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Perspective

Progress in targeted therapy for breast cancer

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Abstract

Breast cancer is a multistep, multifactorial, and heterogeneous disease. Significant transformations have occurred in the systemic management of breast cancer in the past decade. Due to the further understanding of pathogenesis, scientists have found plenty of signaling pathways and correspondingly therapeutic targets in breast cancer, such as hormone receptor, human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), phosphoinositide-3-kinase (PI3K), v-akt murine thymoma viral oncogene homolog (AKT), mechanistic target of rapamycin (mTOR), cyclin-dependent kinase 4/6 (CDK4/6), poly (adenosine diphosphate-ribose) polymerase (PARP), and programmed death-1 (PD-1). Targeted therapy, which optimizes the accuracy of antitumor activity and minimizes toxicity to normal tissues, plays a crucial role in breast cancer treatment in the era of precision medicine. In this review, we aimed to summarize the latest developments in targeted therapy for breast cancer and discuss the existing problems.

Keywords: Breast cancer; Targeted therapy; Precision medicine

Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide; it is a great threat to women's health and puts a heavy burden on patients and the society. Although there have been several breakthroughs in the treatment of breast cancer in the past few decades, the high incidence of relapse and progression after conventional therapies is deeply concerning and indicates a great need for developing new therapeutics for breast cancer. Recently, molecular targeted therapy has been considered a milestone in precision medicine for breast cancer. Distinctive biological processes and diverse genetic mutations are intimately related with the progression of different subtypes and sensitivity to various drugs, such as hormone receptor, human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), mechanistic target of rapamycin (mTOR), and cyclin-dependent kinase 4/6 (CDK4/6). Moreover, there is still no specific therapy for triple-

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negative breast cancer (TNBC), but poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors have shown promising activity in breast cancer associated with *BRCA*, the expression of which is commonly observed in TNBC. This article will mainly focus on the following aspects: HER2 inhibitors [such as trastuzumab, pertuzumab, lapatinib, and trastuzumab emtansine (T-DM1)], phosphoinositide-3-kinase (PI3K)/v-akt murine thymoma viral oncogene homolog (AKT)/mTOR inhibitors (such as everolimus, buparlisib, and ipatasertib), PARP inhibitors (such as veliparib, talazoparib, olaparib, and iniparib), CDK 4/6 inhibitors (such as palbociclib, abemaciclib, and ribociclib), VEGF inhibitors (such as bevacizumab), and immune checkpoint inhibitors (such as pembrolizumab and avelumab). Through this review, readers will be able to understand the latest developments in major targeted therapies for breast cancer and apply them in clinical practice as soon as possible.

HER2 inhibitors

Several predictive factors are correlated with the risk of metastasis in breast cancer, such as the hormone receptor, HER2, and Ki-67 proliferation index.[1] Overexpression of *HER2*, which is observed in about 20% of breast cancer cases, is associated with an aggressive type, a poor prognosis, and a high mortality rate.[2] The *HER2* oncogene, first discovered in 1985 by Schechter et al,[3] is localized to chromosome 17q and encodes a transmembrane tyrosine kinase receptor protein belonging to human epidermal growth factor receptor (HER) family. Besides HER2, there are three other core members of the HER family, HER1, HER3, and HER4. All of them play vital roles in signal transduction for normal cellular growth and division and are closely related to the tumorigenesis and progression of breast cancer. HER2, which is regarded as the first therapeutic target in breast cancer, is still being tested in various clinical trials. Table 1 summarizes the important trials targeting HER2 in breast cancer.[4–8]

Trastuzumab

Trastuzumab, a humanized monoclonal antibody of the immunoglobulin G1 (IgG1) type, was the first monoclonal antibody to revolutionize the treatment strategy for both early and advanced breast cancer. It binds to the extracellular domain IV of HER2 and thereby inhibits the downstream signal transduction that participates in the proliferation, motility, and antiapoptosis of normal cells, and in the invasiveness and angiogenesis of tumor cells.[9]

In 1998, the US Food and Drug Administration (FDA) approved trastuzumab as the first targeted agent for breast cancer. Thereafter, a body of international multicenter clinical trials, including the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, North Central Cancer Treatment Group (NCCTG) N9831, Breast Cancer International Research Group (BCIRG) 006, HERceptin Adjuvant (HERA), and Protocol for Herceptin as Adjuvant therapy with Reduced Exposure (PHARE) trials, have been initiated to determine the efficacy and safety of trastuzumab in postoperative patients with HER2-positive breast

Table 1
Trials targeting HER2 in breast cancer.

Study	Treatment schedule	*n*	Results
CLEOPATRA[4]	Docetaxel plus trastuzumab and pertuzumab *vs.* placebo plus docetaxel and trastuzumab	404 *vs.* 404	PFS: 18.5 *vs.* 12.4 months, $HR = 0.62$, $P < 0.001$
CALGB 40601[5]	Lapatinib plus paclitaxel and trastuzumab *vs.* paclitaxel plus trastuzumab *vs.* lapatinib plus paclitaxel	118 *vs.* 120 *vs.* 67	pCR rate: 56% *vs.* 46% (the paclitaxel plus lapatinib arm was closed in July 2011, based on reports of inferiority and greater toxicity of lapatinib-only regimens), $HR = 0.35$, $P = 0.013$
EMILIA[6]	T-DM1 *vs.* lapatinib plus capecitabine	495 *vs.* 496	PFS: 9.6 *vs.* 6.4 months, $HR = 0.65$, $P < 0.001$ OS: 30.9 *vs.* 25.1 months, $HR = 0.68$, $P < 0.001$
TH3RESA[7]	T-DM1 *vs.* physician's choices (chemotherapy, endocrine therapy or HER2-directed therapy)	404 *vs.* 198	PFS: 6.2 *vs.* 3.3 months, $HR = 0.528$, $P < 0.0001$
MARIANNE[8]	T-DM1 *vs.* T-DM1 plus pertuzumab *vs.* trastuzumab plus taxane	367 *vs.* 363 *vs.* 365	PFS: 14.1 *vs.* 15.2 *vs.* 13.7 months; $HR = 0.91$, $P = 0.31$ (T-DM1 *vs.* trastuzumab plus taxane); $HR = 0.87$, $P = 0.14$ (T-DM1 plus pertuzumab *vs.* trastuzumab plus taxane)

