–0.94); $P = 0.006$]. Median OS was 22.3 months with the 250-mg dose versus 26.4 months with the 500-mg dose [hazard ratio 0.81 (95% CI 0.69–0.96); nominal $P = 0.02$] [23, 24]. The results of comparative studies of fulvestrant 250 mg (whether used alone or in combination) and other endocrine agents should therefore be interpreted in the context of this dosing change.

The phase II FIRST study compared fulvestrant (500 mg/month) with the AI anastrozole (1 mg/day) in postmenopausal women with HR+ locally advanced or MBC not suitable for curative therapy [25]. No previous ET for advanced disease was allowed, although patients could have received ET in the adjuvant

setting if it had been completed more than 12 months before randomization. The clinical benefit rate at 6 months (primary endpoint) was 72.5% for patients treated with fulvestrant and 67.0% for those receiving anastrozole [odds ratio 1.30 (95% CI 0.72–2.38); $P = 0.386$] [25]. At follow-up analysis, the median time to progression was 23.4 months for fulvestrant versus 13.1 months for anastrozole [hazard ratio 0.66 (95% CI 0.47–0.92); $P = 0.01$] [26], and the final OS analysis demonstrated that median OS was longer with fulvestrant (54.1 months) compared with anastrozole [48.4 months; hazard ratio 0.70 (95% CI 0.50–0.98); $P = 0.04$] [27]. The results of this study were the first to show an efficacy benefit for fulvestrant over anastrozole in the first-line setting.

The phase III FALCON study compared fulvestrant (500 mg administered on Days 0, 14, and 28, and every 28 days thereafter) with anastrozole (1 mg/day) in postmenopausal women with HR+, HER2– locally advanced or MBC who had not previously received ET (Table 1) [15]. Treatment with fulvestrant resulted in a significantly longer PFS (primary endpoint) compared with anastrozole [hazard ratio 0.80 (95% CI 0.637–0.999); $P = 0.049$]. Median PFS for fulvestrant was 16.6 months (95% CI 13.83–20.99) versus 13.8 months for anastrozole (95% CI 11.99–16.59). These findings demonstrated the superior efficacy of fulvestrant versus anastrozole in patients with locally advanced or MBC who had not previously received ET [15]. In August 2017, the FDA approved fulvestrant for the first-line treatment of HR+, HER2– ABC in postmenopausal women not previously treated with ET [11]. The recent phase II PARSIFAL study, comparing fulvestrant with letrozole used in combination with the CDK4/6 inhibitor palbociclib, showed comparable 4-year OS rates (both 68%), suggesting that fulvestrant plus palbociclib is a reasonable alternative to letrozole plus palbociclib for the first-line treatment of HR+, HER2– MBC [28].

ET Combined with CDK4/6 Inhibitors

One of the hallmarks of cancer is the deregulation of pathways that regulate cell cycle progression [29]. Cell cycle progression from G1 to S phase is restricted by retinoblastoma (Rb) protein via sequestration of E2F family transcriptional factors. CDK4/6, in complex with D-type cyclins, promote G1 to S phase progression by the phosphorylation and inactivation of the Rb protein [30]. ER-positive (ER+) BC is particularly dependent on CDK4/6 activity for cell proliferation, as cyclin D1 is a direct transcriptional target of the ER, as well as other mitogenic signals that mediate endocrine resistance [31]. Additionally, cyclin D1 amplification is a common event in ER+ BC (58% in luminal B and 29% in luminal A cancers) [32], which could lead to constitutive activation of CDK4/6. In preclinical studies, ER+ BCs are particularly sensitive to CDK4/6 inhibitors [33]. There are three CDK4/6 inhibitors currently available for clinical use in combination with an AI or fulvestrant: palbociclib, ribociclib, and abemaciclib [8–10]. Abemaciclib has also been approved by the FDA for use as monotherapy for patients with refractory, heavily pre-treated, HR+, HER2– MBC, who have progressed on or after prior ET and have received one or two prior chemotherapy regimens for MBC [10]. Approval was based on the results of the phase II, single-arm MONARCH 1 study, which found that 19.7% of patients achieved an objective response when treated with abemaciclib monotherapy in this setting [34].

Recent phase III studies that have assessed the efficacy of fulvestrant monotherapy and fulvestrant or an AI in combination with targeted therapies, including CDK4/6 inhibitors, for the treatment of postmenopausal patients, are summarized in Table 1 [15, 18, 35–41]. Table 2 [41–43] lists the phase III studies that have assessed the use of ET in combination with CDK4/6 inhibitors for the treatment of pre- and perimenopausal patients.

Table 1 Selected phase III clinical trials for postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer

Study design	Treatment comparison	Patients, n	PFS, months: experimental vs. control arm	Hazard ratio (95% CI)	Median follow-up, months	OS, months: experimental vs. control arm	Hazard ratio (95% CI)	Most common adverse events, %: experimental vs. control arm
First-line studies ^a								
PALOMA-2 [35, 44]	R, DB, PC Letrozole + palbociclib vs. letrozole + placebo	666	27.6 vs. 14.5	0.56 (0.46–0.69)	37.6 (letrozole + palbociclib) 37.3 (letrozole + placebo)	NA	–	Neutropenia, 79.5 vs. 6.3 Leukopenia, 39.0 vs. 2.3 Fatigue, 37.4 vs. 27.5 Nausea, 35.1 vs. 26.1 Neutropenia, 74.3 vs. 5.2 Nausea, 51.5 vs. 28.5 Infections, 50.3 vs. 42.4 Fatigue, 36.5 vs. 30.0 Neutropenia, 69.6 vs. 2.1 Nausea, 45.3 vs. 28.2 Fatigue, 31.5 vs. 33.2 Diarrhea, 29.0 vs. 20.3 Arthralgia, 16.7 vs. 10.3 Hot flush, 11.4 vs. 10.3 Fatigue, 11.4 vs. 6.9 Nausea, 10.5 vs. 10.3
MONALEESA-2 [36, 45]	R, DB, PC Letrozole + ribociclib vs. letrozole + placebo	668	25.3 vs. 16.0	0.57 (0.46–0.70)	26.4	NR vs. 33.0 months	0.75 (0.52–1.08)	Neutropenia, 74.3 vs. 5.2 Nausea, 51.5 vs. 28.5 Infections, 50.3 vs. 42.4 Fatigue, 36.5 vs. 30.0 Neutropenia, 69.6 vs. 2.1 Nausea, 45.3 vs. 28.2 Fatigue, 31.5 vs. 33.2 Diarrhea, 29.0 vs. 20.3 Arthralgia, 16.7 vs. 10.3 Hot flush, 11.4 vs. 10.3 Fatigue, 11.4 vs. 6.9 Nausea, 10.5 vs. 10.3
MONALEESA-3 ^a [40, 52]	R, DB, PC Fulvestrant + ribociclib vs. fulvestrant + placebo	726	20.5 vs. 12.8	0.59 (0.48–0.73)	NA	NR vs. 40.0 ^b 33.0 months	0.72 (0.57–0.92)	Neutropenia, 69.6 vs. 2.1 Nausea, 45.3 vs. 28.2 Fatigue, 31.5 vs. 33.2 Diarrhea, 29.0 vs. 20.3 Arthralgia, 16.7 vs. 10.3 Hot flush, 11.4 vs. 10.3 Fatigue, 11.4 vs. 6.9 Nausea, 10.5 vs. 10.3
FALCON [15]	R, DB Fulvestrant vs. anastrozole	524	16.6 vs. 13.8	0.8 (0.64–1.00)	NA	NA	0.88 (0.63–1.22)	Neutropenia, 41.3 vs. 1.9 Fatigue, 40.1 vs. 31.7 Infections and infestations, 39.1 vs. 28.6
MONARCH 3 [39]	R, DB, PC AI + abemaciclib vs. AI + placebo	493	NR vs. 14.7	0.54 (0.41–0.72)	17.8	NA	–	Neutropenia, 41.3 vs. 1.9 Fatigue, 40.1 vs. 31.7 Infections and infestations, 39.1 vs. 28.6

