

Recent advances in the treatment of hormone receptor-positive/human epidermal growth factor 2-positive advanced breast cancer

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Abstract: Hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-positive (HR+/HER2+) advanced breast cancer is a special subtype of cancer with unique features. Major guidelines recommend that combination therapy containing anti-HER2 therapy (e.g., trastuzumab and pertuzumab) should be applied as the first-line treatment for HER2+ advanced breast cancer, regardless of HR status. Endocrine therapy could be relegated to patients who cannot tolerate chemotherapy or as a post-chemotherapy empirical maintenance strategy. Previous studies have shown that the HR pathway interacts with the HER2 pathway, and the HR and HER2 pathways of endocrine therapy combined with targeted therapy can effectively avoid tumor resistance. Therefore, the combination of endocrine and targeted therapies is the preferred treatment plan for HR+/HER2+ patients to replace chemotherapy. In this review, we will discuss research progress regarding endocrine therapy combined with anti-HER2 therapy in patients with advanced breast cancer, to provide more evidence for clinical practice and broader perspectives for related research. In the future, we hope there will be more studies on HR+/HER2+ advanced breast cancer to elucidate the optimal and appropriate treatment for these patients.

Keywords: advanced breast cancer, combination therapy, endocrine therapy, HR+/HER2+, human epidermal growth factor receptor 2, resistance

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Introduction

Human epidermal growth factor receptor 2-positive (HER2+) breast cancer accounts for approximately 20–25% of all cases of breast cancer. It is associated with poor differentiation, strong invasion, early recurrence and metastasis, short survival period, and poor clinical prognosis.¹ Approximately 50% of patients with HER2+ breast cancer are also positive for hormone receptors (HRs), including estrogen receptor (ER) and/or progesterone receptor (PR).² ER+, PR+, and HER2+ cancers are often referred to as “triple-positive breast cancer (TNBC).” In particular, HR+/HER2+ breast cancer is a special subtype of advanced breast cancer (ABC) that has not been clearly defined in terms of biological behaviors and

optimal treatments.³ However, it has a better prognosis if targeted treatments are applied.

In this review, we discuss research advancements in the treatment of HR+/HER2+ ABC with an emphasis on endocrine therapy combined with anti-HER2 therapy.

Clinical features of HR+/HER2+ breast cancer

As mentioned before, HR+/HER2+ tumors are usually called “triple positive,” if both estrogen receptors (ER) and progesterone receptors (PR) are expressed. Less frequently, HR+/HER2+ tumors express only one hormone receptor (either

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ER or PR).⁴ HR+ breast cancer is a hormone-dependent tumor, and estrogen binding to its receptor can promote the transcription of target genes, resulting in the synthesis of new proteins (including PR) and the promotion of cell proliferation. Both estrogen and progesterone regulate breast cell growth and differentiation, which are hallmarks of this cancer. HR+ breast cancer grows relatively slowly and has improved biological behavior compared with HR-negative (HR-) breast cancer. In a previous study,⁵ the recurrence risk of HR+ breast cancer in the first 5 years was lower than that of HR- breast cancer (9.9% versus 11.5%; $p=0.01$), whereas the recurrence risk of HR+ breast cancer was found to increase after 5 years. Clinically, 20–25% of the patients with breast cancer exhibited HER2 overexpression, resulting in highly invasive cancers that are commonly associated with hormone and chemotherapy failure and a poor prognosis.

HR+/HER2+ breast cancer is a distinct subtype, with individualized treatment and outcomes, and its biological behavior has yet to be fully clarified. In a previous report, Nahta and O'Regan⁶ found that the biological characteristics of HR+/HER2+ breast cancer with high ER expression were similar to those of HR+/HER2- breast cancer, whereas those of HR+/HER2+ breast cancer with low ER expression were comparable to those of HR-/HER2+ cancer. Another study demonstrated crosstalk between ER and HER signaling pathways, which can induce resistance to endocrine therapy and anti-HER2 therapy.⁷ In anti-HER2 therapy, ER signaling can be used as an escape mechanism to bypass HER2, block downstream signal transduction, and restore the proliferation, migration, differentiation, and apoptosis of tumor cells, resulting in the failure of the anti-HER2 treatment. Similarly, in patients with HR+/HER2+ breast cancer, endocrine therapy alone is more likely to cause drug resistance. Dual inhibition of ER and HER signaling may be essential to prevent drug resistance in this type of cancer.