HER2: human epidermal growth factor receptor 2; CLEOPATRA: Clinical Evaluation of Pertuzumab and Trastuzumab; PFS: progression-free survival; pCR: pathologic complete response; *HR*: hazard ratio; OS: overall survival; CALGB: Cancer and Leukemia Group B; T-DM1: trastuzumab emtansine.

cancer. The first three trials revealed that trastuzumab in combination with chemotherapy drastically prolonged disease-free survival (DFS) and overall survival (OS) in patients with HER2-positive breast cancer in comparison with the results obtained with chemotherapy alone.[10,11] Moreover, the phase III HERA trial confirmed the standard treatment time with trastuzumab in the adjuvant chemotherapy of early breast cancer. In comparison with chemotherapy alone, combination treatment with 1-year trastuzumab and standard chemotherapy significantly prolonged DFS and OS, and neither DFS nor OS differed between the 1-year arm and 2-year arm of trastuzumab treatment.[12] Meanwhile, in the PHARE trial, a comparison of 6-month versus 12-month trastuzumab treatment in the same setting revealed no statistically significant difference between the two arms, but a hazard ratio (*HR*) of 1.28 suggested a trend in favor of the 12-month treatment arm.[13] Based on above findings, the standard treatment time of trastuzumab is set as 1 year. The NeOAdjuvant Herceptin (NOAH) trial first verified that compared to neoadjuvant chemotherapy alone, neoadjuvant chemotherapy of trastuzumab in combination with chemotherapy significantly improved the pathological complete response (pCR) rate and event-free survival (EFS). A parallel group with HER2-negative breast cancer was also included and received chemotherapy alone. After a 5.4-year follow-up, the results of the NOAH trial indicated a sustained increase in the EFS rate achieved with neoadjuvant therapy involving trastuzumab (58% *vs.* 43%; $HR = 0.64$; $P = 0.016$) and also revealed that pCR was closely correlated with the prolongation of EFS and OS.[14] Recently, the LUX-Breast 1 trial, which compared afatinib plus vinorelbine with trastuzumab plus vinorelbine for patients with HER2-positive metastatic breast cancer who had progressed on trastuzumab, showed that similar median progression-free survival (mPFS) between the two groups (5.5 months *vs.* 5.6 months; $HR = 1.10$; $P = 0.43$), but lower median OS (mOS) in the afatinib group ($HR = 1.48$; $P = 0.0048$). The above results showed that the trastuzumab-based therapy remained the first choice for such patients.[15] All in all, trastuzumab in combination with conventional chemotherapy drugs has improved the prognosis of patients with HER2-positive breast cancer and laid the foundation for targeted therapy in the field of adjuvant therapy and neoadjuvant therapy.

Pertuzumab

Pertuzumab is another monoclonal antibody that binds to the extracellular HER2 dimerization domain. It inhibits the dimerization between HER2 and other HER family members, especially HER3, and also activates antibody-dependent cellular cytotoxicity (ADCC),[16] while trastuzumab just prevents the dimerization between HER2. Hence, the combination of trastuzumab and pertuzumab might synergistically improve antitumor efficacy because of a more comprehensive blockade of the HER2 signaling pathway.

To assess this synergistical action, a decisive phase III trial Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA)[4] was conducted to investigate the efficacy and safety profile of trastuzumab plus pertuzumab in patients with untreated HER2-positive metastatic breast cancer. Patients were randomly assigned to receive docetaxel plus trastuzumab and pertuzumab or docetaxel plus trastuzumab and placebo. The mPFS was prolonged by 6.1 months in the pertuzumab group (18.5 months *vs.* 12.4 months; $HR = 0.62$; $P < 0.001$). An interim analysis of the OS showed a strong trend in favor of the docetaxel plus trastuzumab and pertuzumab regimen, although it was not significant. The safety profile was similar between the groups. The results of the CLEOPATRA trial suggest that pertuzumab could further improve the efficacy of docetaxel plus trastuzumab, which is regarded as the first-line treatment for patients with HER2-positive metastatic breast cancer.

Lapatinib

Lapatinib is a reversible dual EGFR/HER1 and HER2 tyrosine kinase inhibitor (TKI) that works intracellularly, binding to the tyrosine kinase domain of HER1 and HER2, inhibiting the phosphorylation of receptors, and finally blocking the downstream pathways that control the proliferation and survival of tumor cells. Carey et al[5] found that addition of lapatinib to the trastuzumab plus paclitaxel regimen significantly prolonged the DFS in patients with HER2-positive breast cancer ($HR = 0.35$; $P = 0.013$). Subgroup analyses showed that patients who achieved pCR had obviously improved DFS compared to that in the patients who did not achieve pCR ($HR = 0.14$; $P < 0.0001$). Other TKIs, such as neratinib, pyrotinib, and poziotinib, are still being tested in clinical trials.

T-DM1

T-DM1, which is composed of a potent cytotoxic agent, a target-specific antibody, and a stable linker, is the first antibody–drug conjugate used in the treatment of solid tumors. The advantage of T-DM1 is that this

medicine can deliver the microtubule-inhibitory agent directly to HER2-positive tumor cells, which potentially reduces systemic toxicity, enhances antitumor activity, and helps trastuzumab across the blood−brain barrier.

The EMILIA trial[6] was an important randomized phase III study of T-DM1, comparing T-DM1 versus capecitabine plus lapatinib in HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab and taxanes. This trial confirmed that T-DM1 significantly extended PFS and OS with less toxicity compared to the results achieved with lapatinib plus capecitabine. The mPFS and mOS were 9.6 and 30.9 months, respectively, with T-DM1 ($P < 0.001$), and the corresponding values for lapatinib plus capecitabine were 6.4 months and 25.1 months ($P < 0.001$). The incidence of grade 3−4 adverse events was higher in the treatment with lapatinib plus capecitabine than with T-DM1 (57.0% *vs*. 40.8%). Based on the results of the EMILIA trial, the FDA approved T-DM1 as a second-line treatment for HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab and taxanes. The National Comprehensive Cancer Network (NCCN) Guidelines also recommended T-DM1 as a second-line treatment for patients pretreated with trastuzumab.

