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SYSTEMIC THERAPIES (M LIU AND T HADDAD, SECTION EDITORS)

Novel Agents for the Management of Endocrine Resistant Breast Cancer

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Abstract

Purpose of Review Most women with hormone receptor (HR)-positive, HER2-negative (HR+/HER2−) breast cancer will ultimately develop endocrine-resistant disease, either primary or acquired. This review will discuss the proposed mechanisms underlying endocrine resistance and key advances in the treatment of endocrine-resistant breast cancer.

Recent Findings Estrogen receptor 1 mutations (*ESR1*) occur in the majority of patients with HR+/HER2− metastatic breast cancer after prolonged exposure to aromatase inhibitors. Data from the SoFEA trial showed that patients had improved progression-free survival (PFS) after taking fulvestrant compared with exemestane. Fulvestrant is currently the only selective estrogen receptor degrader (SERD) available and development of oral novel SERDs with higher bioavailability and potency are currently being investigated.

Summary Despite significant advances in the treatment of HR+/HER2− breast cancer over the past four decades, a significant proportion of patients do still develop endocrine resistance following optimal endocrine therapy. In this review, we aim to provide an overview of the different classes of novel agents currently being investigated to overcome endocrine resistance.

Keywords Hormone receptor positive · Breast cancer · Endocrine resistance · Aromatase inhibitor · SERD · ESR1

Introduction

Hormone receptor (HR)-positive breast cancer includes estrogen receptor (ER)- and/or progesterone receptor (PR)-positive tumors and constitutes the majority of breast cancer (80–85%) worldwide. There has been significant reduction in mortality in women with HR-positive breast cancer which is thought to be partly due to endocrine-targeted therapies [1]. Despite these therapeutic advances, more women continue to die from HR-positive breast cancer than from any other breast cancer subtype [1]. Endocrine therapy has remained the backbone of treatment for patients with early and metastatic HR-positive breast cancer for over the past four decades [2••]. Unfortunately, some tumors have primary (de novo) resistance whereas others will develop secondary (acquired) resistance to endocrine therapy and will need to be initiated on non-endocrine therapy-based systemic therapies such as cytotoxic chemotherapy. Targeted therapy that can overcome or delay endocrine resistance has therefore been a key area of research in order to delay the time to chemotherapy for patients with metastatic disease, which only has a modest benefit in patients with HR-positive breast cancer. This review will discuss the proposed mechanisms underlying endocrine resistance and key advances in the treatment of endocrine-resistant breast cancer.

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Endocrine Resistance

There are two estrogen receptor genes, estrogen receptor 1 (*ESR1*/ERα) and 2 (*ESR2*/ERβ), that are both expressed in breast cancer. ERα is the dominant form whereas the role of ERβ is less clear. Estrogen receptor and its ligand, estradiol play a crucial role in the growth and progression of breast cancer [3]. *ESR1* is a gene located on chromosome 6 that encodes the ER protein (ERα) [4]. *ESR1* mutations usually occur in the ligand-binding domain of the receptor and can potentially lead to ligand-independent activation of the estrogen receptor [5]. *ESR1* mutations have been associated with acquired resistance to endocrine therapy and are therefore

uncommon in treatment naïve patients. They are however identified in 55% of patients with HR+ve metastatic breast cancer after prolonged exposure to aromatase inhibitors [6]. D538G and Y537S *ESR1* mutations are the two most commonly seen point mutations in the ligand-binding domain of *ESR1* in tumors from patients treated with anti-estrogen therapy for HR+ve metastatic breast cancer [4, 6].

HR positive breast cancers are stimulated by estrogen and therefore the most effective strategy to halt the growth of these tumors is to disrupt estradiol binding to ERα with the use of endocrine therapy [7]. Current endocrine therapies for HR-positive breast cancer include selective estrogen receptor modulators (SERMs; tamoxifen), aromatase inhibitors (AIs; letrozole, anastrozole, and exemestane), luteinizing hormone releasing hormone (LHRH) agonists (goserelin or leuprolide), and selective estrogen receptor degraders (SERDs; fulvestrant) [7].

