Current Oncology Reports (2023) 25:689–698
https://doi.org/10.1007/s11912-023-01393-6

Advances in Endocrine Therapy for Hormone Receptor-Positive Advanced Breast Cancer

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Accepted: 6 February 2023 / Published online: 1 April 2023

Abstract

Purpose of Review To provide an overview of the current management of hormone receptor-positive (HR +) advanced breast cancer as well as highlight ongoing clinical investigation and novel therapies in development.

Recent Findings CDK4/6 inhibition plus endocrine therapy is standard front-line therapy for HR + advanced breast cancer. Continuation of CDK4/6 inhibitors in combination with alternative endocrine therapy has been evaluated in the second-line setting. Alternatively, endocrine therapy in combination with PI3K/AKT pathway targeting agents has been studied, particularly in patients with PI3K pathway alterations. The oral SERD elacestrant has also been evaluated in patients with *ESR1* mutation. Many novel endocrine agents and targeted agents are in development. An improved understanding of combination therapies and sequencing of therapies is needed to optimize the treatment paradigm. Biomarker development is needed to guide treatment decisions.

Summary Advances in the treatment of HR + breast cancer have resulted in improved patient outcomes in recent years. Continued development efforts with identification of biomarkers to better understand response and resistance to therapy are needed.

Keywords Hormone receptor-positive breast cancer · HER2 negative breast cancer · Endocrine therapy · CDK4/6 inhibition · PI3K inhibition · AKT inhibition · PIK3CA mutation · SERDs · SERMs · PROTACs · SERCAs · CERANs · SARMs

Introduction

Breast cancer is the most commonly diagnosed cancer in women and the leading cause of cancer-related deaths globally [1]. Approximately 70% of advanced breast cancer cases (ABC) are hormone (estrogen and/or progesterone) receptor-positive (HR +) and human epidermal growth factor receptor 2 negative (HER2-) per ASCO CAP 2018 criteria [2]. These tumors express estrogen receptor alpha (ERα) and depend on estrogen-mediated growth signaling to proliferate. Endocrine therapy (ET) directly targets circulating estrogen available to bind to the estrogen receptor (ER) or the ER itself. Due to the reliance on ER-mediated signaling, standard practice for the management of HR + metastatic breast cancer generally involves initial treatment with ET, with chemotherapy being utilized in the setting of endocrine resistance [3–5]. Endocrine resistance can generally be divided into either ER-mediated or ER-independent. For example, activating mutations in the ligand binding domain of the estrogen receptor 1 (*ESR1*) gene, which encodes for ERα, are typically acquired as a result of endocrine resistance in HR + MBC, and about 20–40% of HR + patients will acquire an *ESR1* mutation following initial endocrine therapy with an aromatase inhibitor (AI) [6]. However, alterations in *ESR1* occur rarely in untreated patients. Alternatively, ER-independent resistance can be mediated by upregulation of various growth pathways. Alterations in the PI3K/AKT pathway are common

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in HR + breast cancer, and many of these alterations arise in the setting of endocrine resistance.

Previously, ET was generally administered as monotherapy; however, newer targeted agents are now routinely added to ET, resulting in improved survival outcomes. Currently, these agents include cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors and agents that target the PI3K/AKT pathway. However, significant development is ongoing to identify novel strategies to improve both endocrine agents as well as targeted agents. In this review, we outline the current standard of care approach to treating HR + /HER2 − ABC while also highlighting novel and promising endocrine and targeted therapies.

CDK4/6 Inhibitors

CDK/cyclin D1 complexes that drive cell division are hyperactive in cancer [7], and thus the concept of therapeutic CDK inhibition was introduced to halt cell proliferation by inducing G1 cell cycle arrest. CDK4/6 inhibitors were studied early in breast cancer given evidence in transgenic animals that cyclin D1 deficiency strongly impairs mammary epithelial proliferation, implying a role for the CDK4/6 pathway in mammary tissue [8]. Preclinical studies of the CDK4/6 inhibitor palbociclib, showed that the vast majority of the human breast cancer cell lines were sensitive to palbociclib, resulting in RB (retinoblastoma) phosphorylation and cell cycle arrest. The majority of sensitive cell lines had a luminal pattern of gene expression, resulting in further exploration of CDK4/6 inhibitors in HR + breast cancer. Furthermore, studies show that combined inhibition of CDK4/6 and ER halts tumor cell proliferation synergistically.