The randomized phase III trial [Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA)][7] revealed that T-DM1 further showed a better efficacy and safety profile in patients with HER2-positive advanced breast cancer who were previously treated with two or more HER2-directed agents or taxanes than in patients treated with a physician's choices. The physician's choices, which expanded the indications of T-DM1, included chemotherapy, endocrine therapy, or HER2-directed therapy. The mPFS significantly increased in the T-DM1 arm compared to that in the arm involving the physician's choice of treatment (6.2 months *vs*. 3.3 months; $P < 0.0001$). An OS analysis exhibited a trend in favor of T-DM1 ($P = 0.0034$), but the stopping boundary was not reached. A lower incidence of grade 3−4 adverse events was reported in the T-DM1 arm than in the arm involving the physician's choice of treatment (32% *vs*. 43%). In brief, T-DM1 possesses great potential to treat patients with HER2-positive advanced breast cancer previously treated with two or more HER2-directed agents or taxanes. Furthermore, in the MARIANNE study,[8] treatment with T-DM1 and T-DM1 plus pertuzumab resulted in noninferior PFS compared to that achieved with trastuzumab plus a taxane. Neither experimental arm showed PFS superiority in comparison to the result obtained with trastuzumab plus a taxane. The OS was similar among all the arms. In short, the standard first-line treatment for patients with HER-2 positive advanced breast cancer is a taxane plus trastuzumab and pertuzumab. The NCCN Guidelines recommend the use of T-DM1 in patients who are not eligible to receive the standard first-line regimen. The ongoing clinical trials of T-DM1 for patients with advanced breast cancer are focused on further enhancing the treatment activity by combining T-DM1 with conventional chemotherapy drugs, targeted drugs, and endocrine drugs.[17] In a prospective, neoadjuvant, phase II trial, Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early Breast Cancer (ADAPT),[18] patients with HER2-positive and hormone receptor-positive early breast cancer were randomly assigned to a T-DM1 with or without endocrine therapy arm or to a trastuzumab with endocrine therapy arm. The pCR was observed in 41.0% of patients treated with T-DM1, 41.5% of patients treated with T-DM1 and endocrine therapy, and 15.1% of patients treated with trastuzumab and endocrine therapy ($P < 0.001$). Thus, neoadjuvant T-DM1 (with or without endocrine therapy) significantly increases pCR, which might help many patients avoid adverse responses to systemic therapy.

PI3K/AKT/mTOR pathway inhibitors

The PI3K/AKT/mTOR signaling pathway regulates multiple cellular processes to support the growth, survival, and metastasis of tumor cells.[19] Activation of the PI3K/AKT/mTOR pathway occurs in 70% of breast cancer cases and is correlated with a series of gene mutations, such as the loss of phosphatase and tensin homolog deleted on chromosome ten (*PTEN*), mutation of *PIK3CA*, and mutation in *AKT*. This vital pathway also has intimate connections with the downstream pathway of endocrine signaling, resulting in endocrine resistance. The main categories of PI3K/AKT/mTOR signaling pathway inhibitors, including mTOR inhibitors, PI3K inhibitors, AKT inhibitors, and some dual inhibitors, are in the different phases of clinical trial respectively (Table 2).[20−24]

mTOR inhibitors

Everolimus, an oral mTOR inhibitor previously used to prevent rejection-related reactions after kidney or heart transplantation, shows a promising ability to overcome resistance to endocrine therapy and targeted

Table 2
Trials targeting PI3K/AKT/mTOR in breast cancer.

Study	Target	Treatment schedule	*n*	Results
BOLERO-2[20]	mTOR	Everolimus plus exemestane *vs.* placebo plus exemestane	485 *vs.* 239	PFS: 11.0 *vs.* 4.1 months, $HR = 0.38$, $P < 0.0001$
BOLERO-3[21]	mTOR	Everolimus plus trastuzumab and vinorelbine *vs.* placebo plus trastuzumab and vinorelbine	284 *vs.* 285	PFS: 7.00 *vs.* 5.78 months, $HR = 0.78$, $P = 0.0067$
BELLE-3[22]	PI3K	Buparlisib plus fulvestrant *vs.* placebo plus fulvestrant	289 *vs.* 143	PFS: 3.9 *vs.* 1.8 months, $HR = 0.67$, $P = 0.0003$
BELLE-2[23]	PI3K	Buparlisib plus fulvestrant *vs.* placebo plus fulvestrant	576 *vs.* 571	PFS: 6.9 *vs.* 5.0 months, $HR = 0.78$, $P = 0.00021$
LOTUS[24]	AKT	Ipatasertib plus paclitaxel *vs.* placebo plus paclitaxel	62 *vs.* 62	PFS: 6.2 *vs.* 4.9 months, $HR = 0.60$, $P = 0.037$

PI3K: phosphoinositide-3-kinase; AKT: v-akt murine thymoma viral oncogene homolog; mTOR: mechanistic target of rapamycin; PFS: progression-free survival; *HR*: hazard ratio; BOLERO-2: Initial Breast Cancer Trials of Oral Everolimus 2; BOLERO-3: Initial Breast Cancer Trials of Oral Everolimus 3.

therapy in advanced breast cancer. As mTOR is a downstream signal molecule of tumors related to signaling pathways such as hormone receptor and HER2, inhibiting mTOR activation can effectively inhibit the upstream signal transduction which plays a critical role in the growth of tumor cells.