It is unclear why some breast cancers are more sensitive to endocrine therapies and others are not. It is not uncommon for women with HR-positive breast cancer to have late recurrences more than 10 years after diagnosis, which is in contrast to HR-negative tumors that usually recur within the first 3–5 years [1]. Tumors that show no response to first-line endocrine therapies are usually classified as having primary resistance. On the other hand, tumors that show an initial good response to endocrine treatment and then later recur or progress demonstrates an acquired resistance. The mechanism behind endocrine-resistant breast cancer is likely complex and thus represents a major clinical challenge.

Primary (De novo) Endocrine Resistance

Primary resistance is defined as recurrence during adjuvant therapy or within 6–12 months of completion of adjuvant therapy. In the metastatic setting, it represents disease progression less than 6 months after initiating endocrine treatment [6, 8]. Possible mechanisms responsible for inherent tumor insensitivity to endocrine therapy includes the level of ER expression, loss of ER expression, and post-translational modifications of ER and ER independent signaling pathways, such as, fibroblast growth factor receptor (FGFR) over-expression and cyclin D1 amplification and expression [9]. The degree of ER expression is predictive of response to endocrine therapy and therefore the lack of ER expression will result in primary resistance to endocrine therapy. The loss of ER expression occurs in a minority (15–20%) of endocrine-resistant breast cancers and therefore the majority of patients are thought to develop acquired resistance [9].

Cyclin D1 expression and the continuous phosphorylation of the retinoblastoma (*Rb*) gene is another mechanism of endocrine resistance which causes continuous, uninterrupted cell cycle progression and cell proliferation even in the absence of estrogen [5]. Other possible mechanisms of Rb pathway dysregulation that could be responsible for CDK4/6 inhibitors resistance are under investigation, and include Rb loss/ mutation and dysregulation of PDK1. FGFR overexpression activates the mutagen-activated protein kinase (MAPK) and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)-AKT pathways and is commonly co-amplified with the cyclin D1 gene (*CCND1*). *FGFR* amplification occurs in 10% of breast cancers (27% of luminal B subtype) and causes suppression of PR expression and subsequent resistance to endocrine therapy [5]. *FGFR* amplification is also associated with a poor prognosis and early relapse and thus may be a promising area of drug development.

Secondary (Acquired) Endocrine Resistance

Acquired endocrine resistance is defined as recurrence at least 6–12 months after completion of adjuvant therapy or disease progression greater than 6 months after endocrine therapy is initiated in the metastatic setting [6, 8, 9]. There are several possible mechanisms for acquired resistance. ERα gene (*ESR1*) mutations occur in 2% of treatment-naïve tumors but in 25–30% of metastatic tumors [5]. *ESR1* mutations usually occur in the ligand-binding domain of the receptor and can potentially lead to ligand-independent activation of the estrogen receptor [5]. Since ERα is the main target for these drugs either directly (anti-estrogens) or indirectly (aromatase inhibitors), the presence of ERα in a tumor is a primary indicator of the likelihood of eliciting a beneficial response with treatment [1]. Resistance to aromatase inhibitors (AI), and to a lesser extent SERMs/SERDs, have been associated with the *ESR1* mutation [5].

Acquired endocrine resistance is also stimulated by the up-regulation of growth signaling pathways such as human epidermal growth factor receptor 2 (HER2), insulin-like growth factor receptor 1 (IGFR1), FGFR1, and subsequent activation of the MAPK cascade or PI3K pathway [7]. The activation of the PI3K-AKT-mechanistic target of rapamycin (mTOR) signaling pathway that develops in HR-positive breast cancer cells after prolonged estrogen deprivation is thought to emerge as an adaptive mechanism in an effort to escape ER inhibition [3]. Activation of the PI3K-AKT-mTOR pathway has been linked to resistance to endocrine therapy and was seen in 30–40% of patients with HR positive metastatic breast cancer [5].