Treatment of HR+/HER2+ advanced breast cancer

Currently, major guidelines recommend that combination therapy containing trastuzumab should be applied as the first-line treatment for HER2+ ABC, regardless of HR status.⁸

Chemotherapy combined with anti-HER2 therapy

The H0648g and M77001 studies^{9,10} established trastuzumab as the first-line treatment for breast cancer. Chemotherapy combined with trastuzumab can significantly improve progression-free survival (PFS) in patients with HER2+ ABC, regardless of their HR status. The CLEOPATRA study¹¹ confirmed that chemotherapy combined with trastuzumab and pertuzumab could further improve PFS and overall survival (OS) in patients with HER2+ ABC, regardless of their HR status. This makes this dual approach the standard treatment regimen for HER2+ breast cancer.

Lapatinib is a small-molecule tyrosine kinase inhibitor (TKI) that interacts with the intracellular domains of HER2 and the epidermal growth factor receptor (EGFR). It can act on the receptor without the extracellular domain, thereby overcoming problems with trastuzumab resistance. In the EGF100151 study,¹² researchers compared the efficacies of capecitabine plus lapatinib and capecitabine alone. Patients showed disease progression after the previous trastuzumab treatment. The results showed that combining capecitabine with lapatinib significantly prolonged PFS (27.1 weeks versus 18.6 weeks; $p<0.001$), which contributed to the establishment of lapatinib as an effective second-line anti-HER2 therapy.

Although lapatinib combined with capecitabine was once the first choice after trastuzumab treatment failure, the development of trastuzumab emtansine (T-DM1) has challenged the status of lapatinib as a second-line anti-HER2 therapy. The EMILIA study¹³ compared the safety and efficacy of T-DM1 and lapatinib plus capecitabine in patients with HER2+ breast cancer who had previously failed to respond to trastuzumab. The results demonstrated that PFS and OS significantly improved in the T-DM1 group compared with the lapatinib combined with capecitabine group. Therefore, many international guidelines now recommended T-DM1 as the preferred second-line anti-HER2 treatment.

Pyrotinib is an irreversible TKI with dual targets for HER2 and EGFR. A phase II study of pyrotinib¹⁴ compared the safety and efficacy of capecitabine combined with either pyrotinib or lapatinib. The results indicated that the median PFS was 18.1 months [95% confidence interval

(CI), 13.9 months to not reached] with pyrotinib and 7.0 months (95% CI, 5.6–9.8 months) with lapatinib [adjusted hazard ratio (HR), 0.36; 95% CI, 0.23–0.58; $p < 0.001$]. The same phase III study¹⁵ confirmed the improved efficacy of pyrotinib plus capecitabine compared with capecitabine alone; PFS was significantly prolonged [11.1 *versus* 4.1 months, HR=0.18, 95% CI, 0.13–0.26, $p < 0.001$], and adverse reactions were controllable.

In addition, margetuximab,¹⁶ trastuzumab deruxtecan (DS-8201a),¹⁷ and tucatinib,¹⁸ which are novel HER2-targeting agents, have shown strong anti-tumor activity in multi-line treatment after trastuzumab-based treatment failure. They were, therefore, approved by the FDA in 2020. In the Desnity-breast01 study¹⁷ and HER2CLIMB study,¹⁶ the prespecified subgroup analyses revealed a consistent PFS benefit with DS-8201a and tucatinib treatment across all subgroups, including those related to hormone receptor status. Nonetheless, in the Sophia study,¹⁶ consisting of 61.7% HR-positive patients, despite the absence of prespecified subgroup analyses, margetuximab was confirmed to have better efficacy in HER2-positive breast cancer patients.

In summary, the prognosis of HER2+ ABC is gradually improving with the introduction of novel first- and second-line anti-HER2 drugs. However, the HER2 signaling pathway is still the main research and treatment target regardless of HR status. Chemotherapy combined with anti-HER2 therapies remains the gold standard treatment regimen.

Endocrine therapy combined with anti-HER2 therapy

A preclinical study¹⁹ demonstrated the presence of a crosstalk between HER2 and HR signaling pathways, which can mediate endocrine resistance. Therefore, blocking the HER2 and ER signaling pathways simultaneously could yield the best therapeutic effect.

