Endocrine therapy combined with targeted therapy in hormone receptor-positive metastatic breast cancer

Li Bian, Feng-Rui Xu, Ze-Fei Jiang

Department of Breast Oncology, The Fifth Medical Center of Chinese PLA General Hospital, Beijing 100071, China.

Abstract
Increasing numbers of targeted drugs are used in hormone receptor (HR)-positive metastatic breast cancer (MBC) to overcome or delay resistance to endocrine therapy. This study will systemically review the progress made in endocrine therapy combined with targeted therapy in the treatment of HR-positive MBC. From the “AI (aromatase inhibitor) era” represented by aromatase inhibitors, we have gradually entered the “post-AI era” represented by fulvestrant. Under the guidance of research on the molecular mechanism of endocrine therapy resistance, the “combination of endocrine therapy and targeted therapy” era is approaching. The development of drugs that target endocrine therapy resistance has concentrated on cyclin-dependent kinase 4/6 inhibitors, histone deacetylase inhibitors, and inhibitors of drug targets in the phosphatidylinositol 3 kinase-protein kinase B-mammalian target of rapamycin (PI3K-AKT-mTOR) pathway, providing new strategies for HR-positive MBC. Exploring biomarkers to guide the more precise use of targeted drugs in endocrine therapy for MBC is the focus of current and future research.

Keywords: Endocrine therapy; Hormone receptor positive; Metastatic breast cancer; Targeted therapy

Introduction
At present, the classification of breast cancer treatment is based on molecular typing. Hormone receptor (HR)-positive (estrogen receptor-positive and/or progesterone receptor-positive) subgroup accounts for approximately 70% of all breast cancer patients, and endocrine therapy is an important treatment for HR-positive metastatic breast cancer (MBC). From the “aromatase inhibitor (AI) era,” we have gradually entered the “post-AI era” represented by fulvestrant.

With the wide application of endocrine therapy, patients who have progressed during treatment may have resistance to these treatments. In recent years, multiple molecular mechanisms of endocrine therapy resistance have been explored, and consequently many targeted drugs were developed to overcome or delay resistance to endocrine therapy. Thus, the “endocrine therapy plus” pattern of endocrine therapy combined with targeted drugs is now on the horizon.

The development of targeted drugs has focused on cyclin-dependent kinase (CDK) 4/6 inhibitors, histone deacetylase (HDAC) inhibitors, and inhibitors targeting components of the phosphatidylinositol 3 kinase-protein kinase B-mammalian target of rapamycin (PI3K-AKT-mTOR) pathway. Many clinical trials of these targeted drugs plus endocrine therapy have been undertaken worldwide to explore new strategies to overcome or delay resistance to endocrine therapy and improve clinical efficacy. This article reviews the progress made in endocrine therapy combined with targeted drugs in HR-positive MBC.

Progression of Endocrine Therapy for Metastatic Breast Cancer
Fulvestrant is a potent estrogen receptor antagonist. With the widespread application of selective estrogen receptor modulators and AI drugs in adjuvant therapy, fulvestrant has an important role in endocrine therapy for HR-positive MBC.

The Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) study (phase III) validated that the survival of patients with advanced breast cancer (ABC) was significantly improved by fulvestrant 500 mg compared with fulvestrant 250 mg.[1] The China CONFIRM study (phase III) also substantiated the efficacy of fulvestrant 500 mg in Chinese patients.[2] The Fulvestrant First-Line Study Comparing Endocrine Treatments (FIRST) (phase II)[3] and Fulvestrant

Access this article online

Quick Response Code: Website: www.cmj.org
DOI: 10.1097/CM9.0000000000000923

Chinese Medical Journal 2020;133(19)
Received: 05-05-2020 Edited by: Qiang Shi
and Anastrozole Compared in Hormonal Therapy Naive Advanced Breast Cancer (FALCON) (phase III) studies confirmed the advantages of fulvestrant as a first-line endocrine therapy in ABC. These two studies compared fulvestrant 500 mg vs. anastrozole for first-line endocrine therapy of post-menopausal MBC and revealed that fulvestrant significantly improved the progression-free survival (PFS) of patients, with a median time to progression of 23.4 months vs. 13.1 months (hazard ratio [HR] = 0.66; P = 0.01) in the FIRST study and a median PFS 16.6 months vs. 13.8 months (HR = 0.79; P = 0.048) in the FALCON study.

