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# Innovative Approaches for Molecular Targeted Therapy of Breast Cancer: Interfering with Various Pathway Signaling

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**ABSTRACT**

Breast cancer encompasses a diverse array of conditions classified as hormone receptor-positive, human epidermal growth factor receptor 2-positive, and triple-negative breast cancer subtypes, dictating treatment approaches. The therapeutic strategies commonly involve addressing estrogen receptors (ER) and HER2, which have exhibited efficacy in managing cancer. Nevertheless, the prevalence of resistance to these therapies, whether inherent or acquired, persists despite the introduction of novel treatment modalities. Progress in comprehending the biology of tumors has facilitated the identification of fresh targets, such as inhibitors targeting different pathways like phosphoinositide 3-kinase/mammalian target of rapamycin (PI3K/mTOR), cell-cycle regulation, heat shock protein, and epigenetic pathways, demonstrating encouraging outcomes in clinical experiments. For example, the mTOR inhibitor everolimus has been sanctioned for ER+ breast cancer and resistance to aromatase inhibitors in the advanced or metastatic phase. Triple-negative breast cancer, characterized by the absence of estrogen receptors, progesterone receptors, and HER2, currently lacks established targeted therapies. While poly (ADP-ribose) polymerase inhibitors exhibit effectiveness in BRCA-related cancers, their efficiency in addressing triple-negative breast cancer residues is uncertain. This paper furnishes a comprehensive outline of the principal targeted therapies presently employed or under exploration for breast cancer treatment within the three clinical subsets.

**Keywords:** Breast, Cancer, Pathways, Target

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## Introduction

In the year 2022, 2.3 million women received a breast cancer diagnosis, resulting in 670,000 deaths worldwide. Breast cancer can affect women in all countries across the globe, occurring at any age post-puberty, with higher incidence rates observed in older age groups (1). The classification of breast cancer includes hormone receptor-positive (HR-positive) tumors expressing estrogen receptors (ERs) and/or progesterone receptors (PRs), ERBB2-amplified (also known as HER2-amplified) breast cancer, and triple-negative breast cancer (TNBC) lacking ERs and PRs expression along with normal or negative HER2 levels. TNBC comprises diverse subgroups with unique genetic profiles and clinical prognoses (2-4).

A notable challenge is the imperative to individualize treatment strategies for each patient. For example, therapies targeting HER2 are efficacious solely in tumors displaying HER2 amplification or overexpression (5). Similarly, PARP inhibitors demonstrate heightened efficacy in tumors harboring BRCA mutations as monotherapy. The identification of additional mutations associated with heightened drug responsiveness in breast cancer remains uncertain, with plausible candidates including PI3K, AKT, FGFR mutations, and PTEN loss (6).

Barriers to targeted therapies encompass both initial and acquired resistance mechanisms. Acquired resistance commonly develops in advanced-stage patients, with mechanisms leading to treatment refractoriness identified in HER2-positive tumors. These mechanisms entail diminished target expression due to prolonged therapy, activation of downstream mutations, and stimulation of alternate pathways fostering cell proliferation. Primary resistance may arise from target independence, while activation of compensatory pathways could counteract the inhibitory properties of blocking a singular objective or pathway. Although combining therapies to combat these adaptive responses could optimize outcomes, the activation of distinct compensatory pathways based on tumor subtype and treatment modality hinders the universal success of combination therapy. Invasive breast cancer is divided into three therapeutic clinical subtypes: HR-positive, HER2-positive, and triple-negative breast cancer (TNBC), which is defined by the absence of Estrogen Receptor (ER), progesterone receptor, and HER2 expression. Each subtype is not a uniform disease but rather exhibits significant heterogeneity. The advent of high-throughput technologies, especially next-generation sequencing, has broadened our understanding of the genomic complexity and intra-tumoral heterogeneity associated with breast cancer. Additionally, during the metastatic progression, breast cancer can evolve and acquire new mutations, leading to further longitudinal heterogeneity and clonal evolution. Although molecularly targeted therapies have been effectively utilized in breast cancer treatment, the emergence of resistance to these agents poses a significant challenge. There is an immediate need for predictive markers to determine which patients are likely to experience resistance, thus necessitating alternative treatment options. The Human Genome Project has facilitated the sequencing of human DNA and spurred advancements in technologies that identify genomic, transcriptional, proteomic, and epigenetic alterations. The integration of these technologies with innovative drug development has expedited the adoption of personalized medicine. This approach leverages the genetic and environmental underpinnings of diseases to tailor prevention, diagnosis, and treatment to individual patients. The refinement of treatment through targeted therapies-agents that focus on specific enzymes, growth factor receptors, and signal