In the TAnDEM trial,²⁰ researchers evaluated the efficacy of trastuzumab combined with anastrozole as a first-line treatment for HR+/HER2+ ABC. The median PFS in patients administered trastuzumab combined with anastrozole and in those administered anastrozole monotherapy was 4.8 and 2.4 months, respectively (HR=0.63; 95% CI, 0.47–0.84; $p = 0.0016$). In addition, in

patients with HR+/HER2+ cancer confirmed by central evaluation ($n = 150$), median PFS was 5.6 and 3.8 months in the trastuzumab plus anastrozole and anastrozole alone arms, respectively ($p = 0.006$). The eLEcTRA study²¹ was a similar prospective, multicenter, randomized controlled study, comparing the first-line efficacy of letrozole plus trastuzumab and letrozole monotherapy in patients with ABC. The results also showed that letrozole combined with trastuzumab ($n = 26$) significantly prolonged PFS (14.1 *versus* 3.3 months, HR=0.67; 95% CI, 0.35–1.29; $p = 0.23$) compared with letrozole alone ($n = 31$). These findings indirectly suggested that endocrine therapy alone is more likely to induce drug resistance in patients with HR+/HER2+ breast cancer.

In the EGF30008 study,²² researchers aimed to overcome resistance to endocrine therapy and further improve curative effects by blocking the EGFR/HER2/ER pathway *via* endocrine therapy combined with a TKI. This study was a randomized, double-blind, parallel-controlled phase III clinical study of 219 patients with HR+/HER2+ ABC, who were randomly divided into two groups (letrozole + lapatinib and letrozole + placebo). The authors reported that the median PFS in the letrozole + lapatinib and letrozole + placebo groups were 8.2 and 3.0 months (HR=0.71; 95% CI, 0.53–0.96; $p = 0.019$), while the objective response rates were 28% and 15% ($p = 0.021$), respectively. It should be noted that this did not translate into an improvement in OS (33.3 *versus* 32.3 months; HR=0.74; 95% CI, 0.5–1.1; $p = 0.113$).

In the PERTAIN study,²³ researchers evaluated the effects of the dual inhibition of the HR and HER2 pathways on the enhancement of the anti-HER2 pathway. From February 2012 to October 2014, 258 patients with HR+/HER2+ ABC were enrolled in this study. They received first-line pertuzumab or trastuzumab combined with AI. Some patients in both groups were administered induction chemotherapy for 18–24 weeks followed by endocrine-targeted therapy after chemotherapy. After a median follow-up of 31 months, the median PFS was 18.89 months in the pertuzumab plus trastuzumab arm and 15.80 months in the trastuzumab arm (HR, 0.65; 95% CI, 0.48–0.89; $p = 0.0070$). In the two groups, the PFS of patients who did not receive induction chemotherapy was 21.7 and 12.45 months ($p = 0.011$), while those of patients who received

Table 1. Ongoing trials with anti-HER2 blockade and hormonal therapy for treatment of metastatic breast cancer.

Clinical trial	Phase	Population	Treatment arm	Study end point	Country
NCT 04579380	II	≥1 prior line of treatment	Fulvestrant + trastuzumab + tucatinib*	ORR	U.S.
NCT 04407988	II	First-line	Letrozole + pyrotinib*	CBR	China
NCT 04034589	II	≤1 prior line of treatment for metastatic diseases	Fulvestrant + pyrotinib*	PFS	China
NCT 04088110	II	Non-hormonal therapy for metastatic diseases	AI + trastuzumab + pyrotinib*	PFS	China
NCT 04337658	III	First-line	arm A: fulvestrant + trastuzumab ± pertuzumaab arm B: capecitabine + trastuzumab ± pertuzumab	PFS	China

*Single Group Assignment.

AI, aromatase inhibitors; CBR, clinical benefit rate; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; PFS, progression free survival.

induction chemotherapy were 16.89 and 16.85 months, respectively ($p=0.163$). Therefore, endocrine therapy combined with trastuzumab and pertuzumab was able to further improve the PFS of patients with good tolerance. It has thus emerged as a preferred treatment for some patients with HR+/HER2+ ABC. In addition, the PFS in the control group was significantly longer than that in the experimental group in the TAnDEM study,²⁰ which may be related to early-induction chemotherapy for patients with partial visceral metastasis or to the short duration of adjuvant endocrine therapy. Furthermore, variations in the criteria for chemotherapy selection by different researchers may have led to a selection bias in this study.