The incidence of young breast cancer is high in China. However, for pre-menopausal patients with HR-positive MBC, the evidence from high-level clinical studies of first-line endocrine therapy is lacking. The treatment strategies for this subgroup of patients in the guidelines of the Chinese Society of Clinical Oncology state that effective measures should be taken to suppress ovarian function, including drug-induced suppression (goserelin/leuprorelin) or ovariectomy, and that endocrine therapy guidelines should then be followed for post-menopausal patients. The phase II, randomized, open-label, multicenter study of goserelin plus fulvestrant compared with goserelin plus anastrozole (PROOF) study (phase II) compared fulvestrant 500 mg combined with goserelin vs. anastrozole combined with goserelin as first-line endocrine therapy in Chinese pre-menopausal women with HR-positive ABC. The primary endpoint was PFS. In total, 262 cases were included in the study, and the study was close to the time point of the initial analysis.

Molecular Mechanisms of Endocrine Therapy Resistance

Various molecular pathways can lead to estrogen-independent sustained activation of estrogen receptors, thus rendering patients resistant to traditional endocrine drugs. These molecular pathways mainly include: (1) interactions between the cyclin D-CDK4/6-retinoblastoma (Rb) pathway and the estrogen pathway; (2) epigenetic abnormalities modified by HDACs; (3) acquired mutation of ESR1; (4) amplification or mutation of the growth factor receptor tyrosine kinase family; and (5) abnormal cellular microenvironment and immune response.

Studies on the molecular mechanisms of endocrine therapy resistance promoted the development of drugs targeting these molecular pathways/targets. In terms of therapeutic principle, these drugs are not able to reverse drug resistance, rather, they are expected to restore sensitivity to endocrine therapy by inhibiting the pathways/targets that lead to drug resistance. The main approved targeted drugs or those currently in the research phase, as well as the related clinical trials, are presented in Table 1.

Advances in Endocrine Therapy Combined with Targeted Drugs

CDK4/6 inhibitors

CDKs belong to the serine/threonine protein kinase family and are critical kinases involved in cell cycle regulation. CDK4/6 is a crucial regulator of the cell cycle and forms complexes with cyclin D, which phosphorylates Rb to promote the release of EZF transcription factor, which upregulates the transcription of cell cycle-related genes and enables cells to enter S phase. However, CDK4/6 inhibitors can effectively block the progression of cancer cells from G1 phase to S phase. Double suppression of CDK4/6 and ER signals has a synergistic effect in HR-positive breast cancer, and can restore cell cycle control and block the proliferation of breast cancer cells [Table 2].

Since 2015, CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) have been shown to be effective in the PALOMA, MONALEESA, and MONARCH trials, identifying a new treatment pattern for HR-positive advanced breast cancer. These studies began with CDK4/6 inhibitors combined with AI for first-line therapy and progressed to CDK4/6 inhibitors combined with fulvestrant for patients who underwent AI therapy.

Table 1: Targeted drugs and clinical trials in endocrine therapy for HR-positive MBC.

| Drugs               | Pathways/targets                                                                 | Main clinical trials                                                                 |
|---------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| CDK4/6 inhibitor    | Suppression of interaction between CyclinD/CDK4/6/Rb pathway and estrogen pathway | PALOMA[17,9,17-20], MONALEESA[10,11,13,14,16], and MONARCH[12,21] and ACE[27,28] |
| HDAC inhibitor      | Suppression of epigenetic abnormalities in HDAC modification                      |                                                                                      |
| PI3K inhibitor      | Inhibiting activation of PI3K-AKT-mTOR pathway                                   | BELLE-2[29], SANDPIPER[30], and SOLAR-1[31]                                           |
| AKT inhibitor       | Inhibiting activation of PI3K-AKT-mTOR pathway                                   | FAKTION[32]                                                                         |
| mTOR inhibitor      | Inhibiting activation of PI3K-AKT-mTOR pathway                                   | BOLOERO-2[33,34], PECOGO102[35]                                                     |
| FGFR inhibitor      | Inhibiting amplification or mutation of growth factor receptor tyrosine kinase family | Dovitinib II phase[37], and Lucitanib (E-3810) I/IIa phase[38]                         |
| IGF-1R inhibitor    | Inhibiting IGF-1R signaling pathway activation                                    | Ganitumab II phase[39], CALGB40503[40], LEA[41]                                     |
| VEGFR inhibitor     | Inhibiting the binding of vascular endothelial growth factor receptor to VEGF     |                                                                                      |

CDK4/6: Cyclin-dependent kinase; Rb: Retinoblastoma; HDAC: Histone deacetylase; PI3K: Phosphatidylinositol 3 kinase; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; VEGFR: Vascular endothelial growth factor receptor; FGFR: Fibroblast growth factor receptor; IGF-1R: Insulin-like growth factor-1 receptor; HR: Hormone receptor; MBC: Metastatic breast cancer.
Table 2: Summary of main clinical trials including CDK4/6 inhibitors.

