Advances in endocrine and targeted therapy for hormone-receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer

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Abstract
Nearly 70% of breast cancer (BC) is hormone-receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, and endocrine therapy is the mainstay of treatment for this subtype. However, intrinsic or acquired endocrine resistance can occur during the endocrine treatment. Based on insights of endocrine resistance mechanisms, a number of targeted therapies have been and continue to be developed. With regard to HR-positive, HER2-negative advanced BC, aromatase inhibitor (AI) is superior to tamoxifen, and fulvestrant is a better option for patients previously exposed to endocrine therapy. Targeted drugs, such as cyclin-dependent kinases (CDK) 4/6 inhibitors, mammalian target of rapamycin (mTOR) inhibitors, phosphoinositide-3-kinase (PI3K) inhibitors, and histone deacetylase (HDAC) inhibitors, play a significant role in the present and show a promising future. With the application of CDK4/6 inhibitors becoming common, mechanisms of acquired resistance to them should also be taken into consideration.

Keywords: Endocrine therapy; Advanced breast cancer; Endocrine resistance; Targeted therapy

Introduction
Breast cancer (BC) is the most frequent malignancy among women worldwide and is the fifth cause of cancer deaths among females in China.[1,2] It can be subdivided into at least five molecular subtypes by gene-expression profiling, including basal-like, human epidermal growth factor receptor 2 (HER2) overexpressing, luminal A, luminal B, and claudin-low.[3] Approximately 70% of breast cancers are hormone-receptor (HR)+ and HER2-, and endocrine therapy (ET) is the mainstay of treatment for this subtype.[4] Although most early-stage HR+ patients are initially treated with ET, about 30% of them will eventually relapse with metastatic disease.[5] The goal of treatment for HR+/HER2- advanced breast cancer (ABC) is largely palliative, aiming at improving or maintaining the quality of life, prolonging survival, and delaying the beginning of chemotherapy; meanwhile, ET should be the preferred choice as first-line treatment excluding patients with visceral crisis, life-threatening disease, or proof of endocrine resistance.[6-8] In this review, we describe the development of antiestrogenic therapies, the mechanisms of endocrine resistance, the role of targeted therapy options in HR+/HER2- ABC supported by evidence from completed clinical trials, and highlight the mechanisms of acquired resistance to cyclin-dependent kinases (CDK) 4/6 inhibitors.