Targeted Therapies

mTOR Inhibitors

In HR-positive breast cancer, the PI3K-AKT-mTOR pathway controls cell growth through signaling communicated by the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases and ER [10]. Inhibitors of mTOR therefore demonstrate an anti-proliferative effect by blocking the phosphorylation of the activation domain 1 of ER [10].

Everolimus

Everolimus is an oral mTOR inhibitor and is the first targeted therapy FDA approved in 2012 for the treatment of HR positive-, HER2 negative- (HR+/HER2−) breast cancer that has progressed on a non-steroidal aromatase inhibitor (NSAI). This was based on data from the phase III, BOLERO-2 trial, where 724 post-menopausal women with HR+/HER2− breast cancer that had disease progression on a NSAI were randomized to everolimus 10 mg oral daily or placebo plus exemestane 25 mg oral daily. There was an improvement in progression-free survival (PFS) from 3.2 months in the placebo plus exemestane arm to 7.8 months in the everolimus plus exemestane arm with a hazard ratio of 0.45 (95% CI, 0.38–0.54) [11]. Despite the improvement in PFS, there was not a statistically significant improvement in OS, which was a secondary end point. The OS in the everolimus plus exemestane arm was 31 months compared to 26.6 months in the placebo plus exemestane arm with a hazard ratio of 0.89 (95% CI, 0.73–1.10) [11]. The most common grade 3 and 4 adverse events were anemia (6 vs. < 1%), stomatitis (8 vs. 1%), pneumonitis (3 vs. 0%), and fatigue (4 vs. 1%) in the everolimus plus exemestane arm vs. exemestane alone arm, respectively [10]. Everolimus combined with fulvestrant or tamoxifen have also shown improvement in median PFS and clinical benefit rate (CBR), respectively in post-menopausal women with HR+/HER2− breast cancer that had disease progression on a NSAI [12, 13].

PI3K Inhibitors

The PI3K-AKT-mTOR pathway which is the most commonly altered pathway in cancer and mutations, including the *PIK3CA* mutations, has been implicated as a possible mechanism for endocrine resistance in HR-positive breast cancer [14]. Prior studies have reported that an estimated 40% of HR+/HER2− breast cancers harbor *PIK3CA* mutations [14] and therefore several studies have been developed incorporating PI3K inhibitors with endocrine therapy.

Buparlisib (BKM120) is an oral, pan-PI3K inhibitor that showed an improvement in PFS in phase III, BELLE-2 and BELLE-3 trials when combined with fulvestrant [15, 16]. The BELLE-2 study randomized 1147 post-menopausal women with HR+/HER2− metastatic breast cancer after progression on AI to buparlisib or placebo and fulvestrant. There was an improvement in PFS from 5 months in the placebo group to 6.9 months in the combination therapy group with a hazard ratio of 0.78 (95% CI, 0.67–0.89), meeting the study's primary endpoint [15]. Patients with *PIK3CA* mutations detected in their circulating tumor DNA (ctDNA) also had a longer PFS of 7 months if they received combination therapy, compared to 3.2 months for fulvestrant alone [15]. In the BELLE-3 trial of 432 post-menopausal women with HR+/HER2− metastatic breast cancer, there was a 2.1-month improvement in PFS in the buparlisib and fulvestrant arm compared to the fulvestrant alone arm [16]. The magnitude of benefit with the combination was also greater in those patients with *PI3KCA* mutations in ctDNA at study entry (HR = 0.56, $P < .001$) versus the entire population (HR = 0.78, $P < .001$) [16]. Improvement in PFS with buparlisib was however not without significant toxicities, including hyperglycemia, rash, and psychiatric symptoms (such as anxiety, depression and suicidal attempts) [16]. Given the minimal benefit and safety profile, the drug did not move forward in development.