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transducers to disrupt various oncogenic cellular mechanisms-along with other strategies enabled by progress in translational medicine, promises to enhance patient care significantly.

This review will concentrate on emerging targeted therapeutics and considerations for crafting robust clinical trials focusing on breast cancer. For clarity, we will adhere to the current clinic's subclassification terminology.

**Human epidermal growth factor receptor 2 (HER2)/ Estrogen receptor (ER)**

The targeting of Estrogen receptors (ER) and HER2 has been a key focus in the expansion of rehabilitation for breast cancer. Various hormonal treatments, including tamoxifen, aromatase inhibitors (AIs), and fulvestrant, have been approved for managing ER+ breast cancer. Similarly, HER2-targeted drugs like trastuzumab and lapatinib have emerged for HER2+ breast cancer. However, these treatments are not effective for triple-negative breast cancers (TNBC) (7-9).

The estrogen/ER pathway is crucial for HR+ breast cancers, with endocrine therapy showing success. Resistance to endocrine therapy is frequently encountered and presents a significant clinical obstacle. The complexities of endocrine resistance involve the activation of estrogen-independent pathways due to ER and HER2 presence. New therapies are being created for triple-negative breast cancer, as well as for estrogen receptor and HER2-positive conditions that are resistant to treatment. Some ER+ breast cancers have HER2 gene amplification, necessitating dual targeting of ER and HER2. Combinations like letrozole with lapatinib have been approved for ER+ HER2+ breast cancer treatment (10, 11). Effective strategies have been identified in targeting the PI3K pathway and ER in ER-positive HER2-negative breast cancer. The mTOR inhibitor everolimus, in combination with exemestane, has been sanctioned for AI-resistant ER-positive metastatic breast cancer. Encouraging outcomes have also been observed in preliminary trials involving CDK4/6 inhibitors and epigenetic agents (11-14).

ER, a steroid hormonal receptor, shows essential role in ER+ breast cancer cells by regulating propagation, survival, and invasion. When estrogen binds, ER moves to the nucleus to act as a transcription factor. Apart from its genomic functions, ER also has rapid nongenomic effects through interactions with membrane receptors and signaling molecules, and survival pathways (2).

**ER-Targeted Therapies and Endocrine Rehabilitation**

The cornerstone of systemic intervention for hormone receptor-positive breast cancer is endocrine therapy. Different strategies are developed to lower estrogen levels, such as ovarian suppression or ablation in premenopausal individuals, and AIs in postmenopausal individuals, or to regulate the expression or function of estrogen receptors. This includes the use of selective estrogen receptor modulators, which counteract the actions of ER, as well as fulvestrant, which diminishes the activity of ER(15). In the setting of metastatic breast cancer in premenopausal women, tamoxifen exhibits comparable efficacy to ovarian ablation, while the combination of ovarian suppression with tamoxifen showcases enhanced outcomes. Among premenopausal women with early-stage breast cancer, the administration of adjuvant tamoxifen for 5 years leads to a 39% decrease in the risk of breast cancer recurrence and a 30% decline in breast cancer-related mortality, resulting in a substantial absolute decline of 13% in recurrence risk and 9% in mortality risk over 15 years (16-18).