Current antiestrogenic endocrine therapies
Typical ETs currently utilized in the first or second line for HR+ BC include selective estrogen receptor modulators (such as tamoxifen), aromatase inhibitors (AIs, such as anastrozole, letrozole, and exemestane), and selective estrogen receptor down regulators (such as fulvestrant). There are various monotherapies or combination approaches based on prior treatment exposure status and whether early or late relapse since adjuvant therapy in the setting of ABC.[9]
Tamoxifen, one of the most commonly used anti-cancer drugs, was approved as an effective therapy in the metastatic setting in the 1970s. Tamoxifen has both estrogenic and antiestrogenic activities when binding to the ER and these effects are tissue-specific, which relates to some of the side effects such as endometrial cancer and thromboembolic disease. In postmenopausal women, increased levels of tumor estrogen are associated with elevated aromatase levels in breast epithelium, and peripheral tissues such as fat and muscle are responsible for circulating estrogen synthesis. AIs are used to inhibit the aromatase enzyme activity, thereby reducing the production of estrogen. Exemestane is a steroidal AI that irreversibly binds to aromatase, while nonsteroidal agents (anastrozole and letrozole) competitively bind to aromatase. A large meta-analysis of 23-randomized trials demonstrated significantly improved survival for patients receiving anastrozole, letrozole, or exemestane compared to tamoxifen (relative hazards reduction 11%, 95% confidence interval [CI] 1%–19%, P = 0.03). Fulvestrant represents another effective treatment option for this patient population. In contrast to tamoxifen, fulvestrant has a much higher binding affinity to ER without agonist activity, exerting antiestrogenic effects by inhibiting ER dimerization, attenuating ER translocation to the nucleus as well as accelerating ER degradation and downregulation. The initial dose of fulvestrant approved by the US Food and Drug Administration (FDA) was 250 mg monthly, and under this dose, clinical benefit showed no difference between fulvestrant group and AI group in the second-line setting of ABC. Subsequently, the CONFIRM study provided the evidence for approval of higher dose by demonstrating that fulvestrant 500 mg monthly was associated with significantly improved progression-free survival for patients receiving anastrozole, letrozole, or exemestane compared to tamoxifen (relative hazards reduction 11%, 95% confidence interval [CI] 1%–19%, P = 0.03). Fulvestrant was found to show a significantly improved PFS compared to anastrozole (16.6 months vs. 13.8 months, P = 0.048), with the equivalent health-related quality of life and AEs. Further, a phase III trial FALCON was designed to compare fulvestrant 500 mg with anastrozole as first-line endocrine therapy for postmenopausal patients with ABC. Fulvestrant was found to show a significantly improved PFS compared to anastrozole (16.6 months vs. 13.8 months, P = 0.048), with the equivalent health-related quality of life and AEs. In EFFECT, a multicenter phase III trial, a total of 683 women with HR+ ABC progressing or recurring after NSAI were assigned to receive either fulvestrant or exemestane. The result indicated no statistical difference between fulvestrant loading dose with exemestane in terms of time to progression (TTP) and clinical benefit rate. CDK4/6 inhibitors may exert possible efficacy in combination with fulvestrant for these patients, which will be discussed next.

Mechanisms behind endocrine resistance

Despite the efficacy of these selectable ETs, intrinsic or acquired endocrine resistance can occur during first or multiple lines of endocrine treatment, which remains a major challenge to overcome. To date, several potential mechanisms of endocrine resistance were proved, involving multiple resistance pathways and oncogenic drivers. Some of the resistance mechanisms focused on in this review have promoted the progress of new treatments, containing deregulation of the cell cycle, activation of phosphoinositide 3 kinases (PI3K)/ protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, and estrogen receptor α (ESR1) mutations. Deregulation of cell cycle, the process controlled by different regulating proteins, can promote breast tumor progression and endocrine resistance. Cyclin D1, one of three D-type cyclins (D1, D2, and D3), is well known as a direct transcriptional target of the ER. It forms complexes with CDK4 and 6 at the G1 phase of the cell cycle. The CDK4/6-cyclin D complex induces inactivation and phosphorylation of retinoblastoma protein (Rb) and prompts the release of E2F transcription factors, leading to entry into S phase where DNA replication/synthesis occurs and promoting tumor development. Overexpression of cyclin D1 was found in approximately 50% primary breast tumors, with the highest frequency in luminal B subtype. In vitro estrogen-receptor (ER)+ BC cells transfected to overexpress cyclin D1 could grow continually under exposure to antiestrogens. Even when ER+ BC develop resistance to endocrine therapy, cyclin D1 and CDK 4 remain indispensable for them to drive cell proliferation. Several preclinical studies have confirmed that CDK4/6 inhibitors can be effective in ER+ and endocrine-resistant BCs. In patients with ER+ ABC treated with fulvestrant, high CDK6 levels were significantly correlated with shorter PFS upon fulvestrant treatment. The PI3K/AKT signaling pathway is one of the most frequently aberrant (OS), activated pathways in HR+/HER2- ABC and has been associated with resistance to ETs, prompting either dependent or independent ER transcriptional activity. The estrogen-independent activation of...
ER is regulated by crosstalk among the PI3K/AKT, mitogen-activated protein kinase (MAPK), and CDK2/7 pathways, resulting in ligand-independent growth of tumors resistant to various ETs. Molecularly, the activation of insulin-like growth factor (IGF) and the PI3K/AKT and MAPK pathways induced by estrogen activity is associated with the downregulation of ER and PR on the cell surface. Additionally, phosphatase and tensin homolog (PTEN) is a crucial negative regulator of PI3K/AKT signaling, and the loss of the PTEN molecule is largely implicated in endocrine resistance.