Alpelisib (BYL719) is an oral, alpha-selective PI3K inhibitor that is currently being investigated in a phase III clinical trial. Alpha-selective PI3K inhibitors have more specific inhibition of the *PIK3CA* gene than buparlisib (pan-PI3K inhibitor) and are therefore thought to be associated with less side effects [16]. In a phase Ib study of alpelisib plus letrozole, in patients refractory to endocrine therapy, the combination was safe with reversible toxicities (hyperglycemia, nausea, fatigue, and diarrhea) [16]. The phase III, SOLAR-1 trial (NCT02437318) is currently investigating alpelisib plus fulvestrant in men and post-menopausal women with HR+/HER2− metastatic breast cancer that has progressed on an AI. The primary endpoint is PFS and *PIK3CA* mutation status by ctDNA will be assessed as a secondary endpoint. Data from the SANDPIPER trial showed that post-menopausal women with HR+/HER2−, *PIK3CA* mutated advanced or metastatic breast cancer treated with taselisib (a potent alpha-selective PI3K inhibitor) plus fulvestrant, had a statistically significant improvement in PFS from 5.4 (fulvestrant alone) to 7.4 months, with a HR of 0.7 (95% CI, 0.56–0.89) [17].

CDK4/6 Inhibitors

In HR-positive breast cancer, estrogen stimulates cyclin D1 expression and activates cyclin-dependent kinase (CDK) 4 and 5 which causes cell growth and survival. Under normal cell division, cyclin D1 couples with CDK4 to phosphorylate the tumor suppressor, retinoblastoma gene (*Rb*), which causes *Rb* inactivation and progression from G1 to S phase of the cell cycle [2••]. CDK4/6 inhibitors therefore prevent the phosphorylation of *Rb* which in turn halts the cell cycle in the G1 phase. Inhibitors of CDK4 and 6 have shown in vitro inhibitory effects in ER-positive breast cancer cells, synergy with anti-estrogens and also reversed endocrine resistance [2••].

Three oral CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) were granted FDA approval, in combination with a NSAI as first-line treatment for HR+/HER2− metastatic breast cancer [2••, 18, 19]. They all demonstrated similar improvements in PFS (HR of about 0.5; corresponding to an average of 26 months PFS) from the PALOMA-2 (palbociclib plus letrozole), MONALEESA-2 (ribociclib plus letrozole), and MONARCH-3 (abemaciclib plus a NSAI) trials,

respectively [2••, 18, 19]. They are all also approved as second-line options, in combination with fulvestrant, after disease progression on endocrine therapy, with similar improvement in PFS (HR of about 0.5) [20••, 21, 22]. Ribociclib, in combination with fulvestrant, was recently granted expanded approval as an initial endocrine-based therapy or following disease progression on endocrine therapy for postmenopausal women with HR+/HER2− metastatic breast cancer [20••]. There was an improvement in the PFS from 12.8 months in the placebo group to 20.5 months for patients taking ribociclib with a hazard ratio of 0.59 (95% CI, 0.480–0.732) [20••]. The MONALEESA-3 trial is the first study that have evaluated the combination of a CDK4/6 inhibitor (ribociclib) plus fulvestrant as a first-line endocrine therapy in HR+/HER2− metastatic breast cancer [20••].

