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REVIEW

Novel Estrogen Receptor – Targeted Therapies in Hormone-Receptor Positive Breast Cancer

Nina E. Neill[1] · Lauren A. Mauro[1] · Angela Pennisi[1]

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Opinion Statement

Endocrine therapy is the backbone of treatment for HR + /HER2- MBC. The introduction of novel endocrine-based therapies has changed the landscape of metastatic breast cancer care, with even more promising agents on the horizon. Given the consistent success in prolonging PFS and OS, CDK4/6 inhibitors should be used as first-line treatment. Once secondary resistance eventually develops after use of a CDK4/6 inhibitor, use of monotherapy with either AI or fulvestrant has shown poor outcome. For example, in the control group of the EMERALD trial, in which all the patients were required to have previously received a CDK4/6 inhibitor, median progression-free survival with endocrine therapy was only 1.9 months. Based on the emerging evidence, molecular profiling of tissue or liquid biopsy at progression of disease is crucial to select future therapy. For patients whose tumors harbor ESR1 mutations, oral SERDs are the preferred option. For those with PIK3CA or AKT1 mutation or PTEN inactivation, combination therapy with the AKT pathway inhibitor capivasertib is recommended. Alpelisib, the first AKT1 inhibitor approved in combination therapy with fulvestrant in PIK3CA mutated tumors only, is now less in favor given its challenging side effect profile. When mutations are not present, options include combination therapy with the mTOR inhibitor everolimus or changing endocrine therapy and continuing a CDK 4/6 inhibitor. In patients with short response to CDK4/6 inhibitors suggesting endocrine resistant disease, chemotherapy or antibody–drug conjugates should be considered. With better understanding of the mechanisms of resistance to CDK4/6 inhibitors, additional mutations could be identified and potentially targeted in order to provide individualized treatment options. Optimal sequencing of treatment options depends on several factors: (1) the presence of specific molecular aberrations; (2) previous treatment history, duration of response and patient's performance status; (3) balance between maximizing survival benefits with quality of life/toxicities; (4) disease burden. In the upcoming years, we anticipate FDA approvals for more of the SERD molecules both in monotherapy and in combination therapy which will continue to expand the options available for HR + /HER2- MBC patients.

Keywords Breast Cancer · Endocrine Therapy

Introduction

Breast cancer represents the most common cancer in the United States, the National Cancer Institute estimates more than 310,000 new cases will be diagnosed in 2024 [1]. Of these cases, nearly 70% are hormone receptor (HR) positive, defined as the expression of estrogen or progesterone (ER and PR, respectively) as measured by immunohistochemistry [2]. The estrogen receptor has served as a long-standing therapeutic target, classically by selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). However, in recent years, novel estrogen receptor targeting agents have demonstrated increased efficacy, particularly among certain SERM resistant tissue subtypes. Further, agents targeting mutations in the phosphatidylinositol 3-kinase pathway, common in ER + breast cancer, and cyclin dependent kinase 4 and 6 (CDK 4/6) inhibitors have emerged in the treatment landscape, both as monotherapies and in conjunction with ER targeted agents. Through outlining the mechanisms, clinical efficacy, and emerging challenges of these approaches, this article aims to delve into the evolving treatment paradigms for ER + breast cancer.

✉ Nina E. Neill
ninaeneill@gmail.com

[1] Inova Schar Cancer Institute, Fairfax, Virginia, USA

ER Targeted Therapies

Overview

Upon binding by the estrogen hormone, activated ER dimerizes and undergoes intranuclear translocation. The DNA-binding domains of activated ER binds to estrogen-responsive elements and mediates gene transcription. ER has a role in both healthy and neoplastic cell proliferation and growth, and has served as a long-standing therapeutic target in breast cancer with demonstrated receptor expression. PR expression is typically regulated by estrogen signaling, meaning that PR positivity often indicates a functioning estrogen pathway. Conversely, ER positive PR negative tumors may signify a less differentiated phenotype. A backbone of anti-estrogen therapy, fundamental in the treatment of both early and advanced hormone receptor expressing breast cancer, includes SERMs, AIs, and selective estrogen receptor degraders (SERDS).