Currently, three orally bioavailable CDK 4/6 inhibitors: palbociclib, ribociclib, and abemaciclib are FDA-approved for the management of HR + ABC. Palbociclib and ribociclib are small molecules which are structurally similar and have high selectivity towards CDK4/6 while abemaciclib's chemical structure is unique and also allows for inhibition of other kinases, such as CDK9 [9]. As a result, their toxicity profiles differ slightly. Palbociclib and ribociclib are more frequently associated with neutropenia while abemaciclib is more frequently associated with diarrhea. Ribociclib can also result in QTc prolongation and hepatotoxicity. Each of the CDK4/6 inhibitors have also been associated with interstitial lung disease, though incidence is low (< 2%) [10].

Each of the currently approved CDK4/6 inhibitors has been evaluated in combination with ET in the first- and second-line setting (Table 1). Abemaciclib has also been evaluated as monotherapy in later-line settings [11]. Results have generally been consistent across studies, demonstrating improvement in survival outcomes when CDK4/6 inhibitors are added to ET in both the first- and second-line setting. The majority of these trials were limited to postmenopausal patients, but the MONALEESA-7 study evaluated ribociclib versus placebo in combination with goserelin and either tamoxifen or aromatase inhibition specifically in premenopausal patients with HR + ABC [12]. Statistically significant improvement in median progression-free survival (mPFS) (23.8 vs. 13.0 months; HR 0.55) and median overall survival (mOS) (58.7 vs. 48.0 months; HR 0.76) was reported with the addition of ribociclib [12, 13]. As a result, ET in combination with CDK4/6 inhibition is currently considered standard first-line therapy for both premenopausal and postmenopausal patients with HR + ABC.

Since approval of CDK4/6 inhibitors, several important questions have been explored, while others remain unanswered at this time. One important question explored across trials was whether all patients with HR + ABC should be treated with CDK4/6 inhibition in the front-line setting, or if CDK4/6 inhibition could be preserved for the second-line

Table 1 Randomized phase III studies evaluating endocrine therapy in combination with CDK4/6 inhibition

Setting	Study	Patient population	Agents	Median PFS (months)	Median OS (months)
Endocrine-Sensitive	PALOMA-2 [15, 71]	Postmenopausal women ($N=666$)	Palbociclib + letrozole	24.8 vs. 14.5 HR 0.56; $P<0.01$	53.9 vs. 51.2 HR 0.96; $P=0.34$
	MONARCH-3 [14]	Postmenopausal women ($N=493$)	Abemaciclib + non-steroidal AI	28.2 vs. 14.8 HR 0.54; $P<0.01$	Not available
	MONALEESA-2 [22, 72]	Postmenopausal women ($N=668$)	Ribociclib + letrozole	25.3 vs. 16.0 HR 0.57; $P<0.01$	63.9 vs. 51.4 HR 0.76; $P=0.01$
	MONALEESA-7 [12, 13]	Pre- or perimenopausal women ($N=672$)	Ribociclib + goserelin + tamoxifen or AI	23.8 vs. 13.0 HR 0.55; $P<0.01$	58.7 vs 0.48.0 HR 0.76; $P<0.01$
	MONALEESA-3 [23, 26]	Postmenopausal women ($N=726$)	Ribociclib + fulvestrant	20.5 vs. 12.8 HR 0.59; $P<0.01$	53.7 vs. 41.5 HR 0.73; $P<0.01$
Endocrine-Resistant	PALOMA-3 [21, 25]	Pre-, peri-, or postmenopausal women ($N=521$)	Palbociclib + fulvestrant	9.5 vs. 4.6 HR 0.46; $P<0.01$	34.9 vs. 28.0 HR 0.81; $P=0.09$
	MONARCH-2 [24, 27]	Pre-, peri-, or postmenopausal women ($N=669$)	Abemaciclib + fulvestrant	16.4 vs. 9.3 HR 0.55; $P<0.01$	46.7 vs. 37.3 HR 0.76; P = 0.01