| Clinical trials | Drugs | Phase | Post- or pre-menopausal | N   | T   | C   | P     | T   | C   | P     | OS (months) |
|-----------------|-------|-------|-------------------------|-----|-----|-----|-------|-----|-----|-------|-------------|
| PALOMA-1        | Letrozole +/- Fulbo | II    | Post                     | 165 | 55  | 39  | 0.047 | 20.2 | 10.2 | 0.0004 | 37.5  | 33.3 | 0.42 |
| PALOMA-2        | Letrozole +/- Fulbo | III   | Post                     | 666 | 55.3| 34.4| 0.03  | 27.6 | 14.5 | <0.0001| –     | –    | –   |
| MONALEESA-2     | Letrozole +/- Riboto | III   | Post                     | 668 | 52.7| 47.3| <0.001| 23.3 | 16.0 | 9.63 x 10^-4 | –    | –    | –   |
| MONARCH-3       | NSAI +/- Abema | III   | Post                     | 493 | 59  | 44  | 0.004 | 28.1 | 14.7 | 0.00021 | –    | –    | –   |
| MONALEESA-7     | Endo +/- Fulbo | III   | Pre                      | 672 | 51  | 36  | 0.00032| 23.8 | 13.0 | <0.0001| Not  | 40.9 | 0.00973 |
| MONALEESA-3     | Fulvestrant +/- Riboto | III   | Post                     | 726 | 40.9| 28.7| 0.003 | 20.5 | 12.8 | <0.001 | –    | –    | –   |
| MONARCH-2       | Fulvestrant +/- Abema | III   | Post and pre            | 521 | 25  | 11  | 0.0012| 9.5  | 4.6  | <0.0001 | 34.9 | 28.0 | 0.09 |
| MONARCHplus     | NSAI +/- Abema (cohort A) | III   | Post                     | 463 | –   | –   | –     | A: not| 14.7 | 9.63 x 10^-4 | –    | –    | –   |
| MONARCHplus     | NSAI +/- Abema (cohort B) | III   | Post                     | 157 | –   | –   | –     | B: reached| 5.6  | <0.0001 | –    | –    | –   |

– = Not applicable; ORR: Overall response rate; PFS: Progression-free survival; OS: Overall survival; C: Control group; T: Test group; NSAI: Non-steroidal aromatase inhibitor; OFS: Ovarian function suppression; Abema: Abemaciclib; Endo: Endocrine therapy; Fulbo: Fulbociclib; Riboto: Ribociclib.

CDK4/6 inhibitors combined with aromatase inhibitors

Palbociclib is the first CDK4/6 inhibitor to be approved for use since 2015. Similar results were obtained in the PALOMA-1 study (phase II) and the subsequent PALOMA-2 study (phase III). In the PALOMA-2 study, post-menopausal patients who had previously undergone endocrine therapy but who were not resistant to AI received palbociclib plus letrozole vs. placebo plus letrozole. The results demonstrated a significant improvement in PFS with palbociclib plus letrozole vs. placebo plus letrozole (median 27.6 vs. 14.5 months; HR = 0.563; P < 0.001). Subsequently, the results of MONALEESA-2 and MONARCH-3 were similar to those of PALOMA-2, demonstrating that the efficacy of ribociclib or abemaciclib combined with an AI was significantly improved compared with that of AI alone.

In the MONALEESA-7 study (phase III), CDK4/6 inhibitor was first applied to pre-menopausal HR-positive ABC. The results showed median PFS was 23.8 months in the ribociclib + tamoxifen or non-steroidal AI (NSAI) + goserelin group compared with 13.0 months in the placebo + tamoxifen or NSAI + goserelin group (HR = 0.55; 95% confidence interval [CI] 0.44–0.69; P < 0.0001). This confirmed that pre-menopausal patients, on the premise of ovarian function suppression, ribociclib combined with endocrine treatment as first-line therapy could also achieve the same efficacy as that in post-menopausal patients. The results of overall survival (OS) were further reported at the American Society of Clinical Oncology (ASCO) meeting in 2019 and demonstrated that the ribociclib group had significantly prolonged OS and reduced risk of death by 29% compared with the placebo group (not reached vs. 40.9 months; HR = 0.712; P = 0.00973).

CDK4/6 inhibitors combined with fulvestrant

The treatment of HR-positive advanced breast cancer with CDK4/6 inhibitors combined with fulvestrant was mainly studied in PALOMA-3, MONARCH-2, and MONALEESA-3. The results of these studies suggested CDK4/6 inhibitors combined with fulvestrant are the ideal choice for first- or second-line treatment of post-menopausal patients with HR-positive advanced breast cancer. The enrolled populations of the three studies were slightly different. The PALOMA-3 and MONARCH-2 studies included patients who had previously failed on endocrine therapy, but in the MONALEESA-3 study, patients who were treatment naive or had received up to one line of prior endocrine therapy in advanced stage were evaluated.