Numerous genomic alterations have been confirmed in metastatic BCs with de-novo and acquired resistance to endocrine therapy, including ESR1, the gene encoding estrogen receptor-α (ERα). Large-scale next-generation sequencing (NGS) results of metastatic BC tissues revealed that ESR1 mutations were enriched in metastatic BC patients treated with endocrine therapy, but not in primary tumor tissues. It is indicated that these mutations may be a potential mechanism of endocrine resistance in the process of estrogen deprivation, leading to the estrogen-independent constitutive activation of ER. Toy et al found that ERα isomers could be partially inhibited by receptor antagonists such as tamoxifen or fulvestrant while ineffectively inhibited by AI. Adjuvant AI therapy appears to select ESR1 mutations under the pressure of estrogen deprivation and on the contrary, there are no selective ESR1 mutations in treatment with fulvestrant conferring constitutive activation of ERα. Moreover, by using newer techniques with increased sensitivity such as droplet digital PCR (ddPCR), ESR1 mutations can be assessed both in solid tumor tissue and in liquid biopsies including circulating cell-free DNA (cfDNA) and circulating tumor cells (CTCs). Several large clinical trials evaluated the frequencies of ESR1 mutation in cfDNA by ddPCR, indicating that these mutations were associated with more aggressive biological characteristics. In the SoFEEA trial, within the exemestane-treated arm, patients with an ESR1 mutation had a worse PFS compared to patients without detectable ESR1.
mutations (medial PFS 2.6 vs. 8.0 months, \( P = 0.01 \)). And patients with an \( \text{ESR1} \) mutation derived significant benefit from taking a fulvestrant-containing regimen, with an improved PFS vs. exemestane (medial PFS 5.7 vs. 2.6 months, \( P = 0.02 \)).[30] In a secondary analysis of the phase III BOLERO-2 study, \( \text{ESR1} \) mutations were associated with a worse OS compared to wildtype ER.[31]

In recent years, multiple phase III clinical trials have proven the activity and efficacy of various drugs targeting the aforementioned intracellular signaling that might overcome endocrine resistance. Treatment options are expanding with combined therapies of CDK4/6 inhibitors, mTOR inhibitors, PI3K inhibitors, and histone deacetylase (HDAC) inhibitors (Supplementary Table 1, http://links.lww.com/CMJ9/A202).

**Targeted therapy options to overcome endocrine resistance**

**CDK 4/6 inhibitors and emerging acquired resistance**

**Clinical studies of CDK4/6 inhibitors**

Palbociclib, a reversible, oral, small-molecule inhibitor, was the first CDK4/6 selective inhibitor studied and successfully applied in clinical practice. Palbociclib has a synergistic effect with endocrine therapy due to the suppression of both CDK4/6 and cyclin D1, inhibiting Rb phosphorylation and resulting in G1 cell cycle arrest.[32] The phase III PALOMA-2 study confirmed that first-line palbociclib plus letrozole improved the median PFS compared to letrozole alone (24.8 months vs. 14.5 months, \( P < 0.001 \)).[33] Further, the efficacy of palbociclib with fulvestrant was investigated in the second-line setting in the PALOMA-3 trial.[34] The combination of fulvestrant plus palbociclib significantly improved PFS compared to fulvestrant plus placebo (9.5 months vs. 4.6 months, \( P < 0.0001 \)) and prolonged the median OS (34.9 months vs. 28.0 months, \( P = 0.09 \)). Neutropenia was the most common AE in both arms, which could be managed by dose reduction, dose interruption, or cycle delay.[34,35]