AIs such as anastrozole, letrozole, and exemestane, are primarily utilized in post-menopausal or ovarian-suppressed pre-menopausal women and indirectly inhibit ER by blocking peripheral conversion of androgens to estrogen. The use of SERMs is well established, and includes tamoxifen which selectively and antagonistically binds to ER in breast tissue, resulting in competitive inhibition of estrogen binding, prevention of transcription, and delayed cell cycling. Of note, tamoxifen has both estrogen agonistic and antagonistic effects, and has been demonstrated to stimulate ER in bone and endometrium. A limitation of AI and SERMs include the development of intrinsic and acquired resistance mechanisms. Mutations in ESR1, the ligand-binding domain of ER, is a common mechanism of both forms of resistance. Other etiologies include upregulation in the HER2, EGFR and FGFR membrane receptors and activating alterations in PI3K-AKT-mTOR, RAS-MAPK, CDK4/6-RB-EsF pathways.

In recent years, SERDs, a third and mechanistically unique drug class, has emerged. These drugs bind to ER and induce destabilization and proteosome-mediated degradation of the complex. Unlike tamoxifen, SERDs are pure antagonists [3]. The remainder of this section will focus on novel developments in these agents.

Fulvestrant

Fulvestrant (Faslodex ®), as first described in 1991, is the first FDA approved SERD [4]. It is delivered intramuscularly, and like other SERDs, functions as a global ER antagonist with demonstrated efficacy in SERM resistant tumors in preclinical studies [5]. Fulvestrant first received FDA approval for the treatment of ER + advanced or metastatic breast cancer (MBC) that had progressed on tamoxifen [6, 7]. In 2017, fulvestrant obtained FDA approval as monotherapy in previously untreated HR + /HER2- breast cancer. It then received approval in combination with the oral CDK4/6 inhibitor ribociclib as initial therapy, and palbociclib and abemaciclib in ER + /HER2- MBC progressed on endocrine therapy (ET). Most recently, it received FDA approval for use in combination with alpelisib and capivasertib in patients with HR + /HER2- MBC with PIK3CA/AKT1/ PTEN alteration and progression on ET.

The first pivotal trial, FALCON, was a randomized, double-blind study comparing fulvestrant vs anastrozole in post-menopausal women with ER + /HER2- MBC who had not previously received treatment with endocrine therapy [8]. Fulvestrant demonstrated improved median PFS of 16.6 vs 13.8 months, as compared to the anastrozole group. The final overall survival analysis was presented at European Society for Medical Oncology Congress 2023, revealing no significant difference between fulvestrant and anastrozole, with a mean OS of 44.8 and 42.7 months, respectively. Subgroup analysis did reveal improved OS in patients with non-visceral disease treated with fulvestrant (65.2 vs 47.8 months respectively, HR: 0.85), although this was not statistically significant [9]. As is further outlined below, a number of recent Phase III trials of fulvestrant in combination with CDK4/6 inhibitors have demonstrated improved PFS and OS [10–13]. While fulvestrant represents a discrete advancement in the field of ER directed therapies, it has some limitations, including its requisite route of administration. Attempts at the development of oral forms of fulvestrant have been unsuccessful, however other oral SERDs have since been discovered.

Elacestrant

Elacestrant (Orserdu®), is an oral SERD currently approved for the treatment of postmenopausal women and adult men with HR + / HER2-, ESR1 mutated MBC, with progression on endocrine therapy. It is a potent binder of ER-alpha, and in preclinical studies, demonstrated in vitro activity compared to tamoxifen and fulvestrant in cells expressing ESR1 mutation [14]. It received initial FDA approval on the basis of the phase-3 Emerald trial, which studied 478 postmenopausal women and men with HR + /HER2- MBC who had previously progressed on 1–2 lines of endocrine therapy, at least one of which was administered in combination with a CDK4/6 inhibitor. Patients were randomized to elacestrant vs ET of the investigators' choice. ESR1 mutated patients treated with elacestrant had significantly improved PFS of 3.8 vs 1.9 months. The PFS was not statistically significant between the two groups in the ESR1 wildtype subgroup.