The MONALEESA-3 study (phase III) demonstrated significantly improved PFS with ribociclib plus fulvestrant, with a treatment benefit observed irrespective of prior endocrine therapy for advanced disease. Median PFS was 20.5 months (95% CI 18.5–23.5 months) for ribociclib plus fulvestrant vs. 12.8 months (95% CI 10.9–16.3 months) for placebo plus fulvestrant (HR = 0.593; P < 0.001). The results of the MONALEESA-3 study (phase III) had a wider enrolled population, recruiting patients who had received chemotherapy less than or equal to one line or who had received more than one line of endocrine therapy in the advanced stage. The results showed that the median PFS was 9.5 months for palbociclib plus fulvestrant and 4.6 months for placebo plus fulvestrant (HR = 0.497; P < 0.0001).
Among patients with sensitivity to previous endocrine therapy, the median OS was 39.7 months (95% CI 34.8–43.7 months) vs. 29.7 months (95% CI 23.8–37.9 months) (HR = 0.72; absolute difference, 10.0 months). The MONARCH-2 study (phase III) restricted advanced-stage patients from receiving chemotherapy, and thus PFS was longer than that in PALOMA-3. Abemaciclib plus fulvestrant significantly extended PFS vs. fulvestrant alone (median, 16.4 vs. 9.3 months; HR = 0.553; P < 0.001). The MONARCH plus study is a multi-center phase III research led by Chinese experts, with participation by international experts and patients. The main population is Chinese patients, covering two different subgroups of patients. It evaluated the efficacy and safety of abemaciclib plus a NSAI (Cohort A: initial endocrine therapy) and abemaciclib plus fulvestrant (Cohort B: progress in endocrine therapy) in HR-positive MBC. The interim results showed that median PFS was still not reached for abemaciclib plus NSAI (95% CI 22.3 months–not reached) and 14.7 months for placebo plus NSAI in Cohort A (HR = 0.499; P = 0.0001), which suggested that the PFS of abemaciclib therapy has a significant advantage. Median PFS was 11.4 months for abemaciclib plus fulvestrant and 5.6 months for placebo plus fulvestrant in Cohort B (HR = 0.376; P < 0.0001), which also suggested the PFS advantage of abemaciclib therapy.

Histone deacetylase inhibitors

HDACs have important roles in regulating gene expression and modifying chromosome structure. Aberrant gene expression due to epigenetic alterations modified by HDACs correlates with disease progression and resistance to endocrine therapy in breast cancers.[22,23] Epigenetic alterations can be modulated or reversed by HDAC inhibitors.[24] Tucidinostat (formerly known as chidamide) is an oral subtype-specific HDAC inhibitor that was independently developed in China and induces cell cycle arrest, differentiation, and death in cancer cells to alter the tumor microenvironment. At the same time, it enhances tumor immune response via activation of cellular anti-tumor immunity. Tucidinostat down-regulates estrogen-independent growth factor signaling pathways and restores sensitivity to anti-estrogen agents.[25,26]

The ACE study was a randomized, double-blind, placebo-controlled, phase III clinical trial that explored the efficacy and safety of tucidinostat plus exemestane in post-menopausal patients with HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who had failed on tamoxifen and/or NSABs.[27] It is the first phase III clinical trial of HDAC inhibitors in patients with previous endocrine therapy failure and is a major advance in the field of breast cancer therapy by epigenetic regulation. In total, 365 patients who had received at least one endocrine therapy were randomly assigned (2:1) to receive tucidinostat plus exemestane or placebo plus exemestane. After a median follow-up of 13.9 months, median PFS was 7.4 months (95% CI 5.5–9.2 months) in the tucidinostat plus exemestane group and 3.8 months (95% CI 3.7–5.5 months) in the placebo plus exemestane group (HR = 0.75; 95% CI 0.58–0.98; P = 0.033). The overall response rate (ORR) was 18.4% vs. 9.1% and the clinical benefit rate (CBR) was 46.7% vs. 35.5%, respectively, in the two groups. Data for OS were not mature at the efficacy cutoff date. Adverse events were more common with the combination of tucidinostat and exemestane than with placebo plus exemestane, but most of them could be controlled through supportive treatment. Tucidinostat plus exemestane could be a new treatment option for HR-positive MBC populations who have failed on endocrine therapy.