Palbociclib and ribociclib are both given once daily for 3 weeks, followed by 1 week off over 28-day cycles [2••, 19]. Abemaciclib, on the other hand, is the only CDK4/6 inhibitor that is administered twice daily on a continuous schedule [18]. It is structurally distinct from the other CDK4/6 inhibitors (palbociclib and ribociclib) and is 14 times more potent against cyclin D1/CDK4 and cyclin D3/CDK6 in enzymatic assays [18]. Pre-clinical data have demonstrated that abemaciclib crosses the blood brain barrier and therefore may be a future indication for patients with intracranial metastasis [21]. It is also the only CDK4/6 inhibitor that is FDA approved as monotherapy in women with HR+/HER2− metastatic breast cancer whose disease progressed following chemotherapy and endocrine therapy. These data were based on the single arm, open-label, phase II, MONARCH 1 trial that enrolled 132 women who received abemaciclib 200 mg orally twice daily continuously until disease progression or toxicities developed [23•]. The median response duration was 8.6 months (95% CI 5.8, 10.2) with an objective response rate (ORR) of 19.7% (95% CI, 13.3, 27.5) [23•].

In the MONALEESA-7 trial, there was an improvement in the PFS from 13.8 months for patients on the placebo arm to 27.5 months for patients on the ribociclib plus letrozole arm in pre- and peri-menopausal women with HR+/HER2− metastatic breast cancer who received no prior endocrine therapy with a hazard ratio of 0.569 (95% CI, 0.436–0.743) [24]. This is the first trial which showed that pre-menopausal women had a statistically significant improvement in PFS on ribociclib plus letrozole, which was similar to the PFS results previously seen in post-menopausal women [19, 24]. Ribociclib plus letrozole has subsequently been granted FDA approval for first-line therapy of pre-menopausal women with HR+/HER2− metastatic breast cancer. The MONALEESA-7 trial is the only trial that combined a CDK4/6 inhibitor with an AI or tamoxifen and goserelin (GnRH analog) [24]. There was an improvement in PFS when ribociclib was added to either an AI or tamoxifen plus goserelin (PFS 23.8 versus 13 months with a hazard ratio of 0.55) [24]. From subgroup analyses, ribociclib plus tamoxifen/goserelin was not as effective as ribociclib plus AI/goserelin and the tamoxifen arm also resulted in a higher incidence of QT prolongation [24].

The most common adverse event reported with CDK4/6 inhibitors was neutropenia, which occurred in 66.4% of women in the palbociclib arm and 1.4% of women in the placebo arm from the PALOMA-2 trial [19]. Febrile neutropenia was seen in 1.8% of women in the palbociclib arm and no reported cases were seen in the placebo arm [16]. Other grade 3 or 4 adverse events were anemia, leucopenia, nausea, fatigue, and arthralgia [16]. QT interval prolongation to more than 480 msec was also noted in 3.3% of women in the ribociclib arm and was not seen in the placebo arm from the MONALEESA-2 trial [19]. The safety profile for abemaciclib was similar to the other CDK4/6 inhibitors, except for diarrhea, which was seen in 86.4% of patients in the abemaciclib arm versus 24.7% in the fulvestrant arm [21]. While diarrhea was common, it was predictable (occurred early) and manageable with dose reductions or anti-diarrheal medications [21]. Neutropenia was also less commonly seen than with palbociclib or ribociclib [21].

The Impact of CDK4/6 Inhibitors

CDK4 and 6 inhibitors have all been shown to improve PFS regardless of endocrine sensitivity, endocrine combination, or menopausal status. They are generally well tolerated as monotherapy and in combination with non-steroidal aromatase inhibitors or fulvestrant. The side effect profiles are predictable, manageable, and reversible and differences in toxicities can be used to individualize therapy.

We have not yet seen an improvement in OS with the addition of CDK4/6 inhibitors as these phase III trials were not powered to assess OS. It is difficult to demonstrate an OS benefit given the long natural history of HR-positive metastatic breast cancer, added to the fact that these agents are used very early during the course of the disease. Despite no proven benefit to OS, the CDK4/6 inhibitors have a very meaningful role in delaying the time to chemotherapy and improving quality of life.