in select patients. This is particularly relevant for patients with favorable prognosis such as patients with limited bone-only disease [14]. Subgroup analyses of PFS according to stratification factors and other baseline characteristics in the PALOMA-2 study confirmed a consistent benefit of palbociclib across all subgroups, including patients with bone-only disease (HR 0.36) and patients with visceral disease (HR 0.63) [15]. In an exploratory analysis of the study, statistically significant improvement in mPFS was seen in both patients who had received prior chemotherapy or endocrine therapy in the neoadjuvant/adjuvant setting as well as those who had not [16]. Similarly, in a pooled analysis of phase III studies of CDK4/6 inhibition conducted by the FDA, statistically significant improvement in mPFS was seen across all patient subgroups with the addition of CDK4/6 inhibition, including patients with bone-only disease and patients with lobular histology [17]. In a separate pooled analysis of phase III studies conducted by the FDA evaluating the addition of CDK4/6 inhibition to AI in the first-line setting in patients age 75 years or older, similar efficacy of CDK4/6 inhibition was seen in elderly patients compared to the younger patients [18]. Elderly patients reported a decline in quality of life regardless of treatment arm. As a result of these collective data, ET in combination with CDK4/6 inhibition should be considered in the front-line setting for all patients with HR + ABC.

Another important question which has been explored is whether there is a preferred endocrine therapy backbone in combination with CDK4/6 inhibition, particularly in the first-line setting. Prior to widespread use of CDK4/6 inhibition, the randomized phase III FALCON study reported that in the first-line treatment of HR + ABC patients who were endocrine therapy naive, fulvestrant improved mPFS compared to anastrozole (16.6 vs. 13.8 months; $P = 0.0486$) [19]. The phase II PARSIFAL study evaluated the efficacy of palbociclib with fulvestrant versus palbociclib with letrozole as first-line therapy in 486 patients with endocrine-sensitive, HR + /HER2 − ABC and did not report a statistical difference in mPFS (27.9 months in the fulvestrant arm vs. 32.8 months in the letrozole arm; $P = 0.32$) [20]. Thus, the study indicated that when combined with CDK4/6 inhibition, the endocrine therapy backbone is interchangeable, allowing physicians to select the endocrine therapy best suited for each individual patient. As noted later in this review, however, significant innovation is ongoing in the development of novel endocrine agents, and it is possible that a novel preferred agent will emerge for the front-line setting when combined with CDK4/6 inhibition.

Another frequently discussed question is whether the CDK4/6 inhibitors are interchangeable, or if there is a preferred agent in the front-line setting. Given the similar hazard ratios for mPFS in the front-line setting across phase III trials with each of the three agents (Table 1), it was initially felt the CDK4/6 inhibitors were clinically similar despite their mechanistic and dosing differences. However, given lack of direct comparison of agents in clinical trials, this has not been established. The PALOMA-2 and PALOMA-3 studies did not report a statistically significant improvement in mOS [15, 21]. In contrast, MONALEESA-2 [22], MONALEESA-3 [23], MONALEESA-7 [13], and MONARCH-2 [24] have all reported a statistically significant improvement in mOS. Final OS analysis from MONARCH-3 is awaited. Although this raises the questions that the CDK4/6 inhibitors have varying efficacy, it is important to remember that cross-trial comparisons are limited due to study design differences. For example, prior chemotherapy for metastatic disease was allowed in the PALOMA-3 study [25] but was exclusionary in the MONALEESA-3 [26] and MONARCH-2 [27] studies. Furthermore, OS was a secondary endpoint in the PALOMA-2 and PALOMA-3 studies, making it difficult to draw conclusions as a result. It is also notable that long-term survival data from the PALOMA-2 study was disproportionately missing across treatment arms (13% in the experimental arm compared to 21% in the control arm) [16]. Thus, the question regarding an optimal CDK4/6 inhibitor remains unanswered at this time, and as a result, decisions regarding the preferred CDK4/6 inhibitor in the first-line setting should involve an individualized discussion of these factors as well as potential toxicities of individual agents. The ongoing phase III HARMONIA study (NCT05207709) is evaluating ribociclib versus palbociclib in combination with ET in the first-line setting and will help to further resolve the question of efficacy.

Another important question is whether CDK4/6 inhibition should be continued beyond progression, similar to trastuzumab for the treatment of HER2 + metastatic breast cancer. The randomized, phase II MAINTAIN trial explored the efficacy of fulvestrant or exemestane (with change in therapy in the ET backbone) with or without ribociclib as second-line therapy in 200 patients with HR + /HER2 − ABC who previously progressed on ET plus a CDK4/6 inhibitor [28]. The majority of patients had received prior palbociclib (84%), while 11% had received prior ribociclib. mPFS was significantly longer in patients treated with ribociclib (5.33 vs. 2.76 months; $P = 0.004$). The randomized, phase II PACE study evaluated fulvestrant monotherapy versus fulvestrant and palbociclib versus fulvestrant, palbociclib, and avelumab in 220 patients with HR + /HER2 − ABC who had progressed on prior CDK4/6 inhibition [29]. The majority of patients had received prior palbociclib (90.9%), and the study reported no benefit with the addition of palbociclib to fulvestrant compared to fulvestrant monotherapy (mPFS 4.6 vs. 4.8 months; $P = 0.62$). Thus, it remains unclear if the benefit of ribociclib in the MAINTAIN study was due to improved efficacy of ribociclib compared to palbociclib or if there is a benefit of continuing CDK4/6 inhibition beyond