The ACE study has been appraised in Lancet Oncology,[28] and the results of this trial represent an important step in the development of epigenetic therapy for endocrine therapy-resistant breast cancer. The results of Jiang et al provided important insights into the potential of epigenetic targeting to overcome anti-estrogen resistance. HDAC inhibitors could emerge as a new therapeutic tool in the rapidly evolving landscape of targeted therapies for HR-positive MBC.

PI3K/AKT/mTOR pathway target inhibitors

PI3K inhibitors

PI3K gene mutations are closely related to tumor proliferation and metastasis. PIK3CA mutations occur in approximately 40% of patients with HR-positive HER2-negative breast cancer. Pre-clinical studies showed that inhibition of PI3K signaling leads to adaptive activation of the ER pathway, thus overcoming endocrine resistance. At present, PI3K inhibitors mainly include pan-PI3K inhibitors (pictilisib and buparlisib) and selective PI3Kα inhibitors (alpelisib and taselisib).

The BELLE-2 study (phase III) met its primary endpoint for significant improvement in PFS with buparlisib plus fulvestrant vs. placebo plus fulvestrant in an HR-positive MBC population.[29] Median PFS was 6.9 months (95% CI 6.8–7.8) vs. 5.0 months (95% CI 4.0–5.2; HR = 0.78; P = 0.00021). A significant difference in PFS in the buparlisib group vs. the placebo group was recorded in patients with circulating tumor DNA (ctDNA) PIK3CA mutations, and median PFS was 7.0 months vs. 3.2 months (HR = 0.58; P = 0.001). The OS results were not statistically significant, and the incidence of level 3/4 adverse events was high, thus the use of buparlisib in clinical practice should be considered with caution.

Alpelisib and taselisib, as specific PI3Kα inhibitors, have stronger inhibition and lower incidence of adverse events than buparlisib. The SANDPIPER study (phase III) investigated taselisib plus fulvestrant vs. placebo plus fulvestrant in HR+/HER2– ABC patients with PIK3CA mutation.[30] The investigator assessed median PFS was significantly longer in patients treated with taselisib (7.4 months vs. 5.4 months; HR = 0.70; P < 0.01). But because of the modest PFS improvement at the cost of significant toxicity, taselisib will not be further developed.

In the SOLAR-1 study (phase III) conducted in a cohort of patients with PIK3CA-mutated cancer, PFS
was 11.0 months (95% CI 7.5–14.5) in the alpelisib plus fulvestrant group, compared with 5.7 months (95% CI 3.7–7.4) in the placebo plus fulvestrant group (HR = 0.65; 95% CI 0.50–0.85; \( P < 0.001 \)). Alpelisib is the first PI3K inhibitor to be approved by the Food and Drug Administration for HR-positive ABC patients with endocrine resistance, which was also accompanied by the approval of a gene detection kit.

**AKT inhibitors**

The PI3K/AKT signaling pathway is often activated in HR-positive breast cancer and has a correlation with endocrine therapy resistance. The results of the FAKTION study (phase II) investigating the AKT inhibitor capivasertib in HR+HER2− post-menopausal patients with ABC who have failed on previous AI treatment were presented at the ASCO meeting in 2019.\(^{[32]}\) The PFS of the capivasertib combined with fulvestrant group was significantly longer than that of the fulvestrant group (10.3 months vs. 4.8 months; HR = 0.57; 95% CI 0.39–0.84; one-sided \( P = 0.0017 \); two-sided \( P = 0.0035 \)). The secondary endpoint OS also showed an improvement trend (26.0 months vs. 20.0 months). The results of the FAKTION study support further phase III trials on the treatment of HR-positive MBC with capivasertib.

**mTOR inhibitors**

mTOR is a downstream target of the PI3K/AKT signaling pathway. The mTOR inhibitor everolimus was an early targeted drug for HR+HER2− MBC patients. The results of the BOLERO-2 study (phase III) showed that median PFS remained significantly longer with everolimus plus exemestane vs. placebo plus exemestane (investigator review: 7.8 months vs. 3.2 months; HR = 0.45; 95% CI 0.38–0.54; \( P < 0.0001 \); central review: 11.0 months vs. 4.1 months; HR = 0.38; 95% CI 0.31–0.48; \( P < 0.0001 \)).\(^{[33,34]}\) The addition of everolimus to exemestane markedly prolonged PFS in patients with HR-positive ABC with disease recurrence or progression following prior NSAI(s).