We are still not sure when is the best time to add CDK4/6 inhibitors to endocrine therapy. Data from the PALOMA 2, MONALEESA 2, MONALEESA 3, and MONARCH 3 trials have all shown improvements in PFS when CDK4/6 inhibitors plus endocrine therapy are used in the first-line setting for patients with HR+/HER2− metastatic breast cancer [2••, 18, 19, 20••]. The current practice is therefore to offer all patients with HR+/HER2− metastatic breast cancer combined endocrine therapy plus a CDK4/6 inhibitor upfront. Data are however lacking on whether all patients truly need combination therapy, and it is not clear which subset of patients may be spared upfront CDK4/6 inhibitor plus endocrine therapy. The previously mentioned trials were not crossover studies, and

therefore treatment decisions need to be made on an individualized basis taking into consideration tumor biology, toxicities, costs and access to treatment [25]. Upcoming prospective trials will hopefully help determine the optimal sequence of CDK4/6 inhibitors, as a first- or second-line option after progression on endocrine therapy. The SONIA trial (NCT03425838), which began recruiting patients in February 2018 is a multi-center, randomized phase III trial that was designed to determine whether the sequence of an AI plus a CDK 4/6 inhibitor in the first-line setting followed by fulvestrant in the second-line is superior to the first-line AI alone followed by fulvestrant plus CDK4/6 inhibitor in the second-line setting will hopefully answer some of these burning questions.

Given the improvement in PFS with the addition of CDK4/6 inhibitors to endocrine therapy in patients with metastatic breast cancer, there are several ongoing phase III trials evaluating their role in the treatment of early (stage I and II) in HR+/HER2− breast cancer. The PALLAS trial (NCT02513394) is evaluating the role of 2 years of palbociclib in addition to 5 years of adjuvant endocrine therapy, and the MONARCH-E (NCT03155997) is studying 2 years of abemaciclib plus 5 years of adjuvant endocrine treatment.

CDK4/6 Inhibitors: Biomarkers and Resistance

Biomarkers have been studied to determine if they play a role in selection of patients who may benefit from a CDK4/6 inhibitor and explain the mechanism of developing resistance to CDK4/6 inhibitors. ER positivity remains the most effective and reliable predictive marker to determine the group of patients likely to respond to CDK4/6 blockade [25]. Biomarkers, such as cyclin D amplification (*CCDN1*), protein levels of cyclin-D/CDK4/6-Rb pathway, and loss of p16 and *PIK3CA* mutations have all failed to identify responders to CDK4/6 inhibition [20••, 25]. *ESR1* mutations were evaluated in the MONALEESA 2 study [26]. mRNA expression data from baseline tumor samples were collected from 391 of 668 patients and were expressed as high or low using a 50% median expression cutoff [26]. There was a trend towards a longer PFS in patients that had high *ESR1* expression in both the letrozole/ribociclib (29.6 months vs. 22.1 months) and letrozole/placebo arms (16.9 months vs. 13.2 months) [26]. There was also a trend towards a greater benefit with CDK4/6 inhibitors when used in patients with high *ESR1* expression with a hazard ratio of 0.39 (95% CI, 0.25–0.60) and 0.74 (95% CI, 0.51–1.07) in patients with low *ESR1* expression [26].

There are collateral pathways that could potentially bypass endocrine and CDK4/6 inhibition, ultimately leading to resistance and subsequent disease progression. We know that the cyclin-D-CDK4/6 complex phosphorylates *Rb* causing progression in the cell cycle. There are however negative regulators of the complex, such as p16, and an alternate pathway through cyclin E (*CCNE1*) that can also phosphorylate *Rb* [25]. *CCNE1* and *FGFR1* amplifications are associated with poorer outcomes and de novo resistance to CDK4/6 inhibitors [25, 27]. The PALOMA 3 trial demonstrated that patients with low cyclin E levels pre-treatment (from mRNA gene expression) had a longer PFS of 14.1 months versus 7.6 months in patients with high cyclin E levels [22]. Prior data have shown that *FGFR1* is associated with endocrine resistance; however, recent data have also implicated *FGFR1* amplification with resistance to CDK 4/6 inhibition [27]. Combining fulvestrant, palbociclib, and af FGFR inhibitor, erdafitinib, has shown increased activity in FGFR1-mutated pre-clinical models [27] and is currently being investigated in a phase Ib clinical trial (NCT03238196).