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Aromatase inhibition is a recognized strategy for managing ER-positive breast cancer, which constitutes the common cases. Aromatase inhibitor treatment has demonstrated significant efficacy in decreasing tumor size, enhancing survival rates, and lowering the likelihood of cancer recurrence. Selective ER modulators like Tamoxifen and toremifene mimic estrogen's effects; Aromatase inhibitors such as anastrozole, exemestane, and letrozole inhibit estrogen production; while selective ER degraders (SERDs) like fulvestrant and Elacestrant block and degrade ERs. AIs including letrozole, anastrozole, and exemestane have demonstrated similar effectiveness in clinical practice, with no development of cross-resistance between the nonsteroidal and steroidal AIs (19-22).

Options for subsequent lines of endocrine therapy may consist of another AI, fulvestrant, tamoxifen, testosterone, megestrol acetate, or estradiol, along with the recently approved combination of everolimus and exemestane. The higher dose of fulvestrant is now considered the approved dose in this context, based on the findings of the CONFIRM trial. In post-menopausal women with early-stage disease, several large adjuvant trials have shown that monotherapy with an AI for 5 years or a switching strategy from AI to tamoxifen, or from tamoxifen to AI, totaling 5 years of therapy, is more effective than tamoxifen alone. A large trial demonstrated similar efficacy between AI monotherapy and tamoxifen switching strategies. Consequently, AIs have become the preferred approach, or at least a component of the adjuvant hormonal therapy regimen, for postmenopausal women with ER+ breast cancer (23).

**ER+ HER2-Targeted Agents**

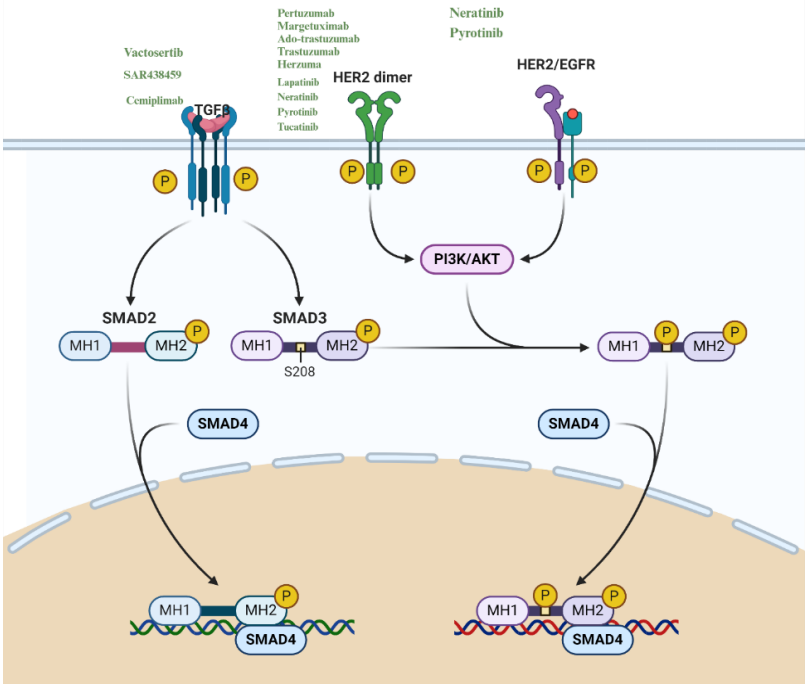


**Fig. 1**. Pathways of TGF-beta, HER2, and HER 2/ EGFR on breast cancer and drugs effective on its pathways.

The HER family, comprising EGFR, HER2, HER3, and HER4, are pivotal tyrosine kinase receptors that are essential for regulating cell growth and survival. In about 10% of ER+ breast cancer instances, there is an amplification of the HER2 gene (ERBB2). Patients with ER+ HER2+ breast cancer have a heightened

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risk of relapse during adjuvant endocrine therapy compared to those with ER+ HER2— disease. This increased risk is due to the failure of complete cell-cycle arrest when treated solely with endocrine agents in the neoadjuvant setting. Research has demonstrated that the inclusion of HER2-targeted agents, such as adjuvant trastuzumab, offers advantages to individuals with HER2+ breast cancer. Notably, the ER+ HER2+ subgroup experiences a notable decrease in relapse rates with trastuzumab treatment (Figure 1) (24, 25).