The subsequent PrECOG 0102 study (phase II) showed that the addition of everolimus to fulvestrant improved the median PFS from 5.1 to 10.3 months (HR = 0.61; 95% CI 0.40–0.92; \( P = 0.02 \)), indicating that the primary trial endpoint was met.\(^{[35]}\)

Especially worthy of attention, the results of SAFIRTOR study, which revealed that patients with high expression of p4EBP1 could obtain longer PFS (9.3 months vs. 5.8 months; \( P = 0.0221 \)) through treatment with everolimus and exemestane, were presented at the ASCO meeting in 2019.\(^{[36]}\) These observations indicated that we should actively screen for biomarkers related to the efficacy of targeted therapy, which can further optimize the application of targeted drugs.

**Other Targeted Drugs**

Studies of fibroblast growth factor receptor (FGFR), insulin-like growth factor-1 receptor (IGF-1R), and vascular endothelial growth factor receptor (VEGFR) inhibitors have also reported preliminary results, but because of the lack of critical phase III clinical trial data or the failure to achieve positive results, our clinical practice has not changed.

Dovitinib is an FGFR inhibitor. For the FGFR pathway-amplified subgroup (\( n = 31 \)), the median PFS was 10.9 months (3.5–16.5 months) vs. 5.5 months (3.5–16.4 months) for dovitinib plus fulvestrant vs. placebo plus fulvestrant (HR = 0.64; met the pre-defined superiority criteria) in a phase II clinical trial.\(^{[37]}\)

Lucitanib (E-3810) is an inhibitor against FGFR types 1 and 2, VEGFR types 1, 2, and 3, and PGR types α and β. In an open-label phase I/IIa study, ORR was 26% (seven of 27) and PFS was 25 weeks in the angiogenesis-sensitive group. In assessable FGFR-aberrant MBC patients, 50% (six of 12) achieved a RECIST partial response with a median PFS of 40.4 weeks.\(^{[38]}\)

Ganitumab is an inhibitor of IGF-1R. Addition of ganitumab to endocrine treatment (exemestane or fulvestrant) in patients with previously treated HR positive locally advanced or MBC did not improve outcomes in a phase II study.\(^{[39]}\) Thus, the results do not support further study of ganitumab in this subgroup of patients.

The CALGB 40503 study (phase III) investigated whether anti-vascular endothelial growth factor (VEGF) therapy with bevacizumab prolongs PFS when added to first line letrozole as treatment for HR-positive MBC. At a median follow-up of 39 months, the addition of bevacizumab resulted in the prolongation of median PFS from 15.6 months with letrozole to 20.2 months with letrozole plus bevacizumab (HR = 0.75; 95% CI 0.59–0.96; \( P = 0.016 \)). There was no significant difference in OS (HR = 0.87; 95% CI 0.65–1.18; \( P = 0.188 \)), with a median OS of 43.9 months with letrozole vs. 47.2 months with letrozole plus bevacizumab.\(^{[40]}\)

In the LEA study (phase III), median PFS was 14.4 months in the endocrine therapy arm and 19.3 months in the endocrine therapy plus bevacizumab arm (HR = 0.83; 95% CI 0.65–1.06; \( P = 0.126 \)). ORR and CBR were 22% vs. 41% (\( P < 0.001 \)) and 67% vs. 77% (\( P = 0.041 \)) respectively.\(^{[41]}\) Additional research is needed to further explore the value of combining VEGFR inhibitors with endocrine therapy in HR-positive breast cancer.

**Anti-HER2 Targeted Therapy Combined with Endocrine Therapy for HR-positive HER2-positive Metastatic Breast Cancer**

TANDEM is the first phase III study of endocrine therapy combined with trastuzumab in HR-positive HER2-positive MBC.\(^{[42]}\) In total, 103 patients received trastuzumab plus anastrozole and 104 received anastrozole alone. Patients in the trastuzumab plus anastrozole arm showed significant improvements in PFS compared with patients receiving anastrozole alone (HR = 0.63; 95% CI 0.47–0.84; median PFS 4.8 vs. 2.4 months; log-rank \( P = 0.0016 \)). The EGF 30008 trial evaluated the effect of the AI letrozole combined with lapatinib as first-line
treatment for HR-positive HER2-positive MBC. In 219 post-menopausal patients, the addition of lapatinib to letrozole significantly reduced the risk of disease progression vs. letrozole alone (HR = 0.71; 95% CI 0.53–0.96; P = 0.019); median PFS was 8.2 vs. 3.0 months. CBR was significantly higher for lapatinib plus letrozole vs. letrozole alone (48% vs. 29%; odds ratio [OR] = 0.4; 95% CI 0.2–0.8; P = 0.003). The above two trials showed that the combination of an AI and anti-HER2 targeted therapy significantly improved PFS compared with AI alone, but OS showed no statistically significant difference. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for breast cancer recommend that endocrine therapy (if pre-menopausal, ovarian ablation, or suppression should be considered) combined with anti-HER2 targeted therapy may be administered for HR-positive HER2-positive MBC. The guidelines of Chinese Society of Clinical Oncology for breast cancer advocate the combination of AIs and anti-HER2 targeted therapy for patients who are not suitable for chemotherapy or have slow progression. For patients with stable disease after anti-HER2 targeted therapy and chemotherapy, targeted therapy combined with AI maintenance therapy can be considered after chemotherapy is stopped.