Post hoc analysis presented at the San Antonio Breast Cancer Symposium 2022, further revealed prolonged PFS of 8.6 months in patients with ESR1 mutation who were treated for 12 or months previously with CDK4/6 inhibitor + ET [15, 16]. There are a number of actively recruiting and ongoing trials investigating elacestrant in the neoadjuvant setting (NCT04797728) and in combination with CDK4/6 inhibitors (NCT05386108, NCT06062498).

Emerging Therapies

The use of oral SERDs in the adjuvant and early-stage breast cancer setting is an ongoing area of active investigation. Further, a number of other novel oral SERDs, to include imlunestrant, giradestrant, rintodestrant, and camizestrant are in various stages of investigation, both as monotherapies and in combination approaches. One such novel agent, imlunestrant, was initially studied in the phase 1a/1b EMBER trial as monotherapy and in combination with oral targeted therapy in patients with MBC and selective non-breast cancers. This trial has finished enrolling patients and initial reports have shown good tolerability and efficacy [17], with full results still to come. Imlunestrant is currently undergoing evaluation in the adjuvant setting in the ongoing Phase 3 EMBER-4 trial (NCT04975308). EMBER-3, a phase 3 trial investigating imlunestrant in combination with the CDK 4/6 inhibitor abemaciclib, vs standard ET is currently enrolling (NCT04975308). Patients must have completed 2–5 years of ET, and have a higher-than-average risk of recurrence based on clinical-pathological features.

Giradestrant is currently being studied in the adjuvant setting in the Phase III lidERA Phase trial (NCT04961996) and as combination therapy with both palbociclib and everolimus in the Phase III persevERA and evERA trials (NCT04546009, NCT05306340 respectively). Phase IB and preclinical trials have indicated tolerability and activity as monotherapy and in combination with palbociclib [18]. The Phase II aceIERA BC trial investigated giradestrant vs ET in advanced breast cancer. It did not reveal a statistically significant change in investigator-assessed PFS (HR 0.81, CI 0.6- 1.10), this translated into the ESR1 mutated subgroup [19].

Camizestrant was compared to fulvestrant in previously treated, advanced ER + breast cancer in the Phase II SERENA-2 Trial. Patients treated with camizestrant had significantly improved PFS of 7.2 and 7.7 months, as compared to those treated with fulvestrant, who demonstrated a mean PFS of 3.7 months. Common adverse effects include visual disturbances, bradycardia, nausea, vomiting, fatigue, asthenia [20]. Camizestrant is being investigated in advanced breast cancer in combination with a CDK4/6 inhibitor in SERENA-4 and SERENA-6 (NCT04964934, NCT04711252). The CAMBRIA-2 trial is a Phase III study investigating camizestrant in the adjuvant setting (NCT05952557). Finally, rintodestrant has demonstrated activity and tolerability in ER + , Her2- MBC in a recent Phase I trial [21].

Most recently to emerge are three new promising classes of drugs: complete estrogen receptor antagonists (CERANs), proteolysis targeting chimeric molecules (PROTACs), and selective estrogen receptor covalent antagonists (SERCAs). CERANs provide full inhibition of estrogen receptor signaling without partial agonist effects, aiming to overcome resistance mechanisms seen in other endocrine therapies. PROTACs recruit and utilize the ubiquitin ligase complex, a component of cellular degradation machinery, to selectively target and degrade estrogen receptors, offering a novel approach that may improve efficacy and limit adverse effects. SERCAs covalently bind and induce ER conformational change leading to irreversible deactivation, presenting a mechanism that could effectively manage tumors that have developed resistance to other therapies. These agents show potential in preclinical and early clinical studies, aiming to address limitations of current treatments and improve outcomes for patients with estrogen receptor-positive advanced breast cancer. Drugs in these classes are under various stages of investigation in the clinical pipeline.