Table 1 continued

Study design	Treatment comparison	Patients, #	PFS, months: experimental vs. control arm	Hazard ratio (95% CI)	Median follow-up, months	OS, months: experimental vs. control arm	Hazard ratio (95% CI)	Most common adverse events, %: experimental vs. control arm
Second-line studies ^a								
PALOMA-3 ^b [41, 50]	R, DB, Fulvestrant + palbociclib vs. PC fulvestrant + placebo	413	9.9 vs. 3.9	0.45 (0.34–0.59)	8.9	34.9 vs. 28.0 ^{§§}	0.81 (0.64–1.03) ^{§§}	Neutropenia, 79.6 vs. 2.9 Infections, 40.1 vs. 29.4 Fatigue, 40.1 vs. 27.9 Nausea, 30.3 vs. 25.0
MONARCH 2 ^c [37, 51]	R, DB, Fulvestrant + abemaciclib vs. PC fulvestrant + placebo	669	16.4 vs. 9.3	0.55 (0.45–0.68)	19.5	46.7 vs. 37.3 ^f	0.76 (0.61–0.95) ^{§§}	Diarrhea, 86.4 vs. 24.7 Nausea, 45.1 vs. 22.9 Fatigue, 39.9 vs. 26.9 Neutropenia, 46.0 vs. 4.0
BOLERO-2 ^d [38, 57]	R, DB, Exemestane + everolimus vs. PC exemestane + placebo	724	7.8 vs. 3.2	0.45 (0.38–0.54)	17.7	31.0 vs. 26.6 ^{§§}	0.89 (0.73–1.10)	Stomatitis, 59 vs. 12 Rash, 39 vs. 7 Fatigue, 37 vs. 27 Diarrhea, 34 vs. 19
SOLAR-1 [18, 64, 65]	R, DB, Fulvestrant + alpelisib vs. PC fulvestrant + placebo	572 ^e	11.0 vs. 5.7	0.65 (0.50–0.85)	20.0	NR vs. 26.9	0.73 (0.48–1.10)	Hyperglycemia, 63.7 vs. 9.8 Diarrhea, 57.7 vs. 15.7 Nausea, 44.7 vs. 22.3 Decreased appetite, 35.6 vs. 10.5

ABC advanced breast cancer, AI aromatase inhibitor, CI confidence interval, DB double-blind, ET endocrine therapy, MBC metastatic breast cancer, NA not available, NR not reached, OS overall survival, PC placebo-controlled, PFS progression-free survival, R randomized

^a In the MONALEESA-3 study, some patients received up to one previous line of ET; however, approximately 50% of patients had not received treatment for ABC

^b Disease relapse or progression after previous ET for ABC during treatment or within 12 months of completion of adjuvant therapy

^c Patients had progressed while receiving neo-adjuvant or adjuvant ET, ≤ 12 months from the end of adjuvant ET, or while receiving first-line ET for MBC. Results are presented for the overall intent-to-treat population, which included pre- and perimenopausal patients

^d Patients had recurrence or progression while receiving previous therapy with a non-steroidal AI in the adjuvant setting or to treat ABC (or both)

^e In total, 572 patients were enrolled; however, 341 patients were included in the PFS analysis

^f OS and hazard ratio data shown are for the whole study population and are not split by menopausal status

[§] OS data shown are mature

AIs in Combination with CDK4/6 Inhibitors

CDK4/6 inhibitors have been studied in combination with AIs for the first-line treatment of postmenopausal patients with HR+, HER2– locally advanced or MBC (Table 1). In the phase III PALOMA-2 study, median PFS was significantly increased to 27.6 months with palbociclib plus letrozole versus 14.5 months with letrozole monotherapy [hazard ratio for disease progression or death 0.56 (95% CI 0.46–0.69); $P < 0.0001$] [35, 44]. Similarly, in the phase III MONALEESA-2 study, the combination of ribociclib plus letrozole significantly improved median PFS versus letrozole [25.3 versus 16.0 months; hazard ratio for disease progression or death 0.57 (95% CI 0.46–0.70); $P < 0.001$] [36, 45]. Furthermore, the addition of abemaciclib to anastrozole or letrozole significantly improved median PFS versus anastrozole or letrozole [not reached vs. 14.7 months; hazard ratio for disease progression or death 0.54 (95% CI 0.41–0.72); $P < 0.001$] in the MONARCH 3 study [39]. Based on these results, the FDA has approved palbociclib, ribociclib, and abemaciclib in combination with an AI for use as first-line treatments for postmenopausal patients with HR+, HER2– ABC or MBC [8–10]. Ribociclib in combination with an AI has also been approved as a first-line treatment for pre- and perimenopausal patients with HR+, HER2– ABC or MBC [9], based on the results of the phase III MONALEESA-7 study (Table 2), which demonstrated significant improvements in median PFS with the addition of ribociclib to ET (anastrozole, letrozole, or tamoxifen plus goserelin) versus ET alone [23.8 vs. 13.0 months; hazard ratio for disease progression or death 0.55 (95% CI 0.44–0.69); $P < 0.0001$] [42]. In a protocol-specified second interim analysis, OS was shown to be significantly prolonged in the ET plus ribociclib group compared with ET plus placebo. The estimated OS at 42 months was 70.2% (95% CI 63.5–76.0) in the ribociclib group and 46.0% (95% CI 32.0–58.9) in the placebo group [hazard ratio for death 0.71 (95% CI 0.54–0.95); $P = 0.00973$] (Table 2) [46].

The survival benefit in the subgroup of patients receiving a non-steroidal AI was consistent with the intention-to-treat population.

Notably, MONALEESA-7 is the first study to show the survival benefit of combining a CDK4/6 inhibitor with ET in the first-line setting in HR+, HER2– ABC in premenopausal women, as previous studies have all been conducted in postmenopausal women [35, 39, 45, 47, 48].