The PERTAIN study assessed pertuzumab combined with trastuzumab plus AI as first-line therapy in patients with HER2-positive HR-positive metastatic/locally advanced breast cancer. In total, 258 patients were randomly assigned (129 per arm): 146 patients were selected to receive induction chemotherapy and 112 patients were not. Median PFS was 18.89 months (95% CI 14.09–27.66 months) in the pertuzumab plus trastuzumab arm and 15.8 months (95% CI 11.04–18.56 months) in the trastuzumab arm (HR = 0.65; 95% CI 0.48–0.89; P = 0.007).

The MonarcHER study compared the efficacy of trastuzumab combined with abemaciclib (CDK4/6 inhibitor) plus fulvestrant and trastuzumab combined with chemotherapy in HER2-positive HR-positive MBC. PFS (the primary endpoint of this study) results were published at the 2019 ESMO meeting. The median PFS was 8.32 months in the trastuzumab + abemaciclib + fulvestrant group, and 5.69 months in the trastuzumab + chemotherapy group. The ORR of the trastuzumab + abemaciclib + fulvestrant group was significantly higher than that of the trastuzumab + chemotherapy group (37.9% vs. 13.9%). It was suggested that the combination of CDK4/6 inhibitors with trastuzumab plus fulvestrant may further improve the efficacy, and the effect of this three-drug regimen is better than that of trastuzumab combined with conventional chemotherapy.

Conclusions

Endocrine therapy has entered a new era with the combination of endocrine drugs with targeted drugs for HR-positive MBC. The CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib, and the HDAC inhibitor tucidinostat have been approved for use in clinical therapy, while many drugs have achieved remarkable results in clinical trials, providing new ideas and strategies for the treatment of HR-positive advanced breast cancer.

For patients who are not resistant to NSAIIs, NSAI plus CDK4/6 inhibitor is an option for first-line treatment, and second-line application of steroidal AI exemestane plus tucidinostat after disease progression is suitable. However, for patients with NSAI resistance, exemestane plus tucidinostat can be selected as the first choice, and these patients can receive fulvestrant plus a CDK4/6 inhibitor after disease progression. We also can give priority to the use of fulvestrant plus a CDK4/6 inhibitor followed by exemestane plus tucidinostat [Figure 1].

In conclusion, in the field of endocrine therapy for MBC, the use of targeted drugs has significantly improved the clinical efficacy of endocrine therapy. Nonetheless, how to more precisely use targeted drugs requires further exploration. If we can identify the patient subgroups that are sensitive to targeted therapy, we can focus on the use of

![Figure 1: The new strategy in endocrine therapy for HR-positive MBC. CDK4/6: Cyclin-dependent kinase; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; MBC: Metastatic breast cancer; NSAI: Non-steroidal aromatase inhibitor.](image)
these drugs in endocrine therapy. To identify targeted treatment-sensitive populations, we need to explore biomarkers. Therefore, efficacy-related biomarkers are the focus of current and future research.

**Funding**

This work was supported by a grant from the Capital Clinical Feature Project of Beijing (No. Z181100001718215).

**Conflicts of interest**

None.