The ALTERNATIVE study²⁴ is another large-scale, randomized controlled study of endocrine therapy combined with a TKI for patients with metastatic breast cancer who had previously received endocrine therapy, trastuzumab therapy, and chemotherapy. The aim was to determine whether the combination of trastuzumab and endocrine therapy could increase the efficacy of lapatinib. The PFS of patients receiving trastuzumab, lapatinib, and AI, lapatinib combined with AI, and trastuzumab combined with AI was 11, 8.3, and 5.7 months, respectively. Compared with trastuzumab single-target therapy plus AI, lapatinib + trastuzumab + AI significantly reduced the

risk of disease progression, and all subgroups in the study benefited from the three-drug combination.

Therefore, dual inhibition of the HR and HER2 pathways in combination with anti-HER2 therapy could significantly improve outcomes in patients with HR+/HER2+ ABC. Similarly, enhanced anti-HER2 therapy can further improve PFS and is well tolerated. Therefore, endocrine therapy combined with “double-target” anti-HER2 therapy may allow patients to avoid chemotherapy and could become the first-line choice for some of these patients. Although previous studies^{20–22,24} have shown significant improvements in PFS, there is no clear explanation as to why survival benefits are not always achieved. This finding necessitates continued exploration of combinations of targeted drugs. The ongoing studies are summarized in Table 1.

Cyclin-dependent kinase (CDK) 4/6 inhibitors and endocrine therapy combined with anti-HER2 therapy

CDK4 and CDK6 are key regulators of human cell division and proliferation. In diverse malignant tumors, CDK4/6 can phosphorylate the retinoblastoma gene by binding to cyclin D, resulting in the release of the transcription factor E2F, upregulation of cell cycle-related genes, and enhanced entry of cells into the S phase. CDK4/6

inhibitors can block tumor cells from transitioning from the G₁ phase to the S phase by selectively inhibiting the functions of CDK4/6.^{25,26} In HR+ breast cancer, CDK4/6 is overactivated, and dual CDK4/6 and ER signaling inhibitors can effectively hamper the growth of these breast cancer cells. Palbociclib, ribociclib, and abemaciclib are three CDK4/6 inhibitors available on the market. The recent addition of these inhibitors to endocrine therapy has remarkably improved the outcome of patients with HR+ ABC compared with the use of anti-estrogens alone, by targeting the cell-cycle machinery and overcoming some aspects of endocrine resistance.²⁷ Thus, the availability of CDK4/6 inhibitors has rapidly changed therapeutic strategies for treating HR+/HER2- ABC.

However, studies have shown that the activation of cyclin D1 and CDK4/6 plays a significant role in the tumorigenesis of HR+/HER2+ breast cancer. Mitogenic signaling from HER2 and HR receptors converges at cell cycle checkpoints and results in a synergistic increase in cyclin D1 expression.^{4,25,28} Aiming at a combination of downstream targets in the HER2 pathway, such as cyclin D and CDK4/6, can improve antitumor efficacy. Indeed, Finn and colleagues²⁵ found that palbociclib has potential antitumor activity in HER2+ cell lines; they showed that palbociclib and trastuzumab had synergistic antitumor effects. In the phase II PATRICIA study,²⁹ the efficacy of palbociclib + trastuzumab was evaluated in postmenopausal women with HER2+ ABC who had previously received two to four prior lines of anti-HER2 therapy. Cohort B included patients with HR+ cancer who were randomly divided into two groups to receive palbociclib + trastuzumab + letrozole or palbociclib + trastuzumab. The PFS rates at 6 months (PFS6) in the two groups were 46.4% and 42.8%, respectively. These findings confirmed the efficacy and safety of CDK4/6 inhibitors combined with trastuzumab in patients with HER2+ ABC who had failed to show adequate responses to previous multi-line therapy, particularly for patients with HR+ breast cancer.

The MonarcHER study³⁰ was a prospective, international multicenter phase II study, comparing the efficacy of abemaciclib plus trastuzumab with or without fulvestrant with that of the chemotherapy prescribed by the attending physician for ABC. The results confirmed that the PFS of patients administered abemaciclib combined with fulvestrant and trastuzumab was better than that

of patients treated with the prescribed chemotherapy plus trastuzumab (8.32 *versus* 5.69 months, HR=0.673). This study was the first prospective randomized controlled study to compare endocrine therapy or chemotherapy combined with targeted therapy for HR+/HER2+ -ABC, further suggesting that endocrine therapy has the potential to replace chemotherapy in patients with HR+/HER2+ breast cancer.