Ribociclib (LEE011) is another orally bioavailable, selective inhibitor of CDK4/6, with received approval in the pre-/peri- and postmenopausal disease settings based on the MONALEESA trials. MONALEESA-2 demonstrated that ribociclib plus letrozole significantly improved PFS compared with placebo plus letrozole for first-line therapy in postmenopausal patients with HR+/HER2- ABC.[36] Subsequently, ongoing trials reported significant PFS improvements with ribociclib in combination with either fulvestrant in postmenopausal patients with advanced breast cancer who were either treatment-naïve or received \( \leq 1 \) line of prior ET in the advanced disease setting (MONALEESA-3) or tamoxifen/nonsteroidal aromatase inhibitor with ovarian function suppression in pre/perimenopausal women (MONALEESA-7).[37,38] In all three phase III trials, the primary endpoint PFS was improved in the treatment arm containing ribociclib vs. that with the placebo arm.[36-38] Of note, MONALEESA-7 first assessed the efficacy of a CDK4/6 inhibitor for premenopausal women in combination with hormonal therapy and goserelin. It enrolled 672 premenopausal patients with HR+/HER2- ABC who may have received either neoadjuvant or adjuvant ET and up to one previous line of chemotherapy for advanced disease. The results showed that median PFS was significantly higher in the ribociclib group (23.8 months vs. 13.0 months, \( P < 0.0001 \)), and OS was significantly longer with a 29% lower risk of death (hazard ratio [HR] for death, 0.71; 95% CI 0.54–0.95). The most common grade 3 or 4 AEs were neutropenia (63.5% vs. 4.5%), hepatobiliary toxic effects (11% vs. 6.8%) and prolonged QT interval (1.8% vs. 1.2%).[38,39]

Abemaciclib (LY2835219) is the latest CDK4/6 inhibitor approved by the FDA for clinical practice, with greater affinity and higher potency for CDK4 in comparison to palbociclib and ribociclib in preclinical models.[40] It was also proved that abemaciclib could cross the blood-brain barrier.[41] In the MONARCH 2 trial, patients who experienced progression on (neo)adjuvant ET were randomly assigned 2:1 to receive abemaciclib or placebo (150 mg, twice daily) combined with fulvestrant (500 mg, monthly). The addition of abemaciclib to fulvestrant significantly extended PFS vs. fulvestrant alone (median, 16.4 months vs. 9.3 months, \( P = 0.001 \)). The most common AEs in the abemaciclib arm were diarrhea, neutropenia, nausea, and fatigue.[42] Furthermore, the MONARCH 3 interim analysis demonstrated that abemaciclib plus a nonsteroidal AI (letrozole or anastrozole) met improved PFS as first-line treatment for HR+ ABC (HR = 0.54, 95% CI 0.41–0.72; \( P = 0.000021 \)).[43] The updated secondary endpoint ORR was also higher in the abemaciclib arm (61.0% vs. 45.5%, \( P = 0.003 \)).[44]

Daily Abemaciclib is responsible for a lower rate of neutropenia than ribociclib and palbociclib gave on a 3-weeks-on and 1-week-off schedule, whereas results in a higher rate of diarrhea, which may due to its higher affinity for CDK4 than CDK6. The differences in the toxicity profiles and dosing schedules among these three agents should be taken into account for deciding treatment strategies.[45]