**References**

1. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanova R, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J Clin Oncol 2010;28:4594–4600. doi: 10.1200/JCO.2010.28.8415.
2. Zhang Q, Shao Z, Shen K, Li L, Feng J, Tong Z, et al. Fulvestrant 500 mg vs 250 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer: a randomized, double-blind registration trial. China. Oncotarget 2016;7:57301–57309. doi: 10.18632/oncotarget.10254.
3. Robertson JF, Lindemann JP, Lombar-Cussac A, Roški J, Felt D, Dewar J, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized ‘FIRST’ study. Breast Cancer Res Treat 2012;136:503–511. doi: 10.1007/s10549-012-1924-7.
4. Robertson JFR, Bondarenko IM, Trischina E, Dvorkin M, Panacci L, Markkola A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (PALOMA1); an international, randomised, double-blind, phase 3 trial. Lancet 2016;388:2997–3005. doi: 10.1016/S0140-6736(16)32893-9.
5. Sztotawskia M, Trinińska-Stryjeawska A, Gropybowska EA, Fabisiewicz A. Resistance to endocrine therapy in breast cancer: molecular mechanisms and future goals. Breast Cancer Res Treat 2019;173:489–497. doi: 10.1007/s10549-018-5023-4.
6. Goei S, DeCristo MJ, Watt AC, Brin-Jones H, Sceneay J, Li BB, et al. CDK4/6 inhibition triggers anti-tumourimmunity. Nature 2017;548:471–475. doi: 10.1038/nature23465.
7. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of estrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2017;18:2587–2594. doi: 10.1016/S1470-2045(17)32758-3.
8. Finn RS, Masarik M, Rugo HS, Jones S, Imm SA, Gelder K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375:1925–1936. doi: 10.1056/NEJMa1607303.
9. Rugo HS, Finn RS, Diéras V, Ettl J, Lipatov O, Joy AA, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer (PALOMA-1): a randomised phase 2 study. Lancet Oncol 2015;16:25–35. doi: 10.1016/S1470-2045(14)71193-9.
10. Finn RS, Masarik M, Rugo HS, Jones S, Imm SA, Gelder K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375:1925–1936. doi: 10.1056/NEJMa1607303.
11. Rugo HS, Finn RS, Diéras V, Ettl J, Lipatov O, Joy AA, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. Breast Cancer Res Treat 2019;174:719–729. doi: 10.1007/s10549-018-50123-4.
12. Hortobagyi GN, Stegger SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 2016;375:1738–1748. doi: 10.1056/NEJMo1609709.
13. Hortobagyi GN, Stegger SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol 2018;29:1541–1547. doi: 10.1093/annonc/mdy155.
14. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huerre J, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 2017;35:3638–3646. doi: 10.1200/JCO.2017.75.6155.
15. Tripathy D, Im SA, Colletti M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for postmenopausal women with hormone receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol 2018;19:904–915. doi: 10.1016/S1470-2045(18)30282-4.
16. Phase III MONALEESA-7 trial of premenopausal patients with HR+/HER2– advanced breast cancer (ABC) treated with endocrine therapy ± ribociclib: Overall survival (OS) results. (abstract LBA1008). Chicago: American Society of Clinical Oncology (ASCO) Annual Meeting, 2019. Available from: https://www.asco.org/search/site/Phase%20III%20MONALEESA-7%20trial%20in%20premenopausal%20patients%20with%20HR%2B%2F%20HER2%5C2B%2520advanced%20breast%20cancer%20%2B%2520ribociclib%20therapy. [Accessed May 19, 2020].
17. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425–439. doi: 10.1016/S1470-2045(15)00613-0.
18. Overall survival (OS) with palbociclib plus fulvestrant in women with hormone receptor-positive (HR+) humoral epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC): Analyses from PALOMA-3. (abstract LBA2-PR). Munich: European Society for Medical Oncology (ESMO) Meeting, 2018. Available from: https://cslide.citmeetingtech.com/esmo2018/attendee/confcal/session/calendar/1=4008/LBA2-PR. [Accessed May 19, 2020].
19. Turner NC, Slamon DJ, Ro J, Bondarenko I, Masuda N, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med 2018;379:1926–1936. doi: 10.1056/NEJMoa1810527.
20. Slade JW, Jr, Toi M, Nevin P, Sohn J, Inoue K, Pivot X, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017;35:3628–3637. doi: 10.1200/JCO.2017.75.6155.
21. Osborne CK, Schiff R. Mechanisms of estrogen resistance in breast cancer. Ann Rev Med 2011;62:233–247. doi: 10.1146/annurev-med-070909-182917.
22. Saxeena NK, Sharma D. Epigenetic reactivation of estrogen receptor: promising tools for restoring response to endocrine therapy. Mol Cell Pharmacol 2010;2:192–202.
23. Falkenberg KJ, Johnstone RW. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat Rev Drug Discov 2014;13:673–691. doi: 10.1038/nrd4360.
24. Ning QZ, Li ZB, Newman MJ, Shan S, Wang XH, Pan DS, et al. Chidamide (CS0353/BHI-8000): a new histone deacetylase inhibitor of the benzamide class with antitumour activity and the ability to enhance immunocell-mediated tumour cell cytotoxicity. Cancer Chemother Pharmacol 2012;69:901–909. doi: 10.1007/s00280-011-1766-x.
25. Wang SA, Spring LM, Bardia A. Genetics to epigenetics: targeting histone deacetylases in hormone receptor-positive metastatic breast cancer. Lancet Oncol 2019;20:746–748. doi: 10.1016/S1470-2045(19)30279-7.