Initial Breast Cancer Trial of OraL EveROlimus-2 (BOLERO-2)[20] is an important phase III trial comparing everolimus plus exemestane with placebo plus exemestane in postmenopausal women with hormone receptor-positive advanced breast cancer that has progressed during or after aromatase inhibitor therapy. In this trial, the mPFS significantly extended in the everolimus plus exemestane arm compared to that in the placebo plus exemestane arm (11.0 months *vs.* 4.1 months, $P < 0.0001$). Although the trial showed a higher incidence of grade 3–4 adverse events in the everolimus plus exemestane arm than in the placebo plus exemestane arm, the health-related quality of life was not worse in the everolimus plus exemestane arm. Based on the results of this study, the FDA approved the application of everolimus plus exemestane in patients with postmenopausal hormone receptor–positive and HER2-negative advanced breast cancer. Recently, the combination of everolimus and endocrine therapy has also been proven to be effective in the Chinese population, and the safety profile was similar to that in previous studies, with a lower incidence of grade 3–4 adverse events.[25] The phase III Breast Cancer Trials of OraL EveROlimus-3 (BOLERO-3),[21] which compared the effect of everolimus plus trastuzumab and vinorelbine with that of placebo plus trastuzumab and vinorelbine in patients with HER2-positive and trastuzumab-resistant advanced breast cancer who had received taxane therapy, concluded that everolimus significantly prolonged mPFS (7.00 months *vs.* 5.78 months; $P = 0.0067$). Serious adverse events were observed in 42% of patients in the everolimus group (20% of patients in the placebo group). Researchers recommended everolimus plus trastuzumab and vinorelbine for patients with HER2-positive and trastuzumab-resistant advanced breast cancer who had received taxane therapy, but they were not sure whether this strategy could result in OS benefits for patients. Furthermore, they highlighted that physicians should pay close attention to adverse events during or after treatment.

PI3K inhibitors

The mTOR inhibitors availably block cell growth and proliferation and elicit AKT phosphorylation through a feedback activation pathway, potentially leading to a resistance to mTOR inhibitors. However, several preclinical studies found that PI3K inhibitors can inhibit or eliminate AKT phosphorylation. Accordingly, PI3K inhibitors might be clinically effective in patients progressing on mTOR inhibitor treatment. PI3K inhibitors mainly include pan-PI3K inhibitors (buparlisib and pictilisib) and α-specific PI3K inhibitors (alpelisib and taselisib).

Buparlisib is an oral pan-PI3K inhibitor that targets all four isoforms of class I PI3K (α, β, δ, and γ). BELLE-3[22] was a phase III study that focused on comparing the efficacy and safety profile of buparlisib to that of placebo when combined with fulvestrant in postmenopausal women with hormone receptor-positive and HER2-negative advanced breast cancer that progressed on or after aromatase inhibitor and mTOR inhibitor therapy. The PFS in the buparlisib arm showed significant extension (3.9 months *vs.* 1.8 months; $HR = 0.67$; $P = 0.0003$). Unfortunately, the safety profile of buparlisib plus fulvestrant does not support its further exploration. Nonetheless, the efficacy of buparlisib

favors the use of PI3K inhibitors plus endocrine therapy in patients with *PIK3CA* mutations. The use of more selective PI3K inhibitors, such as α-specific PI3K inhibitors, is warranted to further improve safety and availability in this setting. Another phase III trial, BELLE-2,[23] showed essentially corresponding results.

All in all, approved novel therapies for postmenopausal patients with hormone receptor-positive and HER2-negative advanced breast cancer include the mTOR inhibitor everolimus plus exemestane or tamoxifen as first-line treatment, and the CDK4/6 inhibitor palbociclib with letrozole or fulvestrant as the second-line therapy. Although the results of the clinical trials were not completely satisfactory, the vital role of PI3K inhibitors in breast cancer treatment should be taken into consideration. It is also worthwhile to further explore triplet combinations of PI3K inhibitors with endocrine therapy and CDK4/6 inhibitors and to use more selective PI3K inhibitors.

AKT inhibitors

Ipatasertib, a highly selective oral small-molecule AKT inhibitor, is being investigated for its efficacy against tumors such as TNBC. Of note, approximately half the number of cases of TNBC show deficient expression of the tumor suppressor *PTEN*, which is associated with high levels of AKT pathway activation. A phase I study of ipatasertib in pretreated patients with diverse tumor types, including breast cancer, showed an acceptable safety profile and preliminary antitumor activity.[26] The LOTUS trial,[24] which investigated the addition of ipatasertib to paclitaxel as the first-line therapy for TNBC patients, found that mPFS was 6.2 months in the ipatasertib arm *vs*. 4.9 months in the placebo arm ($HR = 0.60$; $P = 0.037$). Serious adverse events were reported in 28% of patients in the ipatasertib arm and 15% of patients in the placebo arm. This is the first trial to show favorable results of AKT-targeted therapy for TNBC patients, and it is necessary to conduct further research on the treatment of TNBC with ipatasertib.

PARP inhibitors

PARP family members are involved in the recognition and repair of DNA damage, and thus far, PARP1, PARP2, and PARP3 have been defined as DNA damage–dependent PARPs. The activation of PARP1 is the initial step in the process of DNA damage repair, and then the adenosine ribose polymer catalyzed by PARP can improve the aggregation of the DNA repair complex binding to DNA damage sites, so as to promote base-excision repair and single-strand break repair.[27] In the meantime, *BRCA1/2* can repair DNA double-strand breaks through homologous recombination.[28] In normal cells, these methods work together to maintain the stability of the genome. During tumor treatment, a deficiency of *BRCA1/2* or other homologous-recombination DNA repair proteins sensitizes cells to PARP inhibitions, which lead to genome instability and cell death in tumor cells.[29] Researchers have noted *BRCA1/2* mutations in most cases of TNBC, which makes the resultant tumor more aggressive and results in a worse prognosis compared to that associated with other types of breast cancer because of a lack of distinctive targets. Therefore, more trials are ongoing to determine whether TNBC patients with a mutation in *BRCA1/2* can benefit from treatment with PARP inhibitors (Table 3).[30,31]

Veliparib

Veliparib is an orally dual inhibitor of PARP1 and PARP2. A phase II study[32] investigated the efficacy and safety of veliparib with temozolomide or carboplatin/paclitaxel versus placebo with carboplatin/paclitaxel in patients with *BRCA1/2*-mutated breast cancer, and showed numerical but not statistically significant increases in both PFS and OS. The emergence of veliparib has provided more treatment options.

Talazoparib

Talazoparib is regarded as an important PARP inhibitor. The phase III EMBRACA[30] trial compared

Table 3
Trials targeting PARP in breast cancer.