The PALOMA 3 trial also looked at ctDNA from pre and post treatment blood samples and found that 4.8% of patients developed *Rb* mutations while taking palbociclib (vs. 0% with fulvestrant alone) [22]. Mutations or loss of *Rb* would ultimately render CDK4/6 inhibitors inactive and cause disease progression. Mutations in *PIK3CA* and *ESR1* also developed in both the palbociclib plus fulvestrant and fulvestrant alone arms, with no statistically significant difference between the arms [26].

Emerging mutations from ctDNA may provide clues to the sequence of modifying therapy. Patients with *Rb* mutations would likely need to discontinue the CDK4/6 inhibitor whereas patients who develop *ESR1* mutations may need to switch endocrine therapy (from an AI to fulvestrant) and continue CDK4/6 inhibition [26]. Patients on the other hand that develop a *PIK3CA* mutation may benefit from targeting an additional pathway (such as mTOR) while continuing endocrine therapy and CDK4/6 inhibition. Two phase II clinical trials, TRINITY-1 (NCT02674568) and PASTOR (NCT02599714), are currently evaluating whether adding a mTOR inhibitor to a CDK4/6 inhibitor plus an AI after progression has any added benefit [28]. Combined CDK4/6 inhibition plus alpha-selective PI3K inhibition could also reverse resistance to endocrine therapy, as well as CDK4/6 therapy [28, 29].

HER2 Mutations

HER2 mutation is another well-known mechanism for resistance to endocrine therapies and combined HER2 tyrosine kinase inhibitors (TKI) with anti-estrogens are currently being studied in early phases of clinical trials [3]. *HER2* mutations are seen in approximately 1.6% of patients with breast cancer, with a proposed higher frequency among patients with lobular and metastatic breast cancer [30]. Neratinib is an irreversible pan-HER TKI is currently being studied in the SUMMIT trial, in patients with *HER2*-mutated, non-amplified metastatic breast cancer [3]. The SUMMIT trial is a global, open-label, multi-histology, precision-medicine "basket" study investigating the

safety and efficacy of neratinib in patients with various types of solid tumors with activating *HER2*, *HER3*, or *EGFR* mutations. Preliminary results from the SUMMIT trial showed an ORR of 32% in women with HR+/HER2− breast cancer [31].

Histone Deacetylase (HDAC) Inhibitors

Alterations in gene expression is another possible mechanism for endocrine which may be reversed by HDAC inhibitors such as entinostat [32]. Entinostat was granted FDA breakthrough designation in combination with exemestane for patients with HR+/HER2- metastatic breast cancer after disease progression on a NSAI, based on the ENCORE 301 phase II clinical trial that showed a significant improvement in PFS (2 months) and OS (8.3 months) [33]. The phase III, E2112 trial (NCT02115282), was subsequently developed to confirm the results from the ENCORE 301 trial and these results are eagerly anticipated [32].

Immunotherapy

Immune checkpoint inhibitors have shown promising results in a variety of solid tumor malignancies; however, they have only shown a 6–12% ORR in heavily pre-treated HR+/HER2- metastatic breast cancer [34]. There appears to be an increase in mutational burden in endocrine-resistant breast cancers [35]; however, these tumors are still generally immunologically "cold." Immunotherapy combination strategies to increase immune recognition through enhanced antigen presentation and/or increased T cell homing may increase immunotherapy response [35]. Programmed cell death 1 (PD-1) inhibitors, such as avelumab, are being added to palbociclib after CDK4/6 and endocrine therapy (PACE) trial to determine the optimal subsequent line of therapy in patients with HR+/HER2− metastatic breast cancer that has progressed on endocrine therapy and CDK4/6 inhibition [36]. The PACE trial (NCT03147287) is a multi-center, phase II trial currently underway that randomized patients in a 1:2:1 design to arm A: fulvestrant alone (with option for palbociclib monotherapy crossover at time of progression); arm B: fulvestrant and palbociclib; or arm C: fulvestrant, palbociclib, and avelumab with a primary endpoint of PFS [36]. Data from these and similar trials are eagerly awaited and will inform the sequence of endocrine and targeted therapy.