Trastuzumab combined with anastrozole in the metastatic cases showed meaningfully longer progression-free survival (PFS) and a higher clinical benefit rate (CBR) compared to anastrozole alone in patients with metastatic breast cancer in the phase III trial. However, OS did not show a significant difference. In a single-arm trial for HR+ HER2+ breast cancer patients, trastuzumab combined with letrozole as first- or second-line therapy resulted in an ORR of 26% and a CBR of 52%, with 25% of patients experiencing a durable response lasting over 1 year (26).

**PI3K-AKT-mTOR Pathway Inhibitors**

The PI3K-AKT-mTOR pathway plays a crucial role in transmitting signals for growth and survival, both from outside and inside the cell. Disruption of this pathway is a key factor in endocrine resistance. Studies using preclinical models have shown that ER+ breast cancer with PIK3CA mutations heavily relies on PI3Ka for cell survival. Inhibiting PIK3CA through RNAi or blocking PI3K or AKT with small-molecule inhibitors has been shown to trigger apoptosis in ER+ breast cancer cell lines under conditions of estrogen deprivation (27-29).

Allosteric inhibitors of mTOR complex 1, the rapamycin analogs were among the pioneering compounds to be tested in clinical trials due to their interaction with FKBP12(30, 31). A phase III study demonstrated that the combination of exemestane and everolimus resulted in a median PFS of 10.6 months in postmenopausal women with ER+ HER2— advanced breast cancer resistant to nonsteroidal AIs. This led to FDA approval for its use in the AI-resistant population(32). Clinical trials (NCT01805271 and NCT01674140, phase III) are currently being planned to study the combination of everolimus with hormonal therapy for early-stage ER+ HER2— breast cancer in the adjuvant setting. Everolimus, an oral inhibitor targeting the mammalian target of rapamycin, has shown promise in improving progression-free survival when used with endocrine therapy for postmenopausal women with aromatase inhibitor-resistant metastatic breast cancer. Nevertheless, the potential benefits of incorporating everolimus into ET for early breast cancer in the adjuvant setting are not yet fully understood (33-35).

The antitumor efficacy of rapamycin analogs may be compromised by the feedback up-regulation of AKT. Preclinical investigations suggest that inhibitors targeting AKT or PI3K directly could potentially be more effective. Ongoing clinical trials are assessing various inhibitors targeting AKT or PI3K, including pan-PI3K isoform inhibitors, dual PI3K, and mTOR inhibitors, and isoform-specific inhibitors. One such inhibitor, BKM120, is currently in phase III trials in combination with fulvestrant for patients with metastatic ER+ breast cancer resistant to prior AI therapy or mTOR inhibitor. The Phase III study, conducted at multiple centers, employed a randomized, double-blind, placebo-controlled design to evaluate the efficacy and safety of buparlisib combined with fulvestrant versus fulvestrant alone in postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer that has progressed following treatment with an aromatase inhibitor(36, 37). Furthermore, a distinct inhibitor of PI3K has exhibited favorable results in

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PIK3CA mutant breast cancer in phase I trials. A preliminary report from a phase I study on the a-specific inhibitor BYL719 revealed that 6 out of 18 (33%) patients with heavily treated metastatic breast cancer and PIK3CA mutation experienced tumor shrinkage exceeding 20%, with two of these patients achieving a partial response (38).

**CDK4/6 Inhibitors**

The relationship between estrogen and CDK4/6 activity is significant, as estrogen regulates cyclin D1 through ER. Persistent expression of cyclin D1 and phosphorylation of Rb have been linked to resistance to endocrine therapy in ER+ breast cancer(39, 40). Additionally, ER+ breast cancer with genetic abnormalities in the cyclin D1-CDK4/6 pathway is associated with poor clinical outcomes. Recent findings from the Cancer Genome Atlas project have shown that luminal B ER+ breast cancers with a worse prognosis often have gains in CCND1 (cyclin D1), and losses in CDKN2A (p16) and CDKN2C (p18), which are negative regulators of CDK4/6. Notably, RB1 expression is typically normal in most luminal/ER+ breast cancers, making CDK4/6 inhibitors an attractive option for treating ER+ disease (Figure 2) (40, 41).