Fulvestrant in Combination with CDK4/6 Inhibitors

Fulvestrant has been studied in combination with CDK4/6 inhibitors in both the first- and second-line settings, as summarized in Table 1 (postmenopausal women) and Table 2 (pre- and perimenopausal women). Three separate phase III trials in patients with HR+, HER2– ABC have assessed fulvestrant in combination with the CDK4/6 inhibitors palbociclib (PALOMA-3), ribociclib (MONALEESA-3), and abemaciclib (MONARCH 2) [37, 40, 49]. Results from these studies demonstrated that treatment with each of the CDK4/6 inhibitors in combination with fulvestrant significantly prolonged PFS versus fulvestrant alone (Tables 1, 2) [37, 40, 49]. As a result, the FDA has approved fulvestrant in combination with palbociclib, ribociclib, and abemaciclib for patients with HR+, HER2– ABC or MBC [8–10]. In the OS analysis of PALOMA-3, median OS was not significantly improved with fulvestrant plus palbociclib (34.9 months) versus fulvestrant monotherapy [28.0 months; hazard ratio 0.81 (95% CI 0.64–1.03); $P = 0.09$] in the overall patient population (Table 1) [50]. Despite this, in patients with sensitivity to prior ET, improvements in median OS were observed with fulvestrant plus palbociclib (39.7 months) versus fulvestrant monotherapy [29.7 months; hazard ratio 0.72 (95% CI 0.55–0.94)], suggesting that combination therapy may offer a survival benefit in this patient subgroup [50]. In the subsequent OS analysis of MONARCH 2, fulvestrant in combination with abemaciclib significantly prolonged median OS (46.7 months) versus fulvestrant alone [37.3 months; hazard ratio 0.76 (95% CI 0.61–0.95); $P = 0.01$] (Table 1) [51]. Similarly, in MONALEESA-3, fulvestrant in combination with ribociclib had a significant OS benefit over fulvestrant alone [median OS not reached vs. 40.0 months, respectively; hazard ratio 0.72 (95% CI 0.57–0.92); $P < 0.005$] (Table 1) [52]. In

Table 2 Phase III clinical trials for pre- or perimenopausal women with locally advanced or MIBC

Study design	Treatment comparison	Patients, <i>n</i>	PFS, months: experimental vs. control arm	Hazard ratio (95% CI)	Median follow-up, months	OS, months: experimental vs. control arm	Hazard ratio (95% CI)	Most common adverse events, %: experimental vs. control arm
First-line study ^a								
MONALEESA-7 ^a [42, 46]	R, DB, PC Ribociclib + goserelin + ET or placebo + goserelin + ET ^b	672	23.8 vs. 13.0	0.55 (0.44–0.69)	19.2	NR vs. 40.9 ^f	0.71 (0.54–0.95)	Neutropenia, 75.8 vs. 7.7 Hot flush, 34.0 vs. 33.5 Nausea, 31.6 vs. 19.6 Leukopenia, 31.3 vs. 5.6
Second-line studies ^a								
PALOMA-3 ^c [41, 50]	R, DB, PC Fulvestrant + palbociclib vs. fulvestrant + placebo	108	9.5 vs. 5.6	0.50 (0.29–0.87)	8.9	34.9 vs. 28.0 ^{e,f}	0.81 (0.64–1.03) ^e	Neutropenia, 85.9 vs. 5.6 Infections, 47.9 vs. 33.3 Nausea, 40.8 vs. 36.1 Leukopenia, 56.3 vs. 2.8

Table 2 continued

Study design	Treatment comparison	Patients, <i>n</i>	PFS, months: experimental vs. control arm	Hazard ratio (95% CI)	Median follow-up, months	OS, months: experimental vs. control arm	Hazard ratio (95% CI)	Most common adverse events, %: experimental vs. control arm
MONARCH 2 ^d [43, 51]	R, DB, Fulvestrant + abemaciclib vs. PC fulvestrant + placebo	114	NR vs. 10.5	0.45 (0.26–0.75)	20.4 (fulvestrant + abemaciclib) 19.6 (fulvestrant + placebo)	46.7 vs. 37.3 ^e	0.76 (0.61–0.95) ^e	Diarrhea, 87.3 vs. 23.8 Infections and infestations, 43.7 vs. 26.2 Neutropenia, 59.2 vs. 7.1 Headache, 33.8 vs. 31.0

ABC advanced breast cancer, AI aromatase inhibitor, CI confidence interval, DB double-blind, ET endocrine therapy, GnRH gonadotropin-releasing hormone agonist, LHRH luteinizing hormone-releasing hormone, MBC metastatic breast cancer, NR not reached, OS overall survival, PC placebo-controlled, PFS progression-free survival, R randomized

^a In the MONALEESA-7 study, patients were permitted to have received up to one previous line of chemotherapy for ABC, but previous ET for ABC was not permitted (except for ≤ 14 days of tamoxifen or a non-steroidal AI [letrozole or anastrozole] with or without goserelin, or ≤ 28 days of goserelin before randomization)

^b ET was either tamoxifen or a non-steroidal AI (dependent on previous adjuvant or neo-adjuvant therapy, or investigator/patient preference)

^c Disease relapse or progression after previous ET for ABC during treatment or within 12 months of completion of adjuvant therapy. Premenopausal women received a LHRH agonist

^d Patients had progressed while receiving neo-adjuvant or adjuvant ET, ≤ 12 months from the end of adjuvant ET, or while receiving first-line ET for MBC. Pre- or perimenopausal women received a GnRH agonist

^e OS and hazard ratio data shown are for the whole study population and are not split by menopausal status

^f OS data shown are mature

MONARCH 2 and MONALEESA-3, the OS benefit of combination therapy was largely consistent across subgroups analyzed [51, 52].

In all three studies, randomization was stratified by metastatic site, and approximately 60% of patients with HR+, HER2– ABC had visceral metastases at baseline [37, 40, 49]. In PALOMA-3, PFS was prolonged with the combination of palbociclib plus fulvestrant versus fulvestrant alone in the subgroups of patients with visceral metastases [hazard ratio 0.47 (95% CI 0.34–0.63)] or with non-visceral metastases [hazard ratio 0.43 (95% CI 0.28–0.67)] [49]. Similar results were reported in MONARCH 2, where median PFS was improved with the combination of fulvestrant plus abemaciclib versus fulvestrant alone in the subgroups of patients with visceral metastases [hazard ratio 0.48 (95% CI 0.37–0.63)] or with bone metastases [hazard ratio 0.54 (95% CI 0.36–0.83)], and the metastatic site subgroup did not have a statistically significant interaction with PFS ($P = 0.171$) [37]. These hazard ratios were maintained with updated PFS data at the next interim analysis [visceral metastases, hazard ratio 0.47 (95% CI 0.37–0.60); bone metastases, hazard ratio 0.58 (95% CI 0.40–0.84)] [51].

Results from the MONALEESA-3 study also demonstrated superior PFS with the combination of ribociclib plus fulvestrant, compared with fulvestrant alone, in the subgroup of patients with liver or lung metastases [hazard ratio 0.65 (95% CI 0.48–0.86)] and in the subgroup of patients without liver or lung metastases [hazard ratio 0.56 (95% CI 0.42–0.76)] [40]. The PFS results from these subgroups of patients were therefore consistent with the improved PFS observed with the combined treatment of a CDK4/6 inhibitor plus fulvestrant versus fulvestrant alone in the overall patient population for these three studies [37, 40, 49].