Study	Treatment schedule	*n*	Results
EMBRACA[30]	Talazoparib *vs.* standard chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)	288 *vs.* 144	PFS: 8.6 *vs.* 5.6 months, $HR = 0.54$, $P < 0.0001$
NCT00938652[31]	Iniparib plus gemcitabine and carboplatin *vs.* gemcitabine plus carboplatin	261 *vs.* 288	OS: 11.8 *vs.* 11.1 months, $HR = 0.88$, $P = 0.28$; PFS: 5.1 *vs.* 4.1 months, $HR = 0.79$, $P = 0.027$

PARP: poly (adenosine diphosphate-ribose) polymerase; PFS: progression-free survival; *HR*: hazard ratio; OS: overall survival.

talazoparib with standard chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in women with *BRCA1/2*-mutated metastatic breast cancer. The mPFS in this trial was 8.6 months in the talazoparib group versus 5.6 months in the chemotherapy group ($HR = 0.54$; $P < 0.0001$). The incidences of adverse events were similar between the two groups, and the talazoparib group was related with fewer gastrointestinal disorders and skin or subcutaneous tissue disorders than the chemotherapy group. This drug shows immense potential in the treatment of *BRCA1/2*-mutated metastatic breast cancer.

Olaparib

Olaparib is an oral PARP inhibitor that has shown promising antitumor activity in patients with *BRCA1/2*-mutated breast cancer. In a phase III trial,[33] patients who had received no more than two types of chemotherapy agents for HER2-negative and *BRCA*-mutated metastatic breast cancer were recruited and were assigned to receive olaparib or standard chemotherapy of the physician's choice. The mPFS was 2.8 months longer and the risk of disease progression or death was 42% lower in the olaparib arm than those in the standard chemotherapy arm. The incidences of severe adverse events were 36.6% in the olaparib arm and 50.5% in the standard chemotherapy arm, respectively. More trials are required to further confirm the role of olaparib in this setting.

Iniparib

Iniparib is still an investigational agent. A phase II trial[34] of gemcitabine and carboplatin with or without iniparib in patients with metastatic TNBC showed a statistically significant increase in patients treated with iniparib plus chemotherapy in the clinical benefit rate (56% *vs*. 34%; $P = 0.01$) and mPFS (5.9 months *vs*. 3.6 months; $P = 0.01$) compared to those achieved with chemotherapy alone. No significant difference was observed in the incidence of adverse events between the two groups. However, a phase III trial[31] in the same patient population failed to confirm these efficacy results (OS: $HR = 0.88$, $P = 0.28$; PFS: $HR = 0.79$, $P = 0.027$) with a similar safety profile. However, potential PFS and OS benefits were observed for patients in the second and third line of treatment settings. Another phase II neoadjuvant trial[35] also showed a lack of efficacy when iniparib was administered with paclitaxel in patients with early TNBC. Hence, the potential benefits of iniparib remain to be further evaluated.

CDK4/6 inhibitors

Approximately 75% of patients with metastatic breast cancer are hormone receptor-positive and are commonly treated with endocrine therapy. As resistance develops in almost all patients, attention has been focused on identifying novel approaches to address endocrine therapy resistance. The loss of cell cycle control is a hallmark of cancer.[36] The complex of CDK4/6 and cyclin D is a critical regulator of cell cycle progression and is intimately connected with breast tumorigenesis and resistance to endocrine therapy. Moreover, latest findings indicate that CDK4/6 inhibitors increase tumor immunogenicity by enhancing cytotoxic T-cell-mediated clearance of tumor cells, which provides a rationale for novel combination regimens comprising CDK4/6 inhibitors and immunotherapies.[37] Overall, they are categorized as selective and non-selective inhibitors of CDK and have been tried as monotherapy and combination therapy, respectively (Table 4).[38–42] Thus far, research has been concentrated on three CDK4/6 inhibitors, including palbociclib, abemaciclib, and ribociclib.

Palbociclib

Palbociclib, which selectively binds to the adenosine triphosphate (ATP)-binding site of the CDK4/6 protein, can prevent Rb phosphorylation, inhibit the release of the E2F transcription factor, block the cell cycle between the G1 phase and S phase, and finally stop the proliferation of tumor cells. The phase III Palbociclib Ongoing Trials in the Management of Breast Cancer (PALOMA)-2[38] explored the efficacy and safety of palbociclib plus letrozole versus letrozole alone in untreated postmenopausal women with ER-positive and HER2-negative advanced breast cancer. In the trial, the mPFS increased from 14.5 months (letrozole arm) to 24.8 months (palbociclib plus letrozole) ($HR = 0.58$; $P < 0.001$). The NCCN Guidelines recommend letrozole combined with palbociclib as a first-line treatment option for such patients. Another phase III trial, PALOMA-3,[39] further explored the efficacy and safety of palbociclib plus fulvestrant versus fulvestrant plus placebo in postmenopausal patients with hormone receptor-positive and HER2-negative metastatic breast cancer progressing on endocrine therapy. The mPFS was 9.5 months in the fulvestrant plus palbociclib arm and 4.6 months in the fulvestrant plus placebo arm ($HR = 0.46$; $P < 0.0001$). The incidences of grade 3–4 adverse events were 73% (fulvestrant plus palbociclib arm) and

Table 4
Trials targeting CDK4/6 in breast cancer.

Study	Treatment schedule	*n*	Results
PALOMA-2[38]	Palbociclib plus letrozole *vs.* placebo plus letrozole	444 *vs.* 222	PFS: 24.8 *vs.* 14.5 months, $HR = 0.58$, $P < 0.001$
PALOMA-3[39]	Palbociclib plus fulvestrant *vs.* placebo plus fulvestrant	347 *vs.* 174	PFS: 9.5 *vs.* 4.6 months, $HR = 0.46$, $P < 0.0001$
MONARCH 2[40]	Abemaciclib plus fulvestrant *vs.* placebo plus fulvestrant	446 *vs.* 223	PFS: 16.4 *vs.* 9.3 months, $HR = 0.553$, $P < 0.001$
MONARCH 3[41]	Abemaciclib plus aromatase inhibitor *vs.* placebo plus aromatase inhibitor	328 *vs.* 165	PFS: not reached *vs.* 14.7 months, $HR = 0.54$, $P = 0.000021$
MONALEESA-2[42]	Ribociclib plus letrozole *vs.* placebo plus letrozole	334 *vs.* 334	PFS: not reached *vs.* 14.7 months, $HR = 0.56$, $P = 3.29 \times 10^{-6}$

CDK4/6: cyclin-dependent kinase 4/6; PALOMA: Palbociclib Ongoing Trials in the Management of Breast Cancer; PFS: progression-free survival; *HR*: hazard ratio; MONALEESA-2: Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety-2.