progression. Several ongoing trials are also evaluating the continuation of CDK4/6 inhibition beyond progression: PALMIRA (NCT03809988), EMBER3 (NCT04975308), and POSTMONARCH (NCT05169567).

The question of CDK4/6 inhibition beyond progression is also important for a group of emerging patients. Recently, the FDA approved adjuvant abemaciclib in combination with ET for adjuvant treatment of HR + /HER2 − , node-positive, early breast cancer with high risk of recurrence based on results of the phase III MonarchE study [30], which demonstrated an improvement in invasive disease-free survival with the addition of two years of adjuvant abemaciclib in high-risk patients. Consequently, a portion of HR + first-line ABC patients in the near future will harbor disease resistant to CDK4/6 inhibition. Optimal therapy for these patients remains unclear at this time.

CDK4/6 inhibitors have revolutionized therapy for patients with HR + ABC, resulting in notable improvements in survival outcomes. Despite this success, the majority of patients with metastatic disease eventually relapse, and ongoing innovation is needed. The remainder of this review details additional targeted approaches for HR + ABC, and discusses the significant innovation ongoing to identify novel therapies for patients.

Agents that Target the PI3K/AKT Pathway

The phosphoinositide-3-kinase–protein kinase B/Akt/mammalian target of rapamycin (PI3K-PKB/AKT/mTOR) pathway is a complicated intracellular pathway which is frequently activated in cancer, resulting in disease progression and resistance to cancer therapy [31, 32]. Alterations in this pathway are common in HR + breast cancer, and activation of this pathway has been implicated as a resistance mechanism to ET [33–35]. *PIK3CA*, which encodes for the alpha catalytic subunit (p110α) of PI3K, is the most commonly mutated gene in HR + breast cancer, with mutations found in up to 40% of patients [36]. As a result, this pathway has been a major point of interest for drug development in HR + breast cancer. However, due to the ubiquitous nature of the PI3K pathway and the significant crosstalk that exists between the pathway and other pathways, toxicity and efficacy have been ongoing issues with agents that target the PI3K pathway.

The mTOR inhibitor everolimus was the first agent targeting the PI3K pathway to attain FDA approval. BOLERO-2 was a randomized, phase III trial which compared everolimus versus placebo in combination with exemestane in 724 postmenopausal patients with HR + ABC who had previously progressed on a non-steroidal AI [37]. Up to 1 prior chemotherapy for ABC was allowed. The majority of patients (54%) had received at least 3 prior lines of therapy. The addition of everolimus resulted in statistically significant improvement in mPFS (10.6 vs. 4.1 months; $P < 0.001$), resulting in FDA approval. Grade 3/4 adverse events were more common in the patients treated with everolimus, with stomatitis (8%) being the most frequent and grade 3 pneumonitis reported in 3%. Interestingly, presence of alteration in the PI3K/AKT pathway did not predict for sensitivity to therapy [38], and it is felt this may be related to downstream pathway inhibition.