CDK 4/6 Inhibitors

CDK 4/6 inhibitors have transformed and improved the treatment of both advanced and early-stage breast cancer since the first agent received FDA approval in 2015. Unregulated cell division is one of the main factors that leads to cancer growth, thus blocking this process is a major goal of anticancer therapies [22]. Cells must pass through a series of checkpoints in the cell cycle in order to divide and transitions through these checkpoints are regulated by cyclin-dependent kinases. CDK 4 and 6 are involved in the G1 to S cell cycle checkpoint. As D-type cyclins are increasingly expressed during G1, they bind and activate CDK 4/6. This complex phosphorylates retinoblastoma-associated protein ultimately leading to the transition of the cell to the S phase and thus to DNA replication [23, 24]. HR + breast cancer cells have a particularly high expression of cyclin D1 and are therefore uniquely sensitive to the use of CDK 4/6 inhibitors which stop this process [24].

Three CDK 4/6 inhibitors, all oral, have been FDA approved in the United States for the treatment of MBC: palbociclib, ribociclib, and abemaciclib. Although all were designed to be predominantly selective inhibitors of CDK 4 and 6, palbociclib inhibits both CDK 4 and CDK 6 to similar levels whereas abemaciclib and ribociclib inhibit CDK 4 to a higher degree than CDK 6 [22]. Although all three agents

may cause cytopenias, palbociclib and ribociclib cause these more frequently (necessitating a 3 week on, 1 week off approach for both agents while abemaciclib can be given continuously). Gastrointestinal side effects are moderately common with ribociclib and most common with abemaciclib with a rate of diarrhea of any grade > 80% (although typically controllable with anti-diarrheal agents). Ribociclib was found to have slightly higher rates of elevation in AST and ALT as well as QT prolongation, necessitating monitoring at initiation of treatment. All have been found to have a small risk of pneumonitis and venous thromboembolism [22, 23, 25].

The three CDK 4/6 inhibitors have all been studied in HR + /HER2- patients with MBC in phase 3 randomized trials in combination with AIs as well as in phase 3 randomized trials in combination with fulvestrant. These trials are summarized in Table 1 along with their mPFS and mOS results. The PALOMA-2, MONALEESA-2, and MONARCH-3 trials were all first-line trials that enrolled only postmenopausal women with previously untreated MBC. Patients were allowed to have had adjuvant endocrine therapy in the past but it must have completed > 12 months prior to recurrence thus selecting for patients who are still considered to have endocrine sensitive disease. All three trials showed dramatic improvements in mPFS and MONARCH-3 showed a strong trend towards improvement in mOS, however the MONALEESA-2 trial was the only one to reach statistical significance with improvement in mOS [26–32]. Ribociclib was also studied in solely pre/perimenopausal women in the MONALEESA-7 trial where ribociclib or placebo was combined with endocrine therapy (ovarian suppression plus tamoxifen or AI). Differing from the trials above, patients must not have received prior endocrine therapy in the metastatic setting, but could have had one previous line of chemotherapy in the metastatic setting and could have completed adjuvant endocrine therapy at any time prior to their recurrence. This trial also demonstrated improvement in mPFS and mOS proving that the benefits of CDK 4/6 inhibitors translated to premenopausal women when ovarian suppression was used [33, 34]. All three agents are now approved in combination with AIs in the metastatic setting, however ribociclib and abemaciclib are now more commonly used given their superior results and benefit even in patients with more advanced visceral disease.