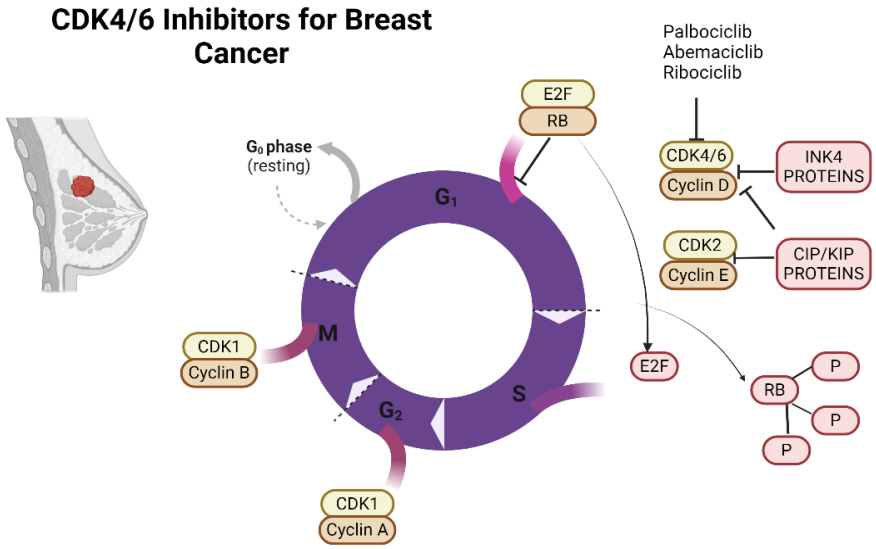


**Fig. 2.** CDK4/6 Inhibitors drugs used for breast cancer. The mechanism and pathways of drug effects.

Palbociclib (PD0332991, Ibrance) in breast cancer cell lines, has shown a preference for ER+ cancer cells, including those resistant to anti-estrogen. When combined with tamoxifen, PD 0332991 has demonstrated a synergistic antitumor effect in both tamoxifen-sensitive and tamoxifen-resistant cell lines. The latest findings from a phase II trial comparing letrozole alone versus letrozole in combination with PD 0332991 as initial treatment for metastatic ER+ HER2—breast cancer indicate a notable increase in progression-free survival duration, with no added safety issues (42, 43).

Ribociclib (LEE011, KISQALI) demonstrates slightly higher potency against cyclin D1/CDK4 compared to cyclin D1, 2, 3/CDK6, with minimal activity against other CDKs (IC50 > 50,000). Postmenopausal women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer can now receive ribociclib, in combination with an aromatase inhibitor, as the FDA has approved this

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treatment as the first-line endocrine-based therapy(44). This decision was supported by the MONALEESA-2 trial and further validated by MONALEESA-3 and MONALEESA-7 phase III trials (45).

Abemaciclib (LY2835219) exhibits slightly higher potency against cyclin D1/CDK4 compared to cyclin D1, 2, 3/CDK6, but then pointedly lower potency against other CDKs. Abemaciclib, in combination with fulvestrant, has been approved by the FDA for the treatment of hormone receptor-positive, HER2-negative advanced, or metastatic breast cancer in women who have experienced disease progression after endocrine therapy(46, 47). Moreover, the FDA has approved the use of abemaciclib alongside endocrine therapy in the adjuvant treatment of adult patients suffering from hormone receptor-positive, HER2-negative, node-positive early breast cancer at a high risk of recurrence. The Ki-67 testing requirement has been eliminated in this decision, which was influenced by the results of the trial (48).