Since the approval of everolimus, there have been ongoing efforts to develop more efficacious and less toxic agents that target the PI3K pathway. More recently, α-specific inhibitors of PI3K have been developed to target patients whose tumors harbor *PIK3CA* mutations. The SOLAR-1 trial evaluated the PI3Kα inhibitor alpelisib versus placebo in combination with fulvestrant in 572 men and postmenopausal women with HR + ABC who had previously progressed on an AI [39]. Patients were enrolled in one of two cohorts depending on presence of mutation in *PIK3CA*. In the *PIK3CA*-mutant cohort, statistically significant improvement in mPFS was reported (11.0 vs. 5.7 months; $P < 0.001$), while no statistically meaningful improvement in mPFS was seen in the *PIK3CA*-wild-type cohort. This resulted in the FDA approval of the combination of fulvestrant and alpelisib in the second-line setting for patients whose tumors harbor *PIK3CA* mutation. Only 20 patients enrolled in the SOLAR-1 study had received prior CDK4/6 inhibition, which is not characteristic of the second-line HR + ABC patient today. The ongoing phase II BYLieve trial is exploring the combination of ET therapy and alpelisib in *PIK3CA*-mutated HR + ABC patients who have previously progressed on ET in combination with CDK4/6 inhibition [40]. A total of 127 patients have been treated with fulvestrant and alpelisib after prior progression on an AI and CDK4/6 inhibition. In these patients, mPFS was 7.3 months (95% confidence interval 5.6–8.3), and in the 100 patients with measurable disease at baseline, 21% experienced partial response, indicating that ET in combination with alpelisib retains activity after progression on CDK4/6 inhibition in biomarker-selected patients. Unfortunately, toxicity continues to be a concern with the PI3Kα inhibitors. In the SOLAR-1 study, grade 3/4 events were seen in 76% of patients and included hyperglycemia (36.6%), rash (20.1%), and diarrhea (6.7%) [39]. This resulted in discontinuation of alpelisib in 25% of patients enrolled on study.

Inavolisib is a novel PI3Kα inhibitor which preferentially targets and degrades mutant PI3K, potentially allowing for greater efficacy and reduced toxicity [41]. Clinically, the combination of fulvestrant and inavolisib was tested in an open-label, phase I/II study which enrolled 60 patients with HR + ABC [42]. Patients had received a median of 2 prior lines of therapy for advanced disease and approximately half of patients (47%) had received prior chemotherapy for advanced disease. The majority of patients had received prior CDK4/6 inhibition (97%) and approximately half (47%) had

received prior fulvestrant. In 54 patients with measurable disease, a partial response rate of 26% was reported. Grade 3 or higher hyperglycemia was reported in 22% of patients, but no grade 3 diarrhea or rash events occurred on trial. Additional studies with inavolisib are ongoing at this time including a phase III study comparing the combination of inavolisib plus fulvestrant with alpelisib plus fulvestrant in the second-line setting (INAVO121; NCT05646862).

AKT inhibitors have also been evaluated in combination with ET for the treatment of patients with HR + ABC. Capivasertib, a potent and selective oral inhibitor of all isoforms of AKT, was first evaluated in combination with fulvestrant in the phase II FAKTION study [43]. HR + ABC patients ($N = 140$) who had progressed on prior AI were randomized to receive capivasertib versus placebo in combination with fulvestrant. After enhanced analysis for PI3K pathway alteration including targeted next-general sequencing and digital droplet PCR, mPFS (12.8 vs. 4.6 months; $P = 0.001$) and mOS (39.0 vs. 20.0 months; $P = 0.005$) were significantly improved in patients with PI3K pathway alteration treated with capivasertib [44]. Grade 3 or higher adverse events were reported in 65% of patients treated with capivasertib including diarrhea (14%), rash (20%), and hyperglycemia (4%). The recently reported phase III CAPItello-291 study evaluated capivasertib versus placebo in combination with fulvestrant in pretreated HR + ABC patients [45]. A total of 708 patients were enrolled, and approximately 70% had received prior CDK4/6 inhibition for ABC. The study reported a statistically significant improvement in mPFS in both the overall study population (7.2 vs. 3.6 months; $P < 0.001$) and in the PI3K/AKT pathway altered population (7.3 vs. 3.1 months; $P < 0.001$) with the addition of capivasertib to fulvestrant. Overall survival is immature at this time. Grade 3 or higher adverse events with capivasertib included diarrhea (9.3%), rash (5.4%), maculo-papular rash (6.2%), and hyperglycemia (2.3%).

Collectively, these studies have established a role for targeting the PI3K/AKT pathway in the treatment of HR + ABC. Today, alpelisib and everolimus remain the only FDA-approved agents that target the PI3K/AKT pathway. However, AKT inhibition has a growing role in this space. It is unclear how PI3Kα inhibitors compare to AKT inhibitors in efficacy and toxicity as cross-trial comparisons are limited in nature. Although not a direct comparison, the ongoing phase Ib/II MORPHEUS study (NCT04802759) contains parallel arms, and ET therapy in combination with inavolisib, the AKT inhibitor ipatasertib, and everolimus is being tested in HR + ABC who have previously progressed on ET in combination with CDK4/6 inhibition. One important question which remains is can agents that target the PI3K pathway be sequenced or combined (as tolerated due to adverse events)? Currently, limited data exists to answer this question, but given the varying points of pathway target, it is likely that sequencing therapy will potentially allow for continued therapy targeting the PI3K/AKT pathway, particularly in patients harboring pathway alterations.