The PALOMA-3, MONALEESA-3 and MONARCH-2 trials all utilized fulvestrant as the endocrine therapy backbone, however there were some notable differences. PALOMA-3 and MONARCH-2 enrolled women of any menopausal status (requiring those who were pre/perimenopausal to be on ovarian suppression) and required patients to either have progressed on an endocrine therapy in the metastatic setting or recur within 12 months of adjuvant endocrine therapy. The MONALEESA-3 enrolled only postmenopausal women and allowed a broader group of patients including those with de-novo metastatic disease, patients who had progressed on prior endocrine therapy for metastatic disease, and those who had just relapsed with a history of adjuvant endocrine therapy regardless of date of completion. All showed improvement in mPFS [10–12, 35, 37–39]. The addition of CDK 4/6 inhibitors to fulvestrant is now considered standard of care for patients who have progressed on monotherapy with AIs (either in the metastatic setting or while on adjuvant setting). While CDK4/6 inhibitors are undoubtedly an important component of the treatment paradigm, the sequencing of their use is still under evaluation. The investigator initiated phase III SONIA trial compared the efficacy, safety and financial toxicity of CDK4/6 inhibitors used in either the first or second line setting. Patients were randomized to one of two arms: AI + CDK4/6 inhibitor followed by Fulvestrant on progression vs Fulvestrant followed by AI + CDK4/6 inhibitor on progression. At a median follow up of 37.3 months, it was determined that there was no statistically significant difference in PFS on 2nd line treatment (31.0 versus 26.8 months, respectively. HR 0.87; 95% CI 0.74 to 1.03) and OS when CDK4/6 inhibitors were deferred to 2nd line use. There was,

Table 1 Prominent studied of CDK 4/6 inhibitors in metastatic HR + /HER2- metastatic breast cancer

Trial	Arms	mPFS (intervention arm vs placebo)	mOS (intervention arm vs placebo)
PALOMA-2 ($n = 666$) [26, 28]	letrozole + palbociclib vs letrozole + placebo	27.6 vs 14.5 months (HR 0.56; 95% CI 0.46–0.69; $p < 0.0001$)	53.9 vs 51.2 months (HR 0.96; 95% CI 0.78–1.18; $p = 0.34$)
PALOMA-3 ($n = 521$) [10, 35]	fulvestrant + palbociclib vs fulvestrant + placebo	9.5 vs 4.6 months (HR 0.46; 95% CI 0.36–0.59; $p < 0.0001$)	34.8 vs 28 months (HR 0.81; 95% CI 0.65–0.99; $p = 0.09$)
MONALEESA-2 ($n = 668$) [30, 36]	Letrozole + ribociclib vs letrozole + placebo	25.3 vs 16.0 months (HR 0.57, 95% CI 0.46–0.70; $p < 0.0001$)	63.9 vs 51.4 months (HR 0.76; 95% CI 0.63–0.93; $p = 0.008$)
MONALEESA-3 ($n = 672$) [11]	Fulvestrant + ribociclib vs fulvestrant + placebo	20.5 vs 12.8 months (HR 0.59, 95% CI 0.48–0.73; $p < 0.001$)	53.7 vs 41.5 months (HR 0.73; 95% CI 0.59–0.90;

however, increased time on CDK4/6 inhibitors when used first line (24.64 vs 8.08 months), correlated with increased treatment-related and financial toxicities [36]. Deferring CDK4/6 inhibitor use until second line may be an appropriate strategy for patients of poorer functional status, for whom the diarrhea, fatigue, and cytopenias that are frequently associated with CDK4/6 inhibitors may be prohibitive. However, with the option to use PIK3CA inhibitors or everolimus in the second line combined with faslodex, depending on mutational status, and the overall short progression free survival on single agent faslodex, it is still recommended in fit patients to use CDK 4/6 inhibitor upfront.