The combination of fulvestrant with palbociclib or abemaciclib has also been examined in pre- and perimenopausal women with HR+, HER2– ABC in studies that used ovarian suppression (Table 2) [37, 49]. Results from the PALOMA-3 study showed that the addition of palbociclib to fulvestrant improved PFS in the pre- and perimenopausal patient subgroup

[hazard ratio 0.50 (95% CI 0.29–0.87)], and improvements were comparable in the postmenopausal patient subgroup [hazard ratio 0.45 (95% CI 0.34–0.59)] [49]. In the MONARCH 2 study, menopausal status was not found to have a significant impact on PFS ($P = 0.25$). Treatment with fulvestrant plus abemaciclib prolonged PFS versus fulvestrant alone in both the pre- and perimenopausal patient subgroup [hazard ratio 0.42 (95% CI 0.25–0.70)] and the postmenopausal patient subgroup [hazard ratio 0.58 (95% CI 0.46–0.73)] [37]. Fulvestrant plus abemaciclib prolonged OS versus fulvestrant alone in both the pre- and perimenopausal patient subgroups [hazard ratio 0.69 (95% CI 0.38–1.25)] and the postmenopausal patient subgroup [hazard ratio 0.77 (95% CI 0.61–0.98)] [51].

Tolerability of CDK4/6 Inhibitors in Combination with ET

Neutropenia is the most common adverse event with both palbociclib and ribociclib when used in combination with ET [37, 40, 41]. Neutropenia was reported in 79.6% (grade 3/4: 61.7%) of postmenopausal patients who received palbociclib in PALOMA-3 and 69.6% (grade 3/4: 53.4%) of patients who received ribociclib in MONALEESA-3 [40, 41]. By comparison, the incidence of neutropenia in postmenopausal women was lower with abemaciclib in MONARCH 2 (46.0%; grade 3/4: 26.5%) [37]. Although the risk of febrile neutropenia and neutropenic sepsis was low (approximately 1%), given the frequency of neutropenia, the FDA recommends monitoring complete blood count before and during the initial months of treatment with any of the three CDK4/6 inhibitors [8–10]. By comparison, the incidence of diarrhea was much higher with abemaciclib [86.4% in MONARCH 2 (and 87.1% at a subsequent follow-up)] than with palbociclib (21.4% in PALOMA-3; 20.1% in postmenopausal patients only) and ribociclib (29.0% in MONALEESA-3) [37, 40, 41, 49, 51], which is reflected by the FDA warning to instruct patients receiving abemaciclib to monitor for diarrhea, and to initiate antidiarrheal therapy and notify healthcare providers at the first sign of diarrhea [10]. Similarly, based on the increased incidence

of grade ≥ 3 elevations in alanine aminotransferase and aspartate aminotransferase observed with ribociclib and abemaciclib [37, 40], the FDA also recommends performing liver function tests to monitor increases in serum transaminase levels before initiating, and during the initial months of treatment with ribociclib or abemaciclib [9, 10]. The FDA also recommends monitoring electrocardiograms for QT interval prolongation before initiation of, and every 2 weeks during, the first month of treatment with ribociclib, and monitoring patients for signs of venous thromboembolism during treatment with abemaciclib [9, 10].

ET in Combination with Inhibitors of the PI3K-AKT-mTOR Pathway

The PI3K-AKT-mammalian target of rapamycin (mTOR) pathway is a crucial signaling pathway that regulates important cellular functions, such as growth, proliferation, differentiation, and survival [53], and there is notable crosstalk among genes within the PI3K pathway and external crosstalk with ER activation/signaling [54]. Components of the PI3K pathway are frequently mutated in BC [54]. Activation of this signaling pathway has been associated with the development of resistance to ET in HR+ BC [55]. Synthetic lethality observed in in vitro studies combining ET with inhibitors of the PI3K pathway has provided the rationale for the clinical development of various inhibitors of this pathway for use in combination with ET [55].

ET Combined with mTOR Inhibitors

In 2012, the FDA approved the combination of the mTOR inhibitor everolimus plus exemestane for the treatment of patients with HR+ MBC who have progressed on prior treatment with an AI [56]. In the phase III BOLERO-2 study (Table 1), the combination of everolimus plus exemestane showed a statistically significant PFS of 7.8 months versus 3.2 months with exemestane monotherapy [hazard ratio 0.45 (95% CI 0.38–0.54); $P < 0.0001$], which was the primary endpoint [38]. However, in a follow-up analysis, the secondary endpoint of median OS

in patients receiving everolimus plus exemestane was reported to be 31.0 months (95% CI 28.0–34.6) versus 26.6 months (95% CI 22.6–33.1) in patients receiving exemestane monotherapy [hazard ratio 0.89 (95% CI 0.73–1.10); $P = 0.14$] [57]. Hence, the addition of everolimus did not have an OS benefit. Adverse events were more commonly reported with everolimus plus exemestane versus exemestane monotherapy; the most common grade 3 or 4 adverse events with combination therapy were stomatitis, fatigue, dyspnea, anemia, hyperglycemia, pneumonitis, and elevated gamma-glutamyltransferase [38]. A frequently encountered side effect of mTOR inhibitors such as everolimus is stomatitis. Recent data from the SWISH study demonstrated that the use of prophylactic dexamethasone mouthwash significantly reduced the incidence and severity of all-grade stomatitis in patients receiving everolimus plus exemestane, suggesting that prophylactic use of dexamethasone mouthwash could be a new standard of oral care for patients receiving everolimus and exemestane [58].

In the phase II PrECOG 0102 study (NCT01797120), fulvestrant 500 mg was studied in combination with everolimus for the treatment of postmenopausal women with HR+, HER2– MBC who have progressed on either steroidal or non-steroidal AI therapy. Median PFS significantly favored combination therapy (10.3 months) versus fulvestrant monotherapy [5.1 months; hazard ratio 0.61 (95% CI 0.40–0.92); $P = 0.02$] [59]. Adverse events occurred more frequently with fulvestrant plus everolimus versus fulvestrant monotherapy; the most commonly reported treatment-related adverse events (any grade) were oral mucositis (53% vs. 12%), fatigue (42% vs. 22%), rash (38% vs. 5%), and anemia (31% vs. 6%) [59].

ET Combined with PI3K Inhibitors

Several PI3K inhibitors have been assessed in combination with ET and have shown promise in the AI-resistant setting. In the phase II FERGI study, the PI3K inhibitor pictilisib was administered in combination with fulvestrant for the treatment of postmenopausal women with ER+, HER2– MBC who were resistant to an AI; however, the addition of pictilisib to fulvestrant

was poorly tolerated and did not significantly improve PFS [60]. In contrast, in the phase III BELLE-2 and BELLE-3 studies, which assessed the addition of buparlisib to fulvestrant in the AI-resistant setting, median PFS was significantly longer with buparlisib plus fulvestrant versus fulvestrant alone [61, 62]. Although this treatment combination was efficacious in postmenopausal women with ET-resistant, HR+, HER2– MBC, it was also associated with significant toxicity [61, 62]. It has consequently been suggested that more selective (i.e., alpha-specific) PI3K inhibitors may offer a superior safety profile for use in this setting [60, 61].

Fulvestrant in combination with taselelisib, a potent beta-sparing PI3K inhibitor, has shown promising activity in patients with HR+, HER2–, *PIK3CA* mutation-positive MBC [63]. The SANDPIPER study compared fulvestrant (500 mg/month) plus taselelisib (4 mg/day) versus fulvestrant alone in postmenopausal women with ER+, HER2–, *PIK3CA* mutation-positive locally advanced or MBC who experienced disease progression or recurrence during or after treatment with an AI. The combination of fulvestrant plus taselelisib significantly improved investigator-assessed PFS compared with fulvestrant monotherapy [hazard ratio 0.70 (95% CI 0.56–0.89); $P = 0.0037$]. Median PFS for the combination therapy was 7.4 months (95% CI 7.26–9.07) versus 5.4 months (95% CI 3.68–7.29) with fulvestrant monotherapy [17]. However, adverse events were more frequently reported with fulvestrant plus taselelisib versus fulvestrant alone; the most common adverse events were diarrhea (60.1% vs. 19.7%), hyperglycemia (40.4% vs. 9.4%), nausea (34.1% vs. 24.4%), and decreased appetite (26.4% vs. 10.3%). Approximately 31% of patients who received fulvestrant plus taselelisib experienced grade ≥ 3 adverse events associated with PI3K inhibition (including diarrhea, colitis, pneumonitis, rash, stomatitis, and hyperglycemia), limiting its clinical application [17].