**Histone Deacetylase Inhibitors**

HDACs and histone acetyltransferases are essential epigenetic regulators that influence gene transcription by altering chromatin structures. The disruption of epigenetic control over ER and growth factor receptor pathways is a major factor in developing endocrine resistance. Studies have demonstrated that HDAC inhibitors can lower ER29 transcription levels and promote apoptotic cell death. Initial clinical trials combining HDAC inhibitors with hormonal therapy in AI-resistant breast cancer patients have displayed promising results, indicating that HDAC inhibition could be an effective approach to address resistance in disease(49). At present, the FDA has approved some HDAC inhibitors for the treatment of hematological malignancies, such as vorinostat, belinostat, romidepsin, and panobinostat. However, the effectiveness of HDAC inhibitors in treating solid tumors has been limited (Figure 3) (50, 51).

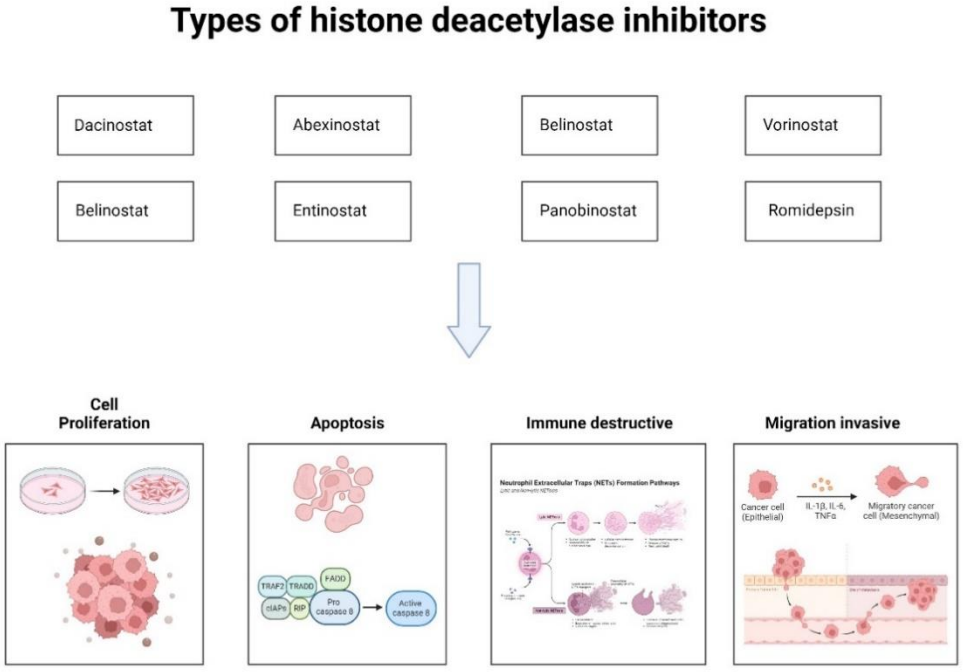


**Fig. 3**. Histone Deacetylase Inhibitors and drugs related to these categories with the mechanisms

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During a phase II study that included vorinostat and tamoxifen for patients with ER+ metastatic breast cancer who had previously not responded to endocrine therapy, the overall response rate was 19% while the clinical benefit rate was 40% (13, 52, 53). Recent findings from a randomized phase II trial investigating the combination of exemestane and entinostat, an oral class 1 HDAC inhibitor, in postmenopausal women with locally recurrent or metastatic ER+ breast cancer that had progressed following non-steroidal AI treatment, indicate encouraging results. The study involved 130 participants, revealing that those treated with entinostat alongside exemestane experienced a median progression-free survival (PFS) of 4.3 months and an overall survival (OS) of 28.1 months, in contrast to 2.3 months and 19.8 months for those receiving exemestane alone. Additionally, research is ongoing into the use of HDAC inhibitors in triple-negative breast cancer (TNBC) to promote estrogen receptor expression and improve responsiveness to endocrine therapies (54).