**Mechanisms of CDK4/6 inhibitor resistance**

Despite the superiority of CDK4/6 inhibitors in treating HR+ patients, 20% of patients exhibited intrinsic resistance (PFS less than 6 months) and the majority recurred within 2 years after beginning treatment.[46] The molecular mechanisms of acquired resistance to CDK4/6 inhibitors are largely based on cell line models, including loss of Rb, increased activity of CDK2 and CDK6, and upregulation of alternated pathways such as PI3K/AKT signaling.[47,48] Preclinical studies have observed that the loss and mutation of Rb is associated with less sensitivity to CDK4/6 inhibitors, as E2F transcription factors are released bypassing the Rb-induced brake irrespective of CDK4/6 status.[49,50] In the clinical setting, somatic Rb mutations, though rare in luminal BC, were detected in cfDNA samples from several patients with disease progression following treatment of palbociclib or ribociclib. These mutations are thought to emerge during the development of resistance.[51] Besides, the combination of cyclin E and CDK2 is also able to phosphorylate Rb, reduce the inhibition of E2F and further promote the
transition from G1 to S phase, suggesting the potential of cyclin E or CDK2 to subvert CDK4/6 inhibition.\textsuperscript{[72]} Herrera-Abreu et al\textsuperscript{[69]} confirmed the amplification of CCNE1 (which encodes for cyclin E1) and increased expression of cyclin E1 in a palbociclib-resistant model. Moreover, knockdown of either CDK2 or CCNE1 in combination with palbociclib significantly enhanced cell cycle arrest in resistant cells, indicating that activation of cyclin E-CDK2 complex is involved in the bypass of CDK4/6 inhibition. Recently, a retrospective gene expression analysis of tumor samples from PALOMA-3 was designed to explore predictive biomarkers for the benefit of fulvestrant plus palbociclib.\textsuperscript{[73]} The results showed that patients with high levels of CCNE1 mRNA had a median PFS of 7.6 months with palbociclib plus fulvestrant, compared to 4.0 months when treated with placebo plus fulvestrant (HR = 0.85, 95% CI 0.58–1.26). In patients with lower CCNE1 expression, the median PFS was 14.1 months with palbociclib plus fulvestrant vs. 4.8 months with placebo plus fulvestrant (HR = 0.32, 95% CI 0.2–0.5; \( P = 0.0238 \)). In another study, Yang et al\textsuperscript{[74]} investigated the resistant clones after exposure to abemaciclib and found gene amplification of CDK6 with reduced sensitivity to abemaciclib, while knockdown of CDK6 increased drug sensitivity. Furthermore, CDK6 overexpression led to lower expression of ER and diminished responsiveness to antihormones. However, the biomarker analysis in PALOMA-2 showed no correlation between CDK4 or CDK6 expression and the efficacy of palbociclib plus letrozole.\textsuperscript{[73]} Since the CDK4/6-Rb-E2F axis is in charge of growth regulation, other alternate signaling pathways can be upregulated to acquire resistance to CDK4/6 inhibitors.\textsuperscript{[75]} Jansen et al\textsuperscript{[67]} identified the 3-phosphoinositide-dependent protein kinase 1 (PDK1), which is implicated in PI3K/ Akt pathway, was highly expressed together with increased levels of phospho-S477/T479 Akt in ribociclib-resistant cells. Pharmacological and genetic inhibition of PDK1 in combination with one CDK4/6 inhibitor restored the sensitivity of cells to ribociclib. PI3K hyperactivation results from endocrine resistance is partly mediated via ligand-independent interaction of ER with CDK4.\textsuperscript{[76]} In addition, amplification of fibroblast growth factor receptor (FGFR)1, mutations of FGFR2, and upregulation of MYC have been found in cell line models of breast and colorectal cancer.\textsuperscript{[77–79]} Based on these investigations, multiple preclinical studies have demonstrated combinations of CDK4/6 inhibitor and PI3K or mTOR inhibitors were more effective in ER+ BC models.\textsuperscript{[69,80,81]}

**mTOR inhibitors**

mTOR is a serine-threonine kinase, a downstream effector of PI3K/AKT signaling pathway, which comprised two separate protein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 relays signals following PI3K/AKT pathway activation and regulates protein synthesis by phosphorylating the ribosomal S6 protein and eukaryotic initiation factor 4B, while mTORC2 contributes to AKT phosphorylation on serine 473 and controls the cellular actin cytoskeleton.\textsuperscript{[82]} Everolimus is a rapamycin analog that binds the intracellular FK506-binding protein 12 (FKBP-12). The everolimus-FKBP-12 complex interacts with mTORC1 and inhibits mTOR signaling.\textsuperscript{[83]} Since PI3K/mTOR pathway is a crucial mediator of cell growth and survival, everolimus that targets mTORC1 represents a possible treatment option for HR+/HER2- ABC.