The phase III SOLAR-1 study (Table 1) [64], evaluating the addition of the alpha-specific PI3K inhibitor alpelisib to fulvestrant versus fulvestrant monotherapy, has recently met its

primary endpoint, demonstrating a significant improvement in PFS in patients with HR+, HER2–, *PIK3CA* mutation-positive ABC that progressed on, or following treatment with, an AI (with or without a CDK4/6 inhibitor) [65]. Median PFS was 11.0 months with alpelisib plus fulvestrant and 5.7 months with fulvestrant monotherapy [hazard ratio for progression or death 0.65 (95% CI 0.50–0.85); $P < 0.001$]. Clinical benefit was also greater with alpelisib plus fulvestrant versus fulvestrant monotherapy (61.0% vs. 45.3%, respectively). For the primary endpoint, *PIK3CA* mutation status was determined using fresh or archival tumor tissues [65]. Adverse events (any grade) were more frequently reported with alpelisib plus fulvestrant versus fulvestrant monotherapy. In the overall population, the most common adverse events that occurred in at least 35% of patients in either the alpelisib plus fulvestrant group or the fulvestrant monotherapy group were hyperglycemia (63.7% vs. 9.8%, respectively), diarrhea (57.7% vs. 15.7%), nausea (44.7% vs. 22.3%), decreased appetite (35.6% vs. 10.5%), and rash (35.6% vs. 5.9%) [65]. This has led to the FDA approval of this combination along with the approval of companion diagnostics to select patients who have *PIK3CA* mutations in tumor tissue specimens and/or in circulating tumor DNA (ctDNA) [19, 64].

ET Combined with AKT Inhibitors

Currently, combining ET with AKT inhibitors is an investigational approach to the treatment of HR+, HER2– MBC. The phase II randomized, double-blind, placebo-controlled FAKTION trial evaluated capivasertib, which is an oral small molecule inhibitor of AKT, in combination with fulvestrant versus placebo combined with fulvestrant in patients with HR+, HER2– MBC who had progressed on prior AI. In the intention-to-treat population, median PFS was 10.3 months for capivasertib versus 4.8 months for placebo [hazard ratio 0.57 (95% CI 0.39–0.84); $P = 0.0035$]. Median OS was 26 months for capivasertib versus 20 months for placebo [hazard ratio 0.59 (95% CI 0.34–1.05);

$P = 0.071$] [66]. In the capivasertib group, notable adverse events included diarrhea, rash, hyperglycemia, and infections. Approximately one-third of the patients in the capivasertib group required dose reduction, which was primarily due to rash and diarrhea. In this study, *PIK3CA* hotspot mutation or *PTEN* null by immunohistochemistry did not affect sensitivity to capivasertib. Additional comprehensive genomic analyses of tumors are ongoing to ascertain biomarkers of response to therapy [66].

Treatment Options After Progression on ET Combined with a CDK4/6 Inhibitor

There are limited data regarding the efficacy of different treatment regimens following disease progression on a CDK4/6 inhibitor with ET. If available, we highly recommend clinical trial options in this setting. Tumor DNA sequencing, either tissue-based or ctDNA-based, for predictive biomarkers, such as *PIK3CA* mutations, neurotrophic receptor tyrosine kinase (*NTRK*) gene fusions, and mismatch repair (MMR)-deficiencies should be considered in addition to germline *BRCA* testing, if not done previously.

Table 3 [67–88] outlines some of the recently reported and ongoing studies employing strategies to tackle resistance with combination therapies in HR+, HER2– MBC. Furthermore, several oral SERDs are also in clinical development, both as monotherapy and in combination with other therapies [73, 76, 77].

The optimal treatment for patients following disease progression on a CDK4/6 inhibitor plus an AI or fulvestrant is unknown; however, several studies are planned or ongoing [70, 89]. For patients who had disease progression while receiving an AI in combination with a CDK4/6 inhibitor, in the absence of visceral crisis (severe organ dysfunction and rapid progression of disease [90]), there are several potential treatment options before consideration of chemotherapy, including an additional line of ET, such as fulvestrant, ET in combination with other targeted agents (e.g., everolimus plus

exemestane) [38, 91], or fulvestrant plus alpelisib in *PIK3CA* mutant tumors [19]. Studies are ongoing to evaluate the role of continued CDK4/6 inhibition in combination with an alternate ET, such as fulvestrant, if an AI was used in combination with a CDK4/6 inhibitor initially [92]. Until the results of these trials are available, such an approach is considered investigational. The combination of everolimus plus exemestane was approved for AI-resistant disease based on the phase III BOLERO-2 study [38]; however, its efficacy following CDK4/6 inhibition is not clear. In a retrospective, two-institute review of patients with HR+, HER2– MBC ($n = 41$) who were treated with everolimus-based combinations after progression on palbociclib-based therapy, modest PFS [median 4.2 months (95% CI 3.2–6.2)], OS [median 18.7 months (95% CI 9.5–not reached)], and objective response rate (ORR; 17.1%) were observed [93]. In the recently reported phase I/II TRINITY-1 study, the safety and efficacy of triplet therapy with the CDK4/6 inhibitor ribociclib (300 mg or 200 mg) plus everolimus (2.5 mg or 5 mg), along with exemestane (25 mg daily), was evaluated in men or postmenopausal women with HR+, HER2– MBC who progressed on prior CDK4/6 inhibitors and up to three lines of therapy (≥ 1 ET and ≤ 1 chemotherapy regimen). TRINITY-1 met its primary efficacy endpoint, demonstrating a clinical benefit rate of 41.1% at week 24. Adverse events were consistent with the known safety profile of the individual drugs [94]. However, this is a single-arm study and further investigation is necessary. Ongoing research that aims to elucidate the intrinsic and acquired resistance mechanisms is also critical for the development of effective interventions following disease progression on CDK4/6 inhibitors.