Three clinical trials evaluated continuing CDK inhibition while changing endocrine therapy backbones after disease progression: MAINTAIN, PACE, and PostMONARCH. In all of them the most common CDK4/6 inhibitor used in the first-line setting prior to disease progression was palbociclib. The postMONARCH study showed a 1.7-month improvement of PFS for patients receiving abemaciclib and fulvestrant compared to fulvestrant alone. MAINTAIN achieved a 2.5-month improvement in PFS for patients receiving endocrine therapy plus ribobiclib as compared to endocrine therapy alone. The PACE trial showed no significant improvements for patients continuing palbociclib while changing from AI to fulvestrant as compared to fulvestrant alone. The above results suggest that it may be reasonable to continue CDK4/6 inhibition with an alternative CDK 4/6 inhibitor at time of progression, particularly in patients treated with palbociclib in the first-line setting and with no actionable mutations; however, additional data are needed to confirm this as a treatment strategy [40, 41].

These agents have more recently been studied in the adjuvant setting for HR + /HER2- breast cancer. In the phase 3 PALLAS trial, 5796 patients with stage IIA-IIIB disease were randomized to receive 2 years of palbociclib or placebo in combination with their endocrine therapy. This was ultimately a negative trial that demonstrated no statistically significant difference in iDFS at 4 years [36]. The phase 3 MonarchE trial that randomized 5601 patients with high risk early breast cancer to receive 2 years of abemaciclib or not in combination with their endocrine therapy was a positive trial and has changed the standard of care for these patients. High risk in this trial was defined as patients with 4 or more positive nodes OR 1–3 positive nodes with either a tumor size 5 cm or more, grade 3 disease, or Ki67 20% or higher. At the 4 year analysis, the iDFS was 6.4% higher in the treatment group [32, 42]. Initial results of the NATALEE phase 3 trial in which 5101 stage IIA-IIIB patients received an AI with or without 3 years of ribociclib showed an improvement in 3 year iDFS from 87.1% to 90.4% (HR 0.75) [43]. On the basis of this trial, ribociclib received FDA approval in September 2024 for the adjuvant treatment of stage II and III ER + breast cancer with high risk features.

PI3K/AKT/mTOR Pathway Inhibitors

Overview

The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of the rapamycin (mTOR) pathway is involved in various crucial cellular functions such as growth, proliferation, metabolism and survival [44]. In HR + breast cancer, PI3K pathway activation promotes acquired resistance to long-term endocrine deprivation [45, 46]. Actionable biomarkers within the pathway can be identified in up to 50% of patients with HR + MBC (30–40% activating *PIK3CA* mutations and 5–10% activating *AKT1* mutations and inactivating *PTEN* alterations) [47–49]. Preclinical and clinical data support the efficacy of combination therapies targeting ER and PI3K/Akt pathway to overcome acquired endocrine resistance [45, 46].

mTOR Inhibitors

Everolimus, an oral mTOR inhibitor, is the first targeted agent approved in combination with exemestane for the treatment of HR + /HER2 − MBC patients based on the findings of the BOLERO-2 trial. In this study, the addition of everolimus to exemestane in patients who progressed on a nonsteroidal AI improved PFS to 7.8 months versus 3.2 months compared to exemestane alone [50]. The most commonly reported AEs in the EVE + EXE arm included stomatitis, rash, fatigue, diarrhea, nausea, decreased appetite, weight loss, and cough, versus nausea and fatigue in the PBO + EXE arm. The most common grade 3/4 AEs with EVE + EXE included stomatitis, fatigue, dyspnea, anemia, hyperglycemia, and gamma-glutamyltransferase increase. Rates of AEs leading to discontinuation were higher in the everolimus arm (21.4%) versus the placebo arm (3.4%). The two most common AEs leading to treatment discontinuation in the everolimus arm were pneumonitis (5.6%) and stomatitis (2.7%). Prophylactic use of dexamethasone oral solution substantially reduced the incidence and severity of stomatitis in patients receiving everolimus (2% with steroid mouthwash vs. 33% without steroid mouthwash) [51]. The synergistic activity of everolimus with endocrine therapy (tamoxifen and fulvestrant) is also supported by other studies [52, 53]. Overall, the toxicity profile of everolimus has limited its use in the clinic.