The BOLERO-2 trial involved patients who had recurrence or progression on previous nonsteroidal AIs. The primary endpoint PFS was met with the advantage for the everolimus plus exemestane.\textsuperscript{[84,85]} Similar safety and efficacy were also demonstrated among the Asian population.\textsuperscript{[86]} However, the combination group did not indicate a statistically significant improvement in OS vs. the placebo group despite the increased toxicity.\textsuperscript{[87]} An exploratory analysis showed that everolimus efficacy was maintained irrespective of genetic alteration of PI3KCA, CCND1, and FGFR1. Genetic status in specific PIK3CA exons (exon 20 vs. 9), as well as different degrees of chromosomal instability, were associated with quantitative differences in PFS benefit with everolimus.\textsuperscript{[88]} Further study in the phase IIb BALLET trial found no difference in AEs between two groups.\textsuperscript{[89]} As stomatitis being the most frequent AE during treatment with everolimus, the phase II, single-arm SWISH trial demonstrated that prophylactic use of dexamethasone mouthwash attenuated the severity of stomatitis.\textsuperscript{[90]}

Another oral mTOR inhibitor temsirolimus was evaluated as first-line therapy in the HORIZON study. There was no improvement in PFS between letrozole/temsirolimus and letrozole/placebo.\textsuperscript{[91]} Recently, vistusertib, a dual inhibitor of mTORC1 and mTORC2, was tested in phase II randomized MANTA trial, assigning 333 postmenopausal women who had failed prior AIs 2:3:3:2 randomly to four arms: fulvestrant alone, fulvestrant plus vistusertib at an intermittent dose, or fulvestrant plus everolimus compared with fulvestrant plus everolimus. The results showed significantly improved PFS in fulvestrant plus everolimus compared with fulvestrant plus daily vistusertib (12.3 months vs. 7.6 months; \( P < 0.01 \)), as well as in fulvestrant plus everolimus compared with fulvestrant alone (12.3 months vs. 5.4 months; \( P = 0.02 \)).\textsuperscript{[92]}

**PI3K inhibitors**

PI3K is activated when coupled to receptor tyrosine kinases (RTKs) such as HER2, epidermal growth factor receptor (EGFR), and IGR-1. Activated PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to produce phosphatidylinositol-3,4,5-trisphosphate (PIP3), which subsequently activates AKT and regulates cell cycle entry, apoptosis and glucose metabolism. AKT also activates mTORC1 that regulates protein synthesis.\textsuperscript{[93]} Constitutive activation of phosphoinositide-3-kinase (PI3K) mostly results from activating mutation or amplification of PIK3CA, the gene that encodes the p110α catalytic subunit of PI3K.\textsuperscript{[85]} Current therapeutic agents targeting mutation associated with endocrine resistance emerge from clinical trials, including pan- (buparlisib) and isoform-specific PI3K inhibitor (taselisib, alpelisib).

Buparlisib, an oral pan-PI3K inhibitor, was assessed for efficacy and safety combined with fulvestrant in the BELLE
trials. The results of BELLE-2 study showed that the addition of buparlisib to fulvestrant significantly increased PFS (6.9 months [95% CI 6.8–7.8] vs. 5.0 months [95% CI 4.0–5.2], \( P = .00021 \)) in postmenopausal women with AI-resistant, HR-positive and HER2-negative ABC. And patients with PIK3CA mutations derived benefit from PI3K-targeted treatment on retrospective analysis of ctDNA.\(^{[94]}\) Recently, OS results from BELLE-2 showed no statistical significance between these two groups whatever PI3K pathway status, however, there is more frequent grade III/IV AEs in the buparlisib arm.\(^{[95]}\) To study further, the BELLE-3 recruited patients who had relapsed on or after ET and mTOR inhibitors. Consistent with the results of BELLE-2, significantly improved median PFS was showed in the buparlisib group compared to the placebo group (3.9 months vs. 1.8 months, \( P = 0.0030 \)). However, the toxicity profile does not support the development of this drug.\(^{[96]}\)