Given the impressive clinical activity of CDK4/6 inhibition in the first-line setting, ET in combination with PI3K/AKT targeting agents is generally administered after progression on ET in combination with CDK4/6 inhibition. Additionally, studies have demonstrated that PI3K/AKT alterations can arise in the setting of CDK4/6 resistance, further supporting the role of PI3K targeting on progression. For example, evaluation of paired baseline and on-progression tumor samples from the PALOMA-3 study demonstrated new driver mutations in *PIK3CA* in both the palbociclib and control arms [46]. In light of this finding, however, it is possible that upfront combination of CDK4/6 inhibition and PI3K/AKT pathway inhibition with ET will result in a more durable tumor response, but toxicity of this triplet combination remains a concern. Additionally, in light of the recent phase II MAINTAIN study discussed above [28], continuation of CDK4/6 inhibition beyond progression has become a potential therapeutic strategy. As such, triplet therapy with ET, CDK4/6 inhibition, and PI3K/AKT pathway inhibition is being evaluated. The randomized, phase III INAVO120 study (NCT04191499) is exploring the efficacy and safety of inavolisib versus placebo in combination with palbociclib and fulvestrant in patients with PIK3CA-mutated, HR + /HER2 − ABC progressing on adjuvant endocrine therapy. Similarly, the randomized, phase Ib/III CAPItello-292 study (NCT04862663) is exploring the efficacy and safety of capivasertib versus placebo in combination with palbociclib and fulvestrant in study patients with endocrine-resistant HR + /HER2 − ABC. Prior CDK4/6 inhibition in the adjuvant setting is allowed.

Novel Endocrine Agents

Significant advances have been made in the treatment of HR + ABC. However, despite our advances, it remains an incurable diagnosis, and ongoing innovation is needed. There are currently significant ongoing efforts to develop novel endocrine and targeted agents.

Selective Estrogen Receptor Degraders (SERDs)

SERDs are small non-steroidal molecules that both antagonize ER transcriptional activity and promote its degradation [47]. SERDs that have been studied to overcome AI or tamoxifen resistance, particularly in the setting of *ESR1* mutation. Fulvestrant is currently the only FDA-approved SERD, but it is administered intramuscularly, increasing the burden of care on patients. Furthermore, given the

intramuscular administration, the bioavailability of fulvestrant is limited [48]. Several orally bioavailable SERDs are in varying stages of clinical development and initial clinical trial results are emerging.

The randomized phase III EMERALD trial evaluated the oral SERD elacestrant versus standard endocrine monotherapy (fulvestrant or AI) in 477 patients with HR + / HER2 – ABC who had previously progressed on 1–2 lines of ET including a CDK4/6 inhibitor [49]. One prior line of chemotherapy for advanced disease was permitted. mPFS was prolonged in all patients (HR 0.70; $P = 0.002$) and in the 228 patients with *ESR1* mutation (HR 0.55; $P = 0.005$). Six-month PFS rates were 34.3% versus 20.4% for the elacestrant versus standard therapy arms in all patients and 40.8% versus 19.1% in patients with *ESR1* mutation. mOS showed a trend favoring elacestrant in all patients and in *ESR1*-mutated patients but is not mature at this time. Grade 3 nausea was reported in 2.5% of patients treated with elacestrant. On the basis of the EMERALD study, elacestrant is now the first oral SERD which is FDA-approved for the treatment of patients with *ESR1*-mutated HR+ ABC who have received at least 1 prior line of endocrine therapy in the advanced setting.

Camizestrant is a next-generation oral SERD and pure ER antagonist. It was compared to fulvestrant in 240 patients with pretreated HR + ABC in the randomized, phase II SERENA-2 study [50]. The majority of patients were enrolled in the second-line setting, approximately half had received prior CDK4/6 inhibition, and approximately one third had *ESR1* mutation. At a dose of 150 mg daily, camizestrant resulted in statistically significant improvement in mPFS in the overall population (7.7 vs. 3.7 months; $P = 0.0161$) and in the *ESR1* mutant population (9.2 vs. 2.2 months; HR 0.55 [95% CI: 0.33–0.89]) compared to fulvestrant. The most common adverse events were photopsia, sinus bradycardia, fatigue, anemia, asthenia, and arthralgia, but were primarily grades 1–2.