Phosphoinositide 3-Kinase Inhibitors

As with mTOR, there has been significant interest and major research investment in targeting upstream signaling via inhibition of phosphoinositide 3-kinase (PI3K). Aberrantly activated PI3K initiates downstream signaling to activate AKT and mTOR, causing cancer cell growth and proliferation.

Among the three classes of PI3Ks (I-III), class I PI3Ks are often abnormally activated in breast cancer [53–56]. Class IA PI3Ks form a heterodimer consisting of a regulatory subunit (p85) and a catalytic subunit (p110). The catalytic p110α, p110β, and p110δ subunits are encoded by *PIK3CA*, *PIK3CB*, and *PIK3CD*, respectively [57]. *PIK3CA* mutation is the most common alteration of this pathway linked to breast cancer, with ≥ 80% of mutations occurring within the helical (E542K and E545K) and kinase (H1047R) domains of p110α [54, 58, 59].

Pan-class I PI3K inhibitors including, buparlisib and pictilisib, were ineffective and their use resulted in severe toxicity suggesting that the use of more selective PI3K inhibitors, such as α-specific PI3K inhibitor, is warranted to further improve safety and benefit. Alpelisib is the first selective PI3Kα inhibitor that showed activity against tumors with *PIK3CA* mutations as a single agent. The phase 3 SOLAR-1 trial evaluated fulvestrant plus alpelisib versus placebo in patients with HR-positive/HER2-negative advanced breast cancer that progressed on AI treatment. The median PFS of patients with a *PIK3CA* mutation was significantly better in the alpelisib plus fulvestrant arm compared with the placebo plus fulvestrant arm (11 vs. 5.7 months) [59]. ORR was also higher in the alpelisib arm than in the control arm (26.6% vs. 12.8%). The OS result in the *PIK3CA*-mutant cohort did not meet the prespecified criteria for statistical significance, although the absolute difference was 8 months. The most common AEs associated with alpelisib (considered on-target effects of p110α inhibition) were hyperglycemia, diarrhea, and rash. In SOLAR-1, patients with HbA1c 6.5%–7.9% were initially allowed to enter the trial, but the study protocol was eventually amended to only include patients with HbA1c ≤ 6.5% and FPG ≤ 140 mg/dL. This was because patients with an HbA1c of 6.5%–8.0% were found to have an increased risk of developing grade ≥ 3 hyperglycemia. Overall, patients with HbA1c ≥ 6.5% at baseline should not initiate alpelisib until good glycemic control is achieved. However, patients with well-controlled type II diabetes (on medication) with HbA1c ≤ 7% at baseline may initiate alpelisib. Fasting plasma glucose should be assessed weekly for at least 2 weeks and every 4 weeks thereafter, in addition to periodic hemoglobin A1c monitoring. Early interventions, such as metformin and diet regulation, can help patients to continue alpelisib. Prophylactic antihistamines are recommended to reduce the frequency and severity of skin rash. Based on the results of the SOLAR-1 trial, the FDA approved the combination of alpelisib plus fulvestrant for patients with HR-positive/HER2-negative *PIK3CA*-mutated advanced breast cancer and MBC in 2019.

Only 20 (6%) patients enrolled in the SOLAR 1 trial were previously exposed to a CDK4/6 inhibitor. Although in this small subset of patients the median PFS was 5.5 months (vs 1.8 months in the control) with 44.4% of patients free of disease progression at 6 months, the study did not provide strong evidence of whether alpelisib is effective and safe after progression on prior CDK4/6 inhibitors.

The phase 2 BYLieve trial was designed as a single-arm study to address this question. In cohort A, patients with HR -positive, HER2- negative advanced breast cancer and a PIK3CA mutation who had progressed after a CDK4/6 inhibitor plus an AI, received alpelisib plus fulvestrant. The primary endpoint, 6-month progression-free survival, was met, with more than 50% (50.4%) of the 121 patients alive without disease progression at 6 months and a median PFS of 7.3 months (while a real-world cohort of similar patients showed the median progression-free survival to be just 3.5 months) [49].