22% (fulvestrant plus placebo arm) respectively. These trials revealed that palbociclib had a synergistic effect with endocrine therapy and could partially reverse sensitivity to endocrine agents, which was a profound breakthrough in endocrine therapy. Based on the results of PALOMA-3, the FDA approved palbociclib plus fulvestrant for postmenopausal patients with hormone receptor-positive and HER2-negative metastatic breast cancer progressing on endocrine therapy. Thus far, the approved indications of palbociclib have been limited to a combination therapy with an endocrine agent (letrozole or fulvestrant).

Abemaciclib

Abemaciclib is an oral, selective, small-molecule inhibitor of CDK4/6, which also breaks down the blood–brain barrier to impede the growth of intracranial tumor cells. In patients with refractory hormone receptor-positive and HER2-negative advanced breast cancer, abemaciclib monotherapy showed clinical effectiveness.[43] In the phase III trial MONARCH 2,[40] which focused on patients with hormone receptor-positive and HER2-negative breast cancer progressing on endocrine therapy, abemaciclib plus fulvestrant therapy resulted in a 7.2-month prolongation of mPFS in comparison with that achieved in the placebo arm ($HR = 0.553$; $P < 0.001$) with tolerable adverse events. MONARCH 3[41] was a phase III trial of abemaciclib or placebo plus an aromatase inhibitor in postmenopausal women with untreated hormone receptor-positive and HER2-negative advanced breast cancer. The mPFS was significantly prolonged in the abemaciclib arm ($HR = 0.54$; $P = 0.000021$). In the abemaciclib arm, diarrhea was the most frequent adverse event (81.3%) but was mainly grade 1 (44.6%).

In short, abemaciclib showed potent antitumor activity as the initial therapy for patients with metastatic disease and in patients who have progressed on endocrine therapy. However, identifying which types of patients may benefit the most from the addition of abemaciclib remains a hotspot to better support more personalized treatment regimens. Further studies and biomarker analyses are warranted to precisely identify patients who may benefit more from this medicine.

Ribociclib

Ribociclib is also an oral, selective, small-molecule inhibitor of CDK4/6. Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety-2 (MONALEESA-2),[42] a randomized phase III trial, evaluated the efficacy and safety of ribociclib combined with letrozole as first-line treatment in postmenopausal women with hormone receptor-positive and HER2-negative recurrent or metastatic breast cancer who had not receive any systemic therapy in comparison with the placebo plus letrozole arm. The PFS was significantly longer in the ribociclib arm than in the placebo arm ($HR = 0.56$; $P = 3.29 \times 10^{-6}$) along with a higher rate of myelosuppression in the ribociclib group (neutropenia: 59.3% *vs.* 0.9%; leukopenia: 21.0% *vs.* 0.6%). Based on this trial, ribociclib was approved by the FDA in 2017, providing more treatment options for such patients.

VEGF inhibitors

Bevacizumab is a humanized monoclonal antibody that competitively binds to VEGF, which regulates angiogenesis and tumor survival. Lots of clinical trials targeting VEGF in breast cancer are ongoing (Table 5).[44–46] The phase III trial Regimens in Bevacizumab for Breast Oncology (RIBBON)-1[44]

Table 5
Trials targeting VEGF in breast cancer.

Study	Treatment schedule	*n*	Results
RIBBON-1[44]	Bevacizumab plus traditional chemotherapy *vs.* placebo plus traditional chemotherapy (capecitabine or taxane/anthracycline)	824 *vs.* 413	Cape cohort: PFS, 8.6 *vs.* 5.7 months, $HR = 0.69$, $P < 0.001$; Tax/Anthra cohort: PFS, 9.2 *vs.* 8.0 months, $HR = 0.64$, $P < 0.001$
RIBBON-2[45]	Bevacizumab plus chemotherapy *vs.* placebo plus chemotherapy	459 *vs.* 225	PFS: 7.2 *vs.* 5.1 months, $HR = 0.78$, $P = 0.0072$
CALGB40503[46]	Bevacizumab plus letrozole *vs.* placebo plus letrozole	174 *vs.* 174	PFS: 20.2 *vs.* 15.6 months, $HR = 0.75$, $P = 0.016$

VEGF: vascular endothelial growth factor; RIBBON: Regimens in Bevacizumab for Breast Oncology; PFS: progression-free survival; *HR*: hazard ratio; CALGB40503: Cancer and Leukemia Group B 40503.

compared the efficacy and safety of bevacizumab plus several traditional chemotherapy regimens (capecitabine or taxane/anthracycline) versus these regimens alone as the first-line treatment for patients with HER2-negative metastatic breast cancer. The mPFS was prolonged by 2.9 months and 1.2 months, respectively (capecitabine arm: from 5.7 months to 8.6 months; $HR = 0.69$; $P < 0.001$; taxane/anthracycline arm: from 8.0 months to 9.2 months; $HR = 0.64$; $P < 0.001$). Statistically significant differences in the OS were not observed between the control and bevacizumab arms. RIBBON-2,[45] another phase III trial, was conducted to evaluate the efficacy and safety of bevacizumab plus chemotherapy versus chemotherapy alone as a second-line treatment for HER2-negative metastatic breast cancer patients who had received cytotoxic treatment. The mPFS increased from 5.1 months to 7.2 months ($HR = 0.78$; $P = 0.0072$), but there was no statistically significant difference in the OS. The incidence of adverse events in the chemotherapy arm was lower than that in the bevacizumab arm (7.2% *vs.* 13.3%). Meta-analyses of these phase III studies confirmed the lack of an OS benefit along with potentially severe adverse events in the bevacizumab arm.[47,48] The FDA withdrew the approval of bevacizumab for breast cancer, but NCCN Guidelines retain the recommendation of bevacizumab plus paclitaxel. Bevacizumab actually has therapeutic effects in patients with HER2-negative breast cancer, however there is no concerted conclusion on the specific role of bevacizumab in adjuvant chemotherapy, the indications of which need further verification.