Table 3 Ongoing/recently completed studies tackling resistance mechanisms in ER+ MBC

Strategies to overcome resistance mechanisms	Treatment comparison	Clinical development and exploration	Status (phase)	Patient characteristics
ET	Elaeostant (RAD190G1T48) vs. G1T48+ palbociclib	NCT02650817 [76]	Completed (Ib)	Postmenopausal women with ER+, HER2–ABC; progression after ≥ 1 prior line of ET for MBC
ET+ PI3K inhibitor	Fulvestrant + taselisib vs. fulvestrant + placebo	NCT03455270 [77]	Ongoing (I)	Part 2: women with ER+, HER2–ABC; progression on or after adjuvant AI or after prior AI for ABC
ET+ PI3K inhibitor	Fulvestrant + alpelisib vs. fulvestrant + placebo	NCT02340221 [67]	Ongoing (III)	Postmenopausal women with HR+, HER2–, <i>PIK3CA</i> mutation-positive ABC; recurrence or progression on or after AI
ET+ CDK4/6 inhibitor ± immunotherapy	Fulvestrant vs. fulvestrant + palbociclib vs. fulvestrant + palbociclib + avelumab	NCT02437318 [82]	Ongoing (III)	Men or postmenopausal women with ER+, HER2–ABC and known <i>PIK3CA</i> status; progression on or after ET
ET+ CDK4/6 inhibitor ± immunotherapy	Pembrolizumab + letrozole + palbociclib	NCT03147287 [68]	Recruiting (II)	Patients with HR+, HER2–ABC; progression on or after ET and CDK4/6 inhibitor
ET+ CDK4/6 inhibitor ± immunotherapy	Pembrolizumab + letrozole + palbociclib	NCT02778685 [69]	Recruiting (II)	Postmenopausal women with newly diagnosed ER+, HER2–MBC

Table 3 continued

Strategies to overcome resistance mechanisms	Treatment comparison	Clinical development and exploration	Status (phase)	Patient characteristics
ET+ CDK4/6 inhibitor + PI3K or mTOR inhibitor	Ribociclib + everolimus + exemestane Palbociclib + everolimus + exemestane LEE011 + exemestane + everolimus vs. LEE011 + exemestane	NCT02732119 [70] NCT02871791 [84] NCT01857193 [71]	Completed (I/II) Ongoing (I/II) Completed (I)	Patients with HR+, HER2– ABC; progression on CDK4/6 inhibitor Patients with HR+, HER2– MBC; progression on CDK4/6 inhibitor and non-steroidal AI Postmenopausal women with HR+, HER2– ABC; progression on or after adjuvant AI or AI for ABC
	LEE011 + letrozole vs. BYL719 + letrozole vs. LEE011 + BYL719 + letrozole Abemaciclib in combination therapies ^a	NCT01872260 [83] NCT02057133 [72]	Completed (Ib) Ongoing (Ib)	Dose-expansion phase: postmenopausal women with HR+, HER2– ABC; no prior systemic treatment for ABC Women with HR+, HER2– MBC; prior systemic ET with ≥ 1 non-steroidal AI for MBC
ET ± CDK4/6 or PI3K inhibitor	LSZ102 vs. LSZ102 + LEE011 vs. LSZ102 + BYL719	NCT02734615 [73]	Recruiting (I)	Patients with HR+, HER2– ABC; progression after ET
ET+ FGFR inhibitor + CDK4/6 inhibitor	Fulvestrant + erdafitinib + palbociclib	NCT03238196 [74]	Recruiting (Ib)	Men or postmenopausal women with HR+, HER2–, FGFR-amplified MBC; ≥ 1 prior line of therapy for MBC
ET+ HDAC inhibitor	Exemestane + entinostat vs. exemestane + placebo	NCT02115282 [75]	Ongoing (III)	Patients with HR+, HER2– ABC; relapse or progression on or after non-steroidal AI
ET+ CDK7 inhibitor	Fulvestrant + SY-1365 Fulvestrant + CT7001	NCT03134638 [86] NCT03363893 [87]	Ongoing (I) Recruiting (Ib/II)	Cohort 5: patients with HR+ MBC post CDK4/6 inhibitor and hormonal therapy Module 2: patients with locally advanced or metastatic HR+ and HER2– BC

Table 3 continued

Strategies to overcome resistance mechanisms	Treatment comparison	Clinical development and exploration	Status (phase)	Patient characteristics
ET+ aurora A kinase inhibitor	Erbumine + ET	NCT0395939 [88]	Ongoing (I)	Patients with MBC post CDK4/6 inhibitor and ET
ET+ BCL-2 inhibitor	Fulvestrant + venetoclax vs. fulvestrant	NCT03584009 [85]	Ongoing (II)	Women with ER+, HER2- locally advanced or MBC who experienced disease recurrence or progression during or after CDK4/6 inhibitor
ET+ immunotherapy	Fulvestrant + pembrolizumab	NCT03933845 [78]	Recruiting (II)	Patients with HR+, HER2- ABC; ≤ 1 prior line of ET (other than fulvestrant) or chemotherapy for ABC
	Pembrolizumab + AI (exemestane, anastrozole, or letrozole)	NCT02648477 [80]	Recruiting (II)	Cohort 2: patients with HR+, HER2- MBC; not resistant to all three approved AIs
	Pembrolizumab + exemestane + leuprolide	NCT02990845 [79]	Recruiting (I/II)	Pre- or perimenopausal women with HR+, HER2- ABC; resistant to front-line ET
ET+ dual immunotherapy	Fulvestrant + durvalumab + tremelimumab	NCT03430466 [81]	Recruiting (II)	Postmenopausal women with HR+, HER2- ABC

ABC advanced breast cancer, AI aromatase inhibitor, BCL-2 B-cell lymphoma-2, CDK cyclin-dependent kinase, ER+ estrogen receptor-positive, ET endocrine therapy, FGFR fibroblast growth factor receptor, HDAC histone deacetylase, HER2- human epidermal growth factor receptor-2-negative, HR hormone receptor, HR+ hormone receptor-positive, MBC metastatic breast cancer, mTOR mammalian target of rapamycin, PI3K phosphoinositide 3-kinase, PIK3CA phosphatidylinositol-4,5-bisphosphate 3-kinase

^a In NCT02057133, abemaciclib is studied in combination with letrozole, anastrozole, tamoxifen, exemestane, everolimus, trastuzumab, LY3023414 plus fulvestrant, pertuzumab plus trastuzumab with loperamide, or ongoing ET

WHAT ARE THE BIOMARKERS WITH CLINICAL UTILITY, OTHER THAN HORMONE RECEPTORS, IN ER+, HER2– MBC?

While many biomarkers are being evaluated in research arenas, those with potential therapeutic implications for clinical use are discussed below.

***ESR1* Mutation**

Of particular interest are the recurrent mutations in *ESR1*, which are highly prevalent in the tumors of women with ABC previously treated with AIs, but rarely occur in primary tumors [16, 95]. These mutations cluster in the ligand-binding domain, leading to estrogen-independent constitutive ER activation and resistance to AIs [95]. Recurrent point mutations have been identified in the *ESR1* ligand-binding domain, with common variants identified as D538G, Y537S, Y537N, and Y537C [95]. However, tumors bearing *ESR1* mutations can retain relative sensitivity to tamoxifen and fulvestrant [95, 96]. In a retrospective analysis of baseline plasma samples from the phase III SoFEA study, Fribbens et al. reported that median PFS significantly improved with fulvestrant-containing regimens versus the steroidal AI exemestane [hazard ratio 0.52 (95% CI 0.30–0.92); $P = 0.02$] in patients with HR+ *ESR1* mutation-positive MBC; this difference was not significant in patients with wild-type *ESR1* [hazard ratio 1.07 (95% CI 0.68–1.67); $P = 0.77$] [16]. These findings demonstrate that fulvestrant may be a more appropriate ET for the treatment of patients with tumors harboring *ESR1* mutations. However, more effective SERDs are needed to optimize ET for *ESR1*-mutated BC, especially for the *ESR1* Y537S mutation, which may be more resistant to fulvestrant than other known *ESR1* mutations [97, 98]. Multiple new ER modulators, including lasofoxifene [99], LSZ102 [73], AZD9833 [100, 101], GDC-9545 [102], SAR439859 [103], G1T48 [77], and ZN-c5 [104] are undergoing clinical evaluation. Of these, an open-label phase II study is comparing

lasofoxifene and fulvestrant for the treatment of pre- and postmenopausal women with ER+/HER2– locally advanced or MBC with an acquired *ESR1* mutation in patients who have disease progression on an AI in combination with a CDK4/6 inhibitor [99].