Inavolisib is an oral small molecule with high in vitro potency and selectivity for PI3Kα inhibition and the ability to promote the degradation of mutant p110α [60]. The phase III INAVO120 study compared inavolisib, in combination with palbociclib and fulvestrant to placebo with palbociclib and fulvestrant in patients with PIK3CA-mutated, HR-positive, HER2-negative MBC who recurred on or within 12 months of adjuvant ET [17]. ORRs were 58.4% with inavolisib and 25.0% with placebo. There was statistically significant improvement in PFS (15 months vs 7.3 months). It was on the basis of this trial that inavolisib in combination with palbociclib and fulvestrant received FDA approval in HR +, Her2-, PIK3CA mutated advanced cancers following progression on or soon after endocrine therapy. The main toxicities that were increased with inavolisib included hyperglycemia, stomatitis, rash, and diarrhea. The triple therapy is very promising as a new standard of care for patients with PIK3CA mutated HR- positive, HER2- negative advanced breast cancer. Primary prophylaxis for hyperglycemia, diarrhea, rash and stomatitis (not offered to patients in the trial) could improve tolerability.

AKT Inhibitors

Capivasertib is an orally bioavailable, small-molecule inhibitor of all three AKT isoforms. In the phase 2 FAKTION trial, treatment with capivasertib in combination with fulvestrant significantly improved PFS and OS as compared with fulvestrant alone among postmenopausal women with MBC who had previously received endocrine therapy [61, 62].

Based on this study, the phase 3 CAPItello-291 trial evaluated the combination fulvestrant plus capivasertib versus fulvestrant plus placebo in patients who had recurrence or progression while on an AI, with or without a CDK4/6 inhibitor [61]. The addition of capivasertib improved both PFS and OS, with the most benefit seen in the pathway-altered population (40.8%). In the overall population the median PFS was 7.2 months in the capivasertib plus fulvestrant group versus 3.6 months in the fulvestrant group while in the AKT pathway-altered population mPFS was 7.3 and 3.1 months in the capivasertib plus

fulvestrant group and fulvestrant group, respectively. Benefit was also seen in those who received a prior CDK4/6 inhibitor (69.1%). The most common adverse events of any grade that were reported in the capivasertib–fulvestrant group were diarrhea, rash, and nausea. Hyperglycemia of any grade occurred in 16.3% of the patients who received capivasertib–fulvestrant and in 3.7% of those who received placebo–fulvestrant. The safety profile of capivasertib compared favorably with that of other agents targeting the PI3K–AKT–PTEN pathway, possibly because the intermittent administration schedule (4 days of treatment followed by 3 days off) allowed to maximize the AKT inhibition and optimize the therapeutic window. In November 2023, the FDA approved the use of capivasertib with fulvestrant for patients with HR + /HER2- MBC with one or more *PIK3CA/AKT1/ PTEN* alterations and experience disease progression after at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of the completion of adjuvant therapy. Finally, in addition to capivasertib, the highly selective oral ATP-competitive AKT inhibitor, ipatasertib, is also under evaluation.

Conclusion

While endocrine therapy has long been the backbone of first-line treatment in hormone receptor expressing breast cancer, the recent wide-spread incorporation of molecular-based personalized medicine and the introduction of several classes of exciting novel targeted therapies has changed the trajectory of advanced breast cancer care. The integration of CDK4/6 inhibitors and agents targeting the PI3K/AKT/mTOR pathway with standard endocrine therapies has changed the treatment paradigm of advanced breast cancer, and is actively being incorporated into the adjuvant setting in localized cancer.

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Declarations

Competing Interest Dr Angela Pennisi and Dr Lauren Mauro conduct clinical trials accruing patients with Astrazeneca, Eli Lilly, Stemline Therapeutics, Radius Pharmaceutical, and Genentech. Dr Lauren Mauro reports personal fees from Eli Lilly and Astrazenca.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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