ESR1 Mutations and Selective Estrogen Receptor Degraders

Selective estrogen receptor degraders (SERDs), such as fulvestrant, have been proposed to be a rational therapeutic approach to inhibiting *ESR1* mutations by promoting receptor degradation and inhibition [37]. In the SoFEA (Study of Faslodex Versus Exemestane With or Without Arimidex) trial, patients with *ESR1* mutations had improvement in PFS after taking fulvestrant compared with exemestane with a hazard ratio of 0.52 (95% CI, 0.30–0.92), whereas patients with wild-type *ESR1* had a similar PFS after receiving either treatment [38].

Fulvestrant is currently approved for first-line treatment, alone or in combination with ribociclib and as a second-line option, alone or in combination with palbociclib and abemaciclib after progression on an AI, in women with HR+/HER2− metastatic breast cancer [20••, 21, 22]. Fulvestrant is currently the only approved SERD used in post-menopausal women with HR-positive metastatic breast cancer. It is administered intramuscularly every 28 days and have been shown from prior studies to have a very low bioavailability [38, 39]. Studies have shown that SERDs were able to block all *ESR1* mutant receptors with significant differences in potency [37]. Some *ESR1* mutations, such as *E380Q* were inhibited at similar concentrations as wild-type receptors, whereas *Y537S* mutants required higher concentrations [37]. Given these limitations, potent orally bioavailable SERDs which could achieve higher steady-state drug levels are being investigated [39].

AZD9496 is a SERD with a high bioavailability and potency that fully inhibited *ESR1* wild type, D538G and Y537S tumors in pre-clinical models [37, 39]. It is currently being investigated in a phase I clinical trial, NCT02248090. ARN-810/GDC-810 (brilanestrant) is another novel oral SERD being studied in an open-label, phase IA/II, randomized study of GDC-0810 versus fulvestrant in post-menopausal women with metastatic HR+/HER2− breast cancer that has progressed on an AI [40]. Early phase I data have shown response on 18F-fluoroestradiol (FES)-PET imaging in patients with *ESR1* mutated tumors [40]. A phase I/Ib, open-label study of an oral SERD, LSZ102, is being studied as monotherapy and in combination with either ribociclib (CDK4/6 inhibitor) or alpelisib (PI3K inhibitor) in patients with HR+/HER2− metastatic breast cancer (NCT02734615).

Whether fulvestrant or any of the newer, oral SERDs will begin to displace aromatase inhibitors as the endocrine therapy of choice for post-menopausal women with *ESR1*-mutated breast cancer remains to be seen.

Conclusion

Targeting resistant pathways with novel agents, usually in combination with endocrine therapy, has led to improved treatment options in patients with HR+/HER2− metastatic breast cancer. Despite recent advances in therapeutic options, the mechanisms of endocrine resistance are still not completely understood and therefore a better understanding of ER biology will hopefully refine our treatment options and sequencing of agents. The current standard of care is a combination of targeted agents (such as CDK4/6 and mTOR inhibitors) plus

endocrine therapy in unselected patients with HR+/HER2− metastatic breast cancer, some of which may have endocrine sensitive disease [3]. We are still not able to reliably predict which subgroup of patients will relapse or progress on endocrine therapy alone. Patient selection therefore remains a challenge as targeted therapies are expensive and may not be easily accessible across all populations [3].

Compliance with Ethical Standards

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