Taselisib is a potent and oral PI3K inhibitor with greater selectivity for mutant PIK3Kα encoded by PIK3CA and has been investigated in the SANDPIPER phase III trial. Patients with PIK3CA mutated tumors who experienced progression on an AI were assigned 2:1 to taselisib plus fulvestrant or placebo plus fulvestrant. The exploratory arm enrolled patients who had wild type tumors. In the mutated arms, PFS was significantly improved in the taselisib group compared to the placebo group (7.4 vs. 5.4 months, HR = 0.70, \( P = 0.0037 \)), while no difference was seen in the wild type arm with the small sample size. Approximately, 15% patients in the investigational arm stopped treatment due to grade 3 or 4 AEs, including diarrhea, hyperglycemia, and colitis.\(^{[97]}\)

Alpelisib is another α isoform-specific PI3K inhibitor which showed synergistic with fulvestrant in HR+/HER2- ABC in patients who progressed on or followed treatment with AIs. In the cohort of patients with PIK3CA-mutated cancer, PFS at a median follow-up of 20 months was 11.0 months (95% CI 7.5–14.5) in the alpelisib plus fulvestrant group vs. 5.7 months (95% CI 3.7–7.4) in the placebo plus fulvestrant group (HR for progression or death, 0.65, 95% CI 0.50–0.85; \( P < 0.001 \)). The most frequent AEs of grade 3 or 4 were hyperglycemia (36.6% vs. 0.7%), rash (9.9% vs. 0.3%), and diarrhea (6.7% vs. 0.3%).\(^{[98]}\)

**Histone deacetylase inhibitors**

In addition to genetic alterations, epigenetic processes including histone modifications are involved in the development of tumor drug resistance.\(^{[100,101]}\) HDACs, accompanied by histone acetyltransferases (HATs), are correlated to chromatin remodeling and transcription regulation by changing the status of histone acetylation. Histone acetylation makes chromatin more relaxed and facilitates gene transcription while deacetylation induces chromatin condensation and represses gene transcription.\(^{[102]}\) With the great impact on epigenetic, aberrant activity of HDACs has been demonstrated in breast cancer. Muller et al.\(^{[103]}\) found that HDAC1 was highly increased in HR+ tumors, whereas HDAC2 and HDAC3 were correlated to HR- tumors with features of more aggressiveness. Moreover, HDACs are recruited abnormally to ERα-target genes and eventually leads to endocrine resistance, which resulting from the loss of any of ERα corepressors including NCoR, SMRT, SPEN, and C Oprah-Tof.\(^{[104]}\) HDAC inhibitors are expected to become anticancer therapeutics in HR+ ABC and means to overcome endocrine resistance based on results of laboratory researches in cell lines,\(^{[105]}\) and several trials have evaluated the role of them taking safety and efficacy into account.

Eninostat (MS-275) is an oral synthetic benzamide derivative HDAC inhibitor which selectively and potently inhibits class I and IV HDAC enzymes. The results of phase II ENCORE 301 study showed improved PFS and OS in the eninostat/exemestane arm compared with exemestane alone\(^{[106]}\) The follow-up randomized phase III E2112 trial has completed accrual to assess the role of eninostat plus exemestane in premenopausal and postmenopausal patients with recurrent HR+/HER2- ABC.\(^{[107]}\) On October 25, 2018, a press release by the sponsor declared that the trial failed to meet its statistical co-primary endpoint of improved PFS.\(^{[108]}\) However, the other co-primary endpoint OS which has not been reported is needed sorely to draw firm conclusion. A randomized phase III trial NCT0338131 is ongoing to compare the clinical benefit of treatment with eninostat and exemestane with that of exemestane alone among Chinese patients with HR+ HER2- advanced BC who progressed on prior a nonsteroidal AI. The primary endpoint is PFS; secondary outcomes include OS, ORR, safety, and tolerability.