Several other oral SERDs (amenacestrant, giredestrant) have also been tested in the endocrine-resistant setting with negative trial results announced, though final data have not been presented [51]. Given the greater magnitude of benefit seen in the *ESR1*-mutant population in the EMERALD and SERENA-2 studies, these agents may be most beneficial in a biomarker-selected population in the endocrine-resistant setting. However, multiple ongoing trials are testing these as well as other novel SERDs (imlunestrant, rintodestrant) in the neoadjuvant/adjuvant setting as well as metastatic setting (endocrine-resistant and endocrine-sensitive disease) as monotherapy and in combination with CDK4/6 inhibition. Combinations with agents that target the PI3K/AKT pathway are also being evaluated. As data with novel endocrine agents including oral SERDs emerges, combination data will be very important in the first- and second-line setting given the established role of CDK4/6 inhibitors and the emerging role of PI3K inhibitors in these settings.

Additional Endocrine Agents in Development

In addition to oral SERDS, several additional classes of novel endocrine agents with distinct mechanisms or action are in development. For example, selective estrogen receptor modulators (SERMs), such as tamoxifen, directly target ERα and compete with estrogen for ER binding and have mixed agonist and antagonist properties [52]. Lasofoxifene is a second-generation SERM that has shown potent preclinical anti-tumor activity in *ESR1* mutant models [53, 54]. In the randomized, phase II ELAINE 1 study, 103 *ESR1*-mutated patients with HR + ABC previously treated with AI plus CDK4/6 inhibition were randomized to receive lasofoxifene versus fulvestrant [55]. The study did not report an improvement in mPFS with lasofoxifene (6.04 vs. 4.04 months; $P = 0.138$), but did report an improvement in ORR (13.2 vs. 2.9%). A randomized, phase III study evaluating lasofoxifene in combination with abemaciclib is planned.

Proteolysis-targeting chimeras (PROTACs) are pure ER antagonists that can be categorized as a new class of SERDs; they are heterobifunctional molecules consisting of a ligand for ER and another ligand that serves as the E3 ubiquitin ligase complex substrate that ultimately leads to polyubiquitylation of ER resulting in proteasomal degradation [56]. The first orally bioavailable PROTAC ARV-471 is currently being evaluated clinically [57]. The phase I/II VERITAC study evaluated the orally bioavailable PROTAC ARV-471 as monotherapy and combination with CDK4/6 inhibition [58]. In 71 pretreated patients (100% prior CDK4/6 inhibition) with HR + ABC, the monotherapy with ARV-471 resulted in a clinical benefit rate of 38.0% overall and 51.2% in 41 patients with *ESR1* mutation. Median PFS was 3.7 months in the overall population and 5.7 months in the *ESR1*-mutated population. The most common adverse events were fatigue, nausea, and AST increase, but grade 3 adverse events were rare. A randomized, phase III trial of ARV-471 versus fulvestrant is planned in the second-line setting (NCT05654623).

H3B-6545 is the first in the selective estrogen receptor covalent antagonist (SERCA) class and targets both wild-type and mutant ER proteins and enforces a unique antagonist conformation [59]. In a phase I/II trial (NCT03250676), 94 heavily pretreated (median 3 prior lines of therapy for ABC) patients with HR + ABC were enrolled, including 58 (62%) patients with *ESR1* mutations [60]. H3B-645 resulted in ORR 17% and mPFS 5.1 months. Results revealed greater anti-tumor activity in patients with the *ESR1* Y537S clonal mutations ($N = 10$) with ORR 30% and mPFS 7.3 months. Clinical results of H3B-6545 in combination with palbociclib (NCT04288089) are anticipated.

Complete estrogen receptor antagonists (CERANs) inactivate ER by inhibiting the 2 activation functions of ER transcription known as AF-1 and AF-2 [61]. OP-1250 an oral CERAN/SERD that is unique because it is also a strong degrader of ER. In preclinical models, the agent has shown activity in the treatment of brain metastases [62]. An ongoing phase I/II study (NCT04505826) evaluated OP-1250 monotherapy in 68 heavily pretreated patients with HR + ABC (32% prior chemotherapy, 96% prior CDK4/6 inhibition, 59% *ESR1*-mutated) [63]. Among 57 patients with efficacy-evaluable disease, 6 partial responses were reported. The most common adverse events were nausea, fatigue, and vomiting, and grade 3 adverse events were rare. Evaluation in combination with palbociclib is ongoing, and a phase III monotherapy study in the second/third-line setting is planned.