The potential impacts of ctDNA *ESR1* mutations on the outcome of patients treated with targeted therapies have been evaluated in clinical trials investigating mTOR inhibitors, as well as CDK4/6 inhibitors. In a secondary analysis of the BOLERO-2 trial, 28.8% of evaluable patients had *ESR1* mutations (Y537S and/or D538G) as detected by cell-free DNA analysis. These mutations were associated with aggressive biology and poor outcome [105]. Similar results were reported with the TRINITI-1 study, with shorter PFS observed in patients with *ESR1* mutations compared with patients with wild-type *ESR1*, as detected by ctDNA genotyping [94]. However, exemestane was the ET partner in both studies. In the BOLERO-2 trial, benefit from addition of everolimus was seen in both wild-type *ESR1* and *ESR1* D538G subgroups [105]. This study lacked sufficient numbers of patients in the *ESR1* Y537S subgroup to draw conclusions on everolimus benefit for this subgroup. In the PALOMA-3 trial, the benefit of CDK4/6 inhibition with palbociclib was observed regardless of *ESR1* mutation status [50]. However, positive selection of *ESR1* Y537S mutation was observed on disease progression in both fulvestrant plus placebo and fulvestrant plus palbociclib treatment arms [106], which is consistent with previous studies demonstrating resistance of *ESR1* Y537S mutation to fulvestrant [107]. The addition of CDK4/6 inhibitors to AI therapy does not appear to prevent emergence of *ESR1* mutations [108].

***PIK3CA* Mutation**

The PI3K-AKT-mTOR pathway is possibly the most commonly altered pathway in human cancers [53]. Mutations in the alpha catalytic subunit of PI3K (*PIK3CA*) are some of the most frequent genomic alterations noted in HR+ BC [109, 110]. *PIK3CA* mutation status is an important predictive biomarker to identify

patients suitable for treatment with alpelisib, a recently approved PI3K inhibitor, in combination with fulvestrant [17, 63]. In addition to tumor testing, *PIK3CA* mutations can be detected by ctDNA testing, which offers a non-invasive option to screen patients for this therapeutic approach. In the SOLAR-1 study, a planned retrospective analysis demonstrated that alpelisib plus fulvestrant significantly improved median PFS versus fulvestrant monotherapy when *PIK3CA* mutations were detectable in plasma ctDNA (10.9 vs. 3.7 months) [64]. *PIK3CA*-mutational analysis in the SOLAR-1 study showed that greater reductions in the risk for disease progression were observed in patients with *PIK3CA* mutations detected in plasma ctDNA [hazard ratio 0.55 (95% CI 0.39–0.79)] versus patients with *PIK3CA* mutations detected in tumor tissue samples [hazard ratio 0.65 (95% CI 0.50–0.85); $P < 0.001$], highlighting the benefit of evaluating mutation status via liquid biopsy [64]. *PIK3CA* mutation status does not appear to predict benefit from CDK4/6 inhibitor therapy when used in combination with fulvestrant [49].

HER2 Mutations

Mutations in *HER2* occur in approximately 2% of patients with BC overall, while, in lobular BC, *HER2* mutations may occur more frequently [111]. A distinct mechanism of resistance to ET appears to be *HER2* mutations [112]. Nayar et al. performed whole exome sequencing of metastatic biopsies to identify mechanisms of resistance in ER+ BC that are resistant to ET, including AI, tamoxifen, and fulvestrant. Activating *HER2* mutations were identified in 8 patients out of 168 samples [112]. Pre-existing mutations were not identified in treatment-naïve primary tumor samples from 4 of 5 patients who were examined, which suggested that these mutations were acquired under selective pressure of ET. These mutations also appeared to be mutually exclusive with *ESR1* mutations. Furthermore, the *HER2* mutations exhibited resistance to tamoxifen, fulvestrant, and palbociclib, which was mitigated following

treatment with a combination of ER-directed therapy and the irreversible *HER2* kinase inhibitor, neratinib [112]. In another study, examination of data derived from 8 BC genome-sequencing studies identified 25 patients with *HER2* somatic mutations in *HER2* gene amplification negative BC [111]. Of the 13 *HER2* somatic mutations that were functionally characterized, 7 were determined to be activating mutations. Furthermore, whereas some of the *HER2* mutations were resistant to lapatinib, a reversible *HER2* inhibitor, all of the mutations were sensitive to neratinib, suggesting that drugs targeting *HER2* may show clinical benefit in patients with *HER2* somatic mutation-positive BC [111]. In line with these studies, a single-arm phase II trial was conducted to assess the clinical benefit rate of neratinib in heavily pre-treated patients with *HER2*-mutated non-amplified MBC [113]. Although this was a small, proof-of-concept study, the pre-defined primary efficacy endpoint was met, as the clinical benefit rate was 31% (90% CI 13–55). Additionally, in the SUMMIT basket trial evaluating neratinib in *HER2*- and *HER3*-mutated cancers, neratinib exhibited the greatest activity in *HER2*-mutant BC ($n = 25$; ORR at Week 8 was 32%) [114].

Neratinib in combination with fulvestrant in patients with ER+ *HER2*-mutated non-amplified BC is being evaluated in several trials [113]. In an amendment of the SUMMIT basket trial examining the combination of neratinib plus fulvestrant ($n = 47$), an ORR of 29.8% and clinical benefit rate of 46.8% was observed [vs. 36.4% and 36.4%, respectively, in the ER-negative neratinib monotherapy subgroup ($n = 11$) and 17.4% and 30.4%, respectively, in the ER+ neratinib monotherapy subgroup ($n = 23$)] [115]. In a triplet therapy cohort of the SUMMIT basket trial, neratinib plus trastuzumab and fulvestrant achieved an overall response rate of 39% in 13 patients with *HER2*-mutant HR+ MBC [116]. In the phase II plasmaMATCH trial, neratinib in combination with fulvestrant showed clinical activity in patients with *HER2*-mutated ER+ BC [117].