Moreover, VEGF, in addition to inducing tumor angiogenesis, also induces the proliferation of breast cancer cells and resistance to endocrine therapy by an autocrine mechanism. High levels of VEGF are intimately associated with an early recurrence and resistance to endocrine therapy. Based on above findings, the combination of antiangiogenic therapy and endocrine therapy may show great potential for patients with hormone receptor-positive metastatic breast cancer. Cancer and Leukemia Group B (CALGB) 40503[46] was a phase III trial of letrozole with or without bevacizumab as first-line treatment for patients with hormone receptor-positive metastatic breast cancer. The addition of bevacizumab contributed to an obvious prolongation in mPFS from 15.6 months to 20.2 months and resulted in a similar outcome in OS. However, these benefits were related to an evident risk of grade 3–4 adverse events, including hypertension and proteinuria. Hence, the combination of an endocrine agent and an antiangiogenic agent has not been recommended as standard treatment for hormone receptor-positive advanced breast cancer. More precise biomarkers will be required to further enhance the function of bevacizumab in this setting.

Immune checkpoint inhibitors

Under normal conditions, the immune checkpoint prevents excessive activation of T cells and inflammatory reactions through a set of cell–cell interactions, to maintain the stability of the immune system. However, the tumor cells always overexpress immune checkpoints, inhibit the activity of T cells, and then evade immune surveillance. Immune checkpoint inhibitors can block the activity of immune checkpoints, so as to recover the activity of T cells and then kill tumor cells. Currently, checkpoint inhibitors mainly include programmed death-1 (PD-1) inhibitors, programmed death-ligand 1 (PD-L1) inhibitors, and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitors. Recent studies have shown a close relationship between PD-L1 and TNBC, for which treatment options were limited.[49]

Pembrolizumab is a highly selective PD-1 antibody, blocking the negative immune regulatory signal mediated by the PD-1 receptor. A phase Ib study[50] evaluated

the efficacy of pembrolizumab in PD-L1-positive TNBC patients. The 6-month PFS rate was 23.3%, and the percentage of grade 3−4 adverse events was 15.6%. Pembrolizumab, which has been approved by the FDA for the treatment of melanoma and pulmonary squamous carcinoma, also shows promise in the treatment of TNBC. A trial[51] presented at San Antonio Breast Cancer Symposium (SABCS) 2015 also showed promising results of the efficacy of avelumab, which is an anti-PD-L1 agent for the treatment of PD-L1-positive TNBC patients. The clinical response rate of avelumab was 44.4% versus 2.6% in the absence of PD-L1 expression. Other immune checkpoint inhibitors, such as atezolizumab and durvalumab, are still undergoing phase I or II clinical trials.

Conclusion

In recent years, great progress has been made in the molecular targeted therapy of breast cancer. Trastuzumab is regarded as the cornerstone of targeted therapy in HER2-positive breast cancer and shows considerable efficacy in both neoadjuvant therapy and adjuvant therapy. Dual-targeted therapy involving trastuzumab and pertuzumab marks a new phase of targeted therapy. T-DM1 plays an important role in heavily pretreated patients with HER2-positive advanced breast cancer and contributes to the breakdown of the blood−brain barrier. CDK4/6 and mTOR inhibitors exhibit the ability to reverse the resistance to endocrine agents and targeted agents to some extent. PARP inhibitors also show immense potential in the treatment of the *BRCA1/2*-mutated subgroup, which usually exists in TNBC.

With an increase in the understanding of the pathogenesis of breast cancer, increasingly effective targeted drugs can be applied to alleviate symptoms in the clinical setting. However, as this is a novel therapeutic strategy, there still exist many problems. First, breast cancer is a heterogeneous disease in which the biomarkers are diverse not only between primary and metastatic tumors but also within a single tumor or during tumor progression. It is hard to search for efficient molecular test technology and find an agent that can be applied to all types of tumor cells, especially tumor stem cells. Moreover, tumor cells gradually resist targeted agents during treatment. Therefore, researchers have to constantly develop new drugs to overcome this *de novo* or acquired resistance. Second, combination therapies indeed enhance tumor cell killing but also cause several adverse events. To some extent, combination treatments also antagonize chemotherapy-induced cell death.[52] Owing to their size, charge, and tight target binding affinity, monoclonal antibodies have a relatively limited distribution. They also present non-specific binding owing to the constant region (Fc) of the monoclonal antibodies. Both of these characteristics limit the efficacy of monoclonal antibodies. Researchers found that some anticancer agents may increase the risk of second primary malignancies. In brief, the future of targeted therapy for breast cancer is full of hope and challenges. With the increase in the knowledge of the pathogenesis of breast cancer, we are hopeful that a cure for breast cancer will be found someday.

Conflicts of interest

There are no conflicts of interest to disclose.

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References

1. van 't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. *Nature*. 2002;415:530−536.
2. Witton CJ, Reeves JR, Going JJ, Cooke TG, Bartlett JM. Expression of the HER1-4 family of receptor tyrosine kinases in breast cancer. *J Pathol*. 2003;200:290−297.
3. Schechter AL, Hung MC, Vaidyanathan L, et al. The neu gene: an erbB-homologous gene distinct from and unlinked to the gene encoding the EGF receptor. *Science*. 1985;229:976−978.
4. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366:109−119.
5. Carey LA, Berry DA, Cirrincione CT, et al. Molecular heterogeneity and response to neoadjuvant human epidermal growth factor receptor 2 targeting in CALGB 40601, a randomized phase III trial of paclitaxel plus trastuzumab with or without lapatinib. *J Clin Oncol*. 2016;34:542−549.
6. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367:1783−1791.
7. Krop IE, Kim SB, González-Martín A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15:689−699.
8. Perez EA, Barrios C, Eiermann W, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: primary results from the phase III MARIANNE study. *J Clin Oncol*. 2017;35:141−148.
9. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist*. 2009;14:320−368.

10. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 2014;32:3744−3752.
11. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365:1273−1283.
12. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet*. 2017;389:1195−1205.
13. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol*. 2013;14:741−748.
14. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet Oncol*. 2014;15:640−647.
15. Harbeck N, Huang CS, Hurvitz S, et al. Afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients with HER2-overexpressing metastatic breast cancer who had progressed on one previous trastuzumab treatment (LUX-Breast 1): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2016;17:357−366.
16. Lee-Hoeflich ST, Crocker L, Yao E, et al. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. *Cancer Res*. 2008;68:5878−5887.
17. Martínez MT, Pérez-Fidalgo JA, Martín-Martorell P, et al. Treatment of HER2 positive advanced breast cancer with T-DM1: a review of the literature. *Crit Rev Oncol Hematol*. 2016;97:96−106.
18. Harbeck N, Gluz O, Christgen M, et al. De-escalation strategies in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (BC): final analysis of the West German Study Group Adjuvant Dynamic Marker-Adjusted Personalized Therapy trial optimizing risk assessment and therapy response prediction in early BC HER2- and hormone receptor-positive phase II randomized trial-efficacy, safety, and predictive markers for 12 weeks of neoadjuvant trastuzumab emtansine with or without endocrine therapy (ET) versus trastuzumab plus ET. *J Clin Oncol*. 2017;35:3046−3054.
19. Vivanco I, Sawyers CL. The phosphatidylinositol 3-kinase AKT pathway in human cancer. *Nat Rev Cancer*. 2002;2:489−501.
20. Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. *Adv Ther*. 2013;30:870−884.
21. André F, O'Regan R, Ozguroglu M, et al. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol*. 2014;15:580−591.
22. Di LA, Johnston S, Lee KS, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2018;19:87−100.
23. Baselga J, Im SA, Iwata H, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18:904−916.
24. Kim SB, Dent R, Im SA, et al. Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2017;18:1360−1372.
25. Gong C, Zhao Y, Wang B, et al. Efficacy and safety of everolimus in Chinese metastatic HR positive, HER2 negative breast cancer patients: a real-world retrospective study. *Oncotarget*. 2017;8:59810−59822.
26. Saura C, Roda D, Roselló S, et al. A first-in-human phase I study of the ATP-competitive AKT inhibitor ipatasertib demonstrates robust and safe targeting of AKT in patients with solid tumors. *Cancer Discov*. 2017;7:102−113.
27. De Vos M, Schreiber V, Dantzer F. The diverse roles and clinical relevance of PARPs in DNA damage repair: current state of the art. *Biochem Pharmacol*. 2012;84:137−146.
28. Venkitaraman AR. Cancer suppression by the chromosome custodians, BRCA1 and BRCA2. *Science*. 2014;343:1470−1475.
29. McCabe N, Turner NC, Lord CJ, et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. *Cancer Res*. 2006;66:8109−8115.
30. Nelson R. San Antonio Breast Cancer Symposium 2017. *Lancet Oncol*. 2018;19:22.
31. O'Shaughnessy J, Schwartzberg L, Danso MA, et al. Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer. *J Clin Oncol*. 2014;32:3840−3847.
32. Han HS, Diéras V, Robson M, et al. Veliparib with temozolomide or carboplatin/paclitaxel versus placebo with carboplatin/paclitaxel in patients with BRCA1/2 locally recurrent/metastatic breast cancer: randomized phase II study. *Ann Oncol*. 2018;29:154−161.
33. Slomski A. Olaparib increased survival in metastatic breast cancer. *JAMA*. 2017;318:690.
34. O'Shaughnessy J, Osborne C, Pippen JE, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med*. 2011;364:205−214.
35. Llombart-Cussac A, Bermejo B, Villanueva C, et al. SOLTI NeoPARP: a phase II randomized study of two schedules of iniparib plus paclitaxel versus paclitaxel alone as neoadjuvant therapy in patients with triple-negative breast cancer. *Breast Cancer Res Treat*. 2015;154:351−357.
36. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646−674.
37. Goel S, DeCristo MJ, Watt AC, et al. CDK4/6 inhibition triggers anti-tumour immunity. *Nature*. 2017;548:471−475.
38. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375:1925−1936.
39. Cristofanilli M, Turner NC, Bondarenko I, 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 (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol*. 2016;17:425−439.
40. Sledge GW, Toi M, Neven P, 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;35:2875−2884.
41. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35:3638−3646.

42. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med*. 2016;375:1738−1748.
43. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2-metastatic breast cancer. *Clin Cancer Res*. 2017;23:5218−5224.
44. Robert NJ, Diéras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol*. 2011;29:1252−1260.
45. Brufsky AM, Hurvitz S, Perez E, et al. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. 2011;29:4286−4293.
46. Dickler MN, Barry WT, Cirrincione CT, et al. Phase III trial evaluating letrozole as first-line endocrine therapy with or without bevacizumab for the treatment of postmenopausal women with hormone receptor-positive advanced-stage breast cancer: CALGB 40503 (Alliance). *J Clin Oncol*. 2016;34:2602−2609.
47. Valachis A, Polyzos NP, Patsopoulos NA, Georgoulias V, Mavroudis D, Mauri D. Bevacizumab in metastatic breast cancer: a meta-analysis of randomized controlled trials. *Breast Cancer Res Treat*. 2010;122:1−7.
48. Li C, Xiang A, Chen X, Yin K, Lu J, Yin W. Optimizing the treatment of bevacizumab as first-line therapy for human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer: an updated meta-analysis of published randomized trials. *Onco Targets Ther.* 2017;10:3155−3168.
49. Muenst S, Schaerli AR, Gao F, et al. Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer. *Breast Cancer Res Treat*. 2014;146:15−24.
50. Nanda R, Chow LQ, Dees EC, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study. *J Clin Oncol*. 2016;34:2460−2467.
51. Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. *Breast Cancer Res Treat*. 2018;167:671−686.
52. McClendon AK, Dean JL, Rivadeneira DB, et al. CDK4/6 inhibition antagonizes the cytotoxic response to anthracycline therapy. *Cell Cycle*. 2012;11:2747−2755.

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