In addition, several similarly designed studies have evaluated the combination of CDK4/6 inhibitors with endocrine therapy and anti-HER2 therapy. These include CDK4/6 inhibitors, trastuzumab, pertuzumab, tucatinib, pyrotinib, AIs, and fulvestrant in treating participants with ER+/HER2+ ABC (Table 2). The findings of these studies are expected to provide clinical evidence for the application of CDK4/6 inhibitors combined with endocrine therapy and anti-HER2 therapy in patients with HR+/HER2+ ABC. However, none of the research designs mentioned above have been involved in head-to-head studies with chemotherapy.

Selection of endocrine therapy or chemotherapy as the optimal treatment

Endocrine therapy or chemotherapy: which is the optimal treatment combined with anti-HER2 agents? Currently, few studies have compared the relative efficacies of combined endocrine therapy plus anti-HER2 therapy and of chemotherapy plus anti-HER2 therapy for the treatment of HR+/HER2+ ABC.

A retrospective study³¹ analyzed patients with this type of cancer who received endocrine therapy or chemotherapy between 2010 and 2015 using data from the US National Cancer Database. In total, 6,234 patients were enrolled in the study, of whom 60% underwent endocrine therapy and 40% received chemotherapy as a first-line treatment. The results showed that anti-HER2 therapy combined with endocrine therapy significantly improved the median OS rate compared with chemotherapy (56.0 *versus* 46.8%, $p=0.004$) and the 5-year survival rate (47.5% *versus* 39.8%, $p<0.001$). This was the first real-world study to contrast chemotherapy with endocrine therapy in patients with HR+/HER2+ ABC. Overall, the findings showed that most patients in the United States of America received endocrine therapy as their first-line treatment. This supports the fact that endocrine therapy combined with anti-HER2 therapy could be a suitable first-line treatment

Table 2. Ongoing trials with CDK 4/6 inhibitors and anti-HER2 blockade and/or hormonal therapy for metastatic breast cancer treatment.

Clinical trial	Phase	Population	Treatment arm	Study end point	Country
NCT 03772353	Ib/II	≤1 prior line of anti-HER2 therapy	SHR6390 + letrozole + pyrotinib*	The number of patients in the phase Ib part of the study with any AE. PFS (phase II part)	China
NCT 04095390	II	First-line	arm A: SHR6390 + letrozole + pyrotinib arm B: SHR6390 + capecitabine + pyrotinib	ORR	China
NCT 02657343	Ib/II	Cohort A: at least one previous line of anti-HER2 therapy Cohort B: at least trastuzumab, pertuzumab, TDM1 Cohort C: at least trastuzumab, pertuzumab, TDM1	Cohort A: ribociclib + T-DM1* Cohort B: ribociclib + trastuzumab* Cohort C: ribociclib + trastuzumab + fulvestrant*	MTD CBR	U.S.
NCT 04293276	II	≤1 prior line of treatment for metastatic diseases	SHR6390 + pyrotinib*	ORR	China
NCT 03054363	Ib/II	≤1 prior line of anti-HER2 therapy	Palbociclib + letrozole + tucatinib*	The number of patients in the phase Ib part of the study with any AE. PFS (phase II part)	U.S.
NCT03304080	I/II	First-line	Palbociclib + trastuzumab + pertuzumab + anastrozole*	DLT MTD CBR	U.S.
NCT02448420	II	2–4 previous lines of HER2 therapy	arm A: palbociclib + trastuzumab arm B: palbociclib + trastuzumab + letrozole arm C: palbociclib + trastuzumab + endocrine therapy (luminal intrinsic subtype delimited by PAM50)	PFS at 6 months	Spain.
NCT 02947685	III	A standard chemotherapy containing anti-HER2 based induction therapy of metastatic disease	arm A: trastuzumab + pertuzumab + endocrine therapy + palbociclib arm B: trastuzumab + pertuzumab + endocrine therapy	PFS	U.S.

*Single Group Assignment.

AE, adverse events; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DLT, dose-limiting toxicity; HER2, human epidermal growth factor receptor 2; MTD, maximum tolerated dose; ORR, objective response rate; PFS, progression free survival; T-DM1, trastuzumab emtansine.

regimen for patients with HR+/HER2+ ABC, suggesting a potential paradigm shift toward chemotherapy-sparing regimens. However, as appropriate for retrospective analyses of observational studies, statistical conclusions identify associations among treatment cohorts but avoid causality, for which statistical inference may require a randomized study.