Germline *BRCA1* and *BRCA2* Mutations

Germline *BRCA* mutation status has therapeutic implications in the form of two recently approved poly (ADP-ribose) polymerase (PARP) inhibitors; olaparib and talazoparib [118, 119]. In the phase III OlympiAD study, patients with germline *BRCA* mutations and HER2– MBC who had received no more than two prior chemotherapy regimens for metastatic disease were randomly assigned to olaparib versus the physician's choice of a standard single-agent chemotherapy [120]. Of the 302 patients who underwent randomization, 205 patients were assigned to the olaparib group and 97 patients to the standard-therapy group. Median PFS was significantly longer with olaparib compared with the standard therapy [7.0 vs. 4.2 months; hazard ratio for PFS 0.58 (95% CI 0.43–0.80); $P < 0.001$]. The hazard ratio for PFS was better in the triple-negative subgroup [0.43 (95% CI 0.29–0.63)] than in the HR+ subgroup [0.82 (95% CI 0.55–1.26)]. The response rates were also higher in the olaparib group compared with the standard-therapy group (59.9 vs. 28.8%) with lower rates of grade ≥ 3 adverse events (36.6% in the olaparib group vs. 50.5% in the standard-therapy group) [120]. In the final prespecified analysis of OS in the overall OlympiAD study population, median OS was not significantly different between treatment arms [19.3 months with olaparib and 17.1 months with standard therapy; hazard ratio 0.90 (95% CI 0.66–1.23); $P = 0.513$; note that OlympiAD was not powered to show any difference in OS between treatment groups], and findings were consistent across pre-defined subgroups, including HR status [in the HR+ subgroup, median OS was 21.8 months with olaparib and 21.3 months with standard therapy; hazard ratio 0.86 (95% CI 0.55–1.36); $P =$ not significant] [121]. In a similarly designed phase III, open-label, 2:1 randomized study, talazoparib was compared with the physician's choice of a standard single-agent chemotherapy in patients with ABC and germline *BRCA* mutations [122]. Median PFS was

8.6 months in the talazoparib group versus 5.6 months in the standard-therapy group [hazard ratio for disease progression or death 0.54 (95% CI 0.41–0.71); $P < 0.001$]. The hazard ratio for PFS was better in the HR+ subgroup [0.47 (95% CI 0.32–0.71)] than in the triple-negative subgroup [0.60 (95% CI 0.41–0.87)]. At the time of the interim analysis, the median hazard ratio for death was 0.76 (95% CI 0.55–1.06; $P = 0.11$). Furthermore, the ORR determined by the investigators was greater for patients who received talazoparib compared with standard therapy (62.6 vs. 27.2%, respectively). Hematologic grade 3–4 adverse events were observed in 55% of patients who were treated with talazoparib versus 38% of patients who were treated with standard therapy. Although the majority of non-hematologic adverse events were grade 1 in severity in patients who received talazoparib, non-hematologic grade 3 adverse events occurred in 32% of patients in the talazoparib group compared with 38% of patients in the standard-therapy group. Significant improvements in patient-reported outcomes were observed in patients who received talazoparib compared with standard therapy [122].

WHAT ARE THE EVOLVING PARADIGMS IN THE MANAGEMENT OF HR+, HER2– MBC?

The role of precision medicine in oncology is evolving rapidly and is poised to play a very important role at every stage in the management of MBC, with the goal of improving patient stratification and tailoring therapy based on druggable targets. In order to fully harness the potential of genomics in oncology, tumor DNA sequencing information is required to recognize biomarkers with prognostic and predictive significance for guiding future therapy and individualizing treatment. While tissue biopsy remains the current gold standard, genomic assessment from ctDNA is an emerging attractive tool since it is a blood-based assay

compared with obtaining a tissue biopsy by invasive methods [123]. ctDNA testing is able to detect the active circulating tumor clone in the background of clonal heterogeneity that exists in metastatic disease [123, 124], and also offers the possibility of less-invasive longitudinal monitoring of disease genomic profiles [124]. Since bone is the most common site of distant metastasis in ER+ BCs [125], and 50% of bone biopsy specimens have insufficient tissue for biomarker testing [126], this non-invasive testing will be an important option in this setting. If a liquid biopsy is planned, it is important to remember to do so at the time of progression. Concordance and discordance rates between the various platforms can be a challenge; however, further developments in this area may help solve this in future [124]. Genomic profiling tests are currently available to help guide appropriate treatment decisions [127]. In order to obtain regulatory drug approvals based on genomic alterations, innovative study designs such as basket and umbrella trials will have an increasingly important role to play [128]. The MATCH and TAPUR studies are examples of precision oncology clinical trials that explore treatment options based on molecular alterations [129, 130]. Another important component to help advance precision oncology is to maintain large-scale repositories of real-world data, including clinical, genomic, molecular, and imaging information, along with patient-reported outcomes, which can be shared among researchers. Real-world data repositories currently in progress include the Metastatic Breast Cancer Project and CancerLinQ. The increasing use of genomic and molecular testing in oncology generates an exponential volume of data. Therefore, there is a growing need to create novel models for sharing and integrating genomic, molecular, clinical, and patient-reported outcome data wherein artificial intelligence techniques, such as machine learning and deep learning, could play a key role. All these approaches make the future management of MBC challenging and promising at the same time.

CONCLUSIONS

Remarkable progress has been made in the management of ER+ MBC from agents that target the ER pathway to agents that target the various cellular mechanisms responsible for cancer survival and resistance to therapy. The data discussed above demonstrate the recent advancements in the field and the areas of ongoing research. In summary, the combination of ET and CDK4/6 inhibitor therapy is becoming a standard frontline therapy for ER+ MBC, with several clinical studies showing a survival benefit when a CDK4/6 inhibitor is combined with ET over ET alone [47, 51, 52]. However, the optimal sequence of treatment for patients who have had disease progression while receiving treatment with ET in combination with a CDK4/6 inhibitor is unknown. Sequencing therapies is an important aspect of managing MBC, and the goal is to improve survival, balance disease control, and maintain quality of life. In the absence of rapidly progressing disease, extensive visceral disease burden, and endocrine resistance, ET alone or in combination with other targeted therapies are the preferred treatment options for subsequent lines of therapy for ER+ disease. Although there are some unique side effects related to ET and targeted therapies, they are generally tolerated better than chemotherapy, which paves the way for clinically meaningful advancements and a better quality of life. Options for subsequent lines of therapy will depend on which agents have previously been used; fulvestrant alone or in combination with CDK4/6 inhibitors may be considered, if not used previously. For patients who have progressed on ET with CDK 4/6 inhibitors, the combination of ET with everolimus and the combination of fulvestrant with alpelisib in patients with *PIK3CA* mutations are additional treatment recommendations.

For patients with disease progression following up to three sequential ET therapy regimens for advanced disease, chemotherapy may be considered [6]. The treatment approach may be similar for premenopausal patients once they have been rendered postmenopausal based on serum estradiol levels with ovarian suppression.

The cornerstone of these recent advances lies in our increasing understanding of the molecular biology of BC and the utilization of cancer genomic tools. Genomic assessment with either tumor tissue or blood-based ctDNA assays are increasingly used. Drug approvals based on genomic markers of both somatic and germline mutations include alpelisib in combination with fulvestrant in *PIK3CA*-mutated ER+ MBC, and PARP inhibitors for *BRCA1*- and *BRCA2*-mutated tumors. In addition, tumors with *ESR1* and *HER2* mutations are finding their place in clinical decision making.

The armamentarium available to manage MBC is increasing, with many promising novel agents and synergistic combination therapies on the horizon. Further advancements in our understanding of intra-tumoral heterogeneity, better predictive markers of sensitivity and resistance to selected therapies, innovative study designs, wider application of genomic tumor assessment tools, including ctDNA testing, and increased integration of genomic data in the clinical setting will help us make better treatment decisions for our patients. In addition, the use of artificial intelligence technology to aid complex decision making may be another potential tool to help treat MBC in the near future. However, the challenge of managing and applying the vast body of genomic data at a patient level, sharing the data for a wider understanding, and the economic impact of all of this has to be borne in mind.

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