Selective androgen receptor modulators (SARMs) are a novel class of ET that exhibit both agonist and antagonist activity against androgen receptor (AR). Enobosarm is the first in its class that targets the AR receptor and inhibits growth of AR + HR + breast cancer cells. A phase II trial evaluated enobosarm in 36 postmenopausal women with AR + HR + ABC patients were randomly assigned to enobosarm monotherapy at two dose levels [64]. In patients with ≥ 40% AR expression, ORR of 48% and median radiographic PFS of 5.47 months was reported. The ongoing phase III ARTEST trial (NCT04869943) is comparing enobosarm versus standard endocrine therapy (exemestane or SERM) in patients with AR + (≥ 40%), HR + ABC resistant to prior CDK4/6 inhibition. Collectively, these ongoing trials of novel endocrine agents and combinations are likely to significantly impact the treatment paradigm of HR + advanced breast cancer.

Novel-targeted Agents

In addition to endocrine agents, significant effort is also ongoing in the development of novel-targeted therapies. Many groups have attempted to better understand resistance mechanisms to CDK4/6 inhibition to develop novel therapeutic strategies. Preclinically, the loss of RB and cyclin E have been associated with resistance to CDK4/6 inhibition [65]. In preclinical models with palbociclib-resistant HR + breast cancer cell lines, combined inhibition of CDK2/cyclin E and CDK4/6-reduced cell proliferation and overcame cycle E-associated resistance to CDK4/6 inhibitor independent of the RB status which is promising for the future of CDK2-specific kinase inhibitors.

Non-endocrine therapeutic strategies have also been developed for the treatment of HR + ABC. Poly (ADP-ribose) polymerase (PARP) inhibition has been evaluated in patients with germline mutations in *BRCA1/2*, which results in defective DNA damage response. Currently, two PARP inhibitors (olaparib [66] and talazoparib [67]) are FDA-approved for patients with germline *BRCA1/2*-mutated ABC on the basis of phase III studies which demonstrated improvement in mPFS compared to standard chemotherapy in endocrine-resistant disease. Additional agents targeting the DNA damage response pathway are in development and studies are underway to expand the activity of these agents beyond germline *BRCA1/2* mutation to other alterations of the DNA damage response pathway.

Antibody–drug conjugates (ADCs) combine monoclonal antibodies specific to cell surface antigens present on tumor cells with highly potent anti-cancer agents linked via a chemical linker. Currently, two ADCs have demonstrated clinical activity in endocrine-resistant HR + ABC with improvement demonstrated in mPFS and mOS compared to standard chemotherapy. These include trastuzumab deruxtecan evaluated in the DESTINY-Breast04 study [68] and sacituzumab govitecan evaluated in the TROPiCS-02 study [69, 70]. Many additional ADCs are in development.

Conclusions

Significant advances have been made in the treatment of HR + ABC. The addition of CDK4/6 inhibitors to ET has significantly impacted survival outcomes. Upon progression on endocrine therapy and CDK4/6 inhibition, change in endocrine therapy backbone and continued CDK4/6 inhibition versus addition of agents that target the PI3K/AKT pathway can be considered. Alternatively, the oral SERD elacestrant is an option in patients with *ESR1*-mutated disease. Significant innovation is ongoing to identify novel endocrine strategies as well as targeted therapies. With the growing number of endocrine therapy options available to patients, particularly after progression on CDK4/6 inhibition, an improved understanding of the safety and efficacy of combining and sequencing therapies is needed. Continued efforts in biomarker development are urgently needed to better understand response and resistance to various therapies.

Declarations

Conflict of Interest Sharvina Ziyeh and Lauren Wong declare no conflict of interest. Reva Basho is an employee of the Ellison Institute for Transformative Medicine (EITM), a public good for-profit (the Institute comprises both a for-profit entity, whose profits will be reinvested into future public health and disease research, as well as a not-for-profit research foundation), which draws collaborators from across conventional health fields, as well as from a broad range of other disciplines, to study disease and potential ways to prevent, detect, and treat the disease. RB has received consulting fees from AstraZeneca, Pfizer, Seattle Genetics, and Gilead. She has received payments for speaking engagements from Eli Lilly, MJH Healthcare, and WebMD.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by Sharvina Ziyeh and Lauren Wong.

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