Based on the rapidly changing environment with multiple new molecules entering the market, may

patients with advanced disease look towards a chemotherapy-free option? The MonarchHER study³⁰ aimed to determine whether endocrine therapy combined with anti-HER2 therapy using CDK4/6 inhibitors could become a routine therapeutic strategy for HR+/HER2+ patients. Even though the authors suggested that a chemotherapy-free regimen might be an alternative treatment option for patients with HR+/HER2+, the study was a phase II trial, whose enrolled population only included patients in whom multi-line

therapy had failed. Therefore, further research is necessary to confirm whether the conclusions of the study can be realized in front-line therapy.

Other studies (presented in Table 1) are ongoing prospective clinical studies of endocrine therapy plus anti-HER2 therapy *versus* chemotherapy plus anti-HER2 therapy or not. We hope these studies will add new data to elucidate the optimal regimen for HR+/HER+ MBC. To the best of our knowledge, no studies have yet compared chemotherapy, anti-HER2 therapy plus endocrine therapy, and chemotherapy plus anti-HER2 therapy. Although there is no clarity in the literature regarding endocrine therapy in patients with TPBC, it may replace cytotoxic therapy in HR+/HER2- ABC, instead of being a supplementary solution to chemotherapy.

Populations that would benefit from endocrine therapy combined with anti-HER2 therapy

The determination of the specific populations that would benefit from endocrine therapy combined with anti-HER2 therapy is still under investigation. A retrospective study³² showed that different levels of HR expression influenced the effects of endocrine therapy. Indeed, the biological behaviors of HR+/HER2+ breast cancer were found to be more similar to those of HER2-overexpressing breast cancer when the expression rates of ER and PR were less than 50%; thus, these patients are expected to benefit more from chemotherapy combined with anti-HER2 treatment. In contrast, when the ER expression rate is more than 50%, patients are expected to benefit more from endocrine therapy; however, the benefits of chemotherapy and anti-HER2 therapy are limited. In the PerELISA study,³³ the expression of Ki-67 after 2 weeks of letrozole treatment was used to determine whether the tumor had a molecular response type to screen the population that would benefit from endocrine therapy combined with anti-HER2 treatment. In addition, following the analysis of significant correlations among the intrinsic subtype determined by Prediction Analysis of Microarray 50 (PAM50), KI-67, and polymerase chain reaction, the intrinsic subtype determined by PAM50 can be used to further divide patients into subgroups that may provide insights into the potential results of chemotherapy.³⁴ In another study, PAM50 was used to classify HR+/HER2+ breast cancer. Based on the expression of CDCA8, BCL-2, and STC2, patients with luminal-A-type

cancer were screened, and these patients showed improved survival. However, the benefits of trastuzumab treatment were reduced, and patients benefited more from endocrine therapy. The accuracy of screening for the population that would benefit from endocrine therapy by analyzing genomic heterogeneity was higher than that of screening for luminal type A based on the ER expression rate.

The screening tool PAM50 is still in a clinical research stage. We expect that PAM50 and other tools will have potential applications in screening for patients who would benefit from endocrine therapy in the future.

Summary

In conclusion, HR+/HER2+ breast cancer is a clinical subtype with biological characteristics and treatment responses that differ from those of other subtypes. Endocrine therapy combined with anti-HER2 therapy can effectively prevent antitumor drug resistance. With the extensive application of CDK4/6 inhibitors in patients with HR+/HER2- cancer and the development of anti-HER2 therapy *via* various mechanisms, CDK4/6 inhibitors combined with endocrine therapy and therapy for HR+/HER2+ ABC have become a major research interest, especially since initial therapeutic effects have been observed in early treatment. However, it is too early to conclude that chemotherapy should be exempted in HR+/HER2+ ABC patients. Major guidelines recommend that chemotherapy combined with targeted therapy is still the optimal regimen for HR+/HER2+ ABC patients. Some patients who cannot tolerate chemotherapy may prefer to undergo endocrine therapy combined anti-HER2 therapy. With the increasing number of studies on CDK4/6 inhibitors and endocrine therapy plus anti-HER2 therapy in HR+/HER2+ ABC patients and the approval of novel anti-HER2 drugs, the appropriate populations suitable for receiving endocrine therapy combined with targeted therapy will increase, and biomarkers of relevant dominant populations will gradually be revealed.

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