Chidamide (tucidinostat) is another oral subtype-selective benzamide class of HDAC inhibitor approved in China, which can selectively inhibit HADC1, 2, 3, and 10 enzymes.\(^{[109]}\) In phase III ACE study, 365 patients who failed ET were randomly assigned 2:1 to receive chidamide 30 mg twice weekly or placebo in combination with exemestane 25 mg daily. The primary endpoint PFS is significantly improved in the chidamide group compared to placebo (median 7.4 months vs. 3.8 months, \( P = 0.0336 \)), while the final OS is not yet available. The most common grade 3 or 4 AEs were neutropenia, thrombocytopenia, and leukopenia in the chidamide group.\(^{[110]}\) This study is in support of the safety and efficacy of chidamide for the therapy of BC among the Chinese population.

**Conclusions**

Based on clinical trials and studies discussed above, although no international consensus has been made on the optimal sequence of treatment for HR+/HER2- ABC patients, ET alone, including tamoxifen, AIs or fulvestrant, is the preferred initial option for selected patients without visceral crisis or concern of endocrine resistance, as well as for pre-/peri-menopausal women after adequate ovarian suppression. AI is considered superior to tamoxifen, and fulvestrant is a better choice for patients who have previously received ET or those with ESR1 mutations. If prior adjuvant tamoxifen was used in pre-/peri-menopausal women, then AI or fulvestrant could be chosen with
ovarian suppression. And if prior adjuvant AI was used, fulvestrant is then a considerable choice.

So far, with the in-depth understanding of the mechanisms of endocrine drug resistance, a series of new targeted drugs have been developed. With proven efficacy, CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) and mTOR inhibitor (everolimus) have been approved and recommended by clinical guidelines. CDK4/6 inhibitors, combined with AIs (with or without ovarian suppression), can be suggested in the first-line setting, with CDK4/6 inhibitors plus fulvestrant used in patients who progressed within 12 months from adjuvant AI treatment or those with ESR1 mutations. The selection of first-line therapy would be impacted by prior adjuvant therapy, individual patient toxicity, availability or access to drugs. In the second-line setting and beyond, CDK4/6 inhibitors should be included if these were not used in the first-line setting, and fulvestrant plays an important role in this regard. The mTOR inhibitor everolimus plus exemestane remains a reasoned second/third line selection after progression on ET (tamoxifen/AIs/fulvestrant with or without CDK4/6 inhibitors). To date, only palbociclib combined with AIs has been approved by the State Food and Drug Administration (SFDA) of China for treating postmenopausal patients in the first-line setting. It is worth noting, for example, the hematological toxicity associated with the use of CDK4/6 inhibitors as well as the management of mucositis when using everolimus. Besides, PI3K inhibitors provide another promising option of treatment in combination with fulvestrant for PIK3CA-mutated patients before giving up on ET. Other promising new drugs, such as HDAC inhibitors, AKT inhibitors, FGFR inhibitors, and immune checkpoint inhibitors, are also investigated in clinical trials. The clinical application of these drugs has greatly improved the therapeutic effect and constantly changed clinical practice. Further studies should continue to explore predictive biomarkers, identify optimal sequence of all available treatments and explore new targeted therapy drugs, in order to overcome endocrine resistance, to make different drugs play a synergistic antitumor effect, and finally, to improve outcomes and quality of life of HR+/HER2- ABC patients.

Conflicts of interest
None.

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