Vorinostat, commonly referred to as suberoylanilide hydroxamic acid, is an oral inhibitor targeting class I and II histone deacetylases (HDACs). It received clinical approval for use in patients suffering from cutaneous T-cell lymphoma. Both preclinical studies and clinical trials have demonstrated that Vorinostat exhibits therapeutic potential when used in conjunction with other antitumor agents in the treatment of breast cancer. Moreover, the combination of Vorinostat with the CDK inhibitor flavopiridol has shown a synergistic effect, resulting in increased lethality in breast cancer cells through the inhibition of the ERK1/2 and AKT signaling pathways, as well as the modulation of apoptosis pathways. Additionally, research utilizing breast cancer cells with brain metastases and an intracranial xenograft model revealed that Vorinostat enhances radio-sensitivity. This compound also promotes the radio-sensitivity of breast tumor cells, thereby reducing lung metastasis through the inhibition of MMP-9, DNA repair proteins, and the regulation of autophagy and endoplasmic reticulum stress (55, 56).

Entinostat demonstrated a synergistic impact in suppressing tumor growth through increased infiltration of CD8+ T cells, stimulation of inflammation-related gene expression, enhancement of T cell reactions to antigens, and decrease in VISTA expression in murine models of 4T1 carcinoma and colon cancer (57). Various treatment combinations, including vaccines, entinostat, ICIs, and chemotherapy, have demonstrated encouraging effectiveness in treating advanced breast cancer. Both breast cancer cells and prostate tumor cells have displayed sensitivity to entinostat-induced T-cell-mediated lysis. Entinostat has been observed to alter tumor-related antigens like PSA, brachyury, CEA, and MUC1, while also enhancing the production of proteins crucial for tumor immune recognition and antigen processing. The combination of entinostat with immunotherapy shows promise as a potential treatment approach for breast cancer (58).

Romidepsin has been found to inhibit tumor growth in numerous kinds of cancers. For instance, in colon cancer cells, romidepsin reduced cellular immune functions by increasing PD-L1 expression through histones H3 and H4 acetylation and BRD4 modulation (59). Romidepsin also enhanced the number of FOXP3+ regulatory T cells, decreased IFN-γ+ CD8+ T cells, and balanced Th1/Th2 ratio in the tumor microenvironment in subcutaneous and colitis-related cancer models. Additionally, Romidepsin-induced tumor suppression was reversed by anti-PD-1 antibody treatment in colon cancer cells. A case report suggested that romidepsin could be a safe and effective treatment for anaplastic large cell lymphoma (ALCL) without affecting cellular immunity to HTLV-1. Romidepsin also improved paclitaxel sensitivity and prevented tumor metastasis in inflammatory breast cancer (59, 60).

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Panobinostat, exerts a tumor-suppressive effect in various types of cancer (61, 62). Its role in breast carcinogenesis and progression has been confirmed. Panobinostat has been shown to increase the acetylation of glucose-regulated protein 78 and induce endoplasmic reticulum stress by upregulating p-eIF2α, as well as increasing the expression of Bax, and BAK, leading to enhanced caspase-7 activity in breast cancer cells. Additionally, Panobinostat inhibits the proliferation of breast cancer cells by modulating aromatase gene expression and enhances the anti-tumor effect of letrozole in hormone-dependent breast cancer (63, 64).

In various human cancers, mocetinostat, an inhibitor of class I/IV HDAC, has been identified as a potent agent for inhibiting tumorigenesis and tumor progression. Moreover, it has been shown to upregulate APCL expression in breast cancer, thereby inhibiting the Wnt/β-catenin signaling pathway (65). Mocetinostat modulates class I HDAC promoters, resulting in elevated active histone marks and improved IFN-γ activity to regulate class II transactivator. In murine models, mocetinostat reduces Tregs and MDSCs while boosting the CD8+ population within tumors. Moreover, the pairing of mocetinostat with PD-L1 antibody exhibits a synergistic impact in mouse lung tumor models. Furthermore, when paired with the BET inhibitor JQ1, mocetinostat diminishes the survival rate of breast cancer cells by adjusting the expression of cell cycle-related genes (66).

**Methylenetetrahydrofolate dehydrogenase – cyclohydrolase 1and 2 (MTHFD 1 and MTHFD2) inhibitors**

Cancer cells enhance their demand for nucleotides by increasing one-carbon (1C) metabolism, which involves the upregulation of enzymes such as MTHFD1 and MTHFD2. TH9619 serves as a powerful inhibitor of the dehydrogenase and cyclohydrolase functions of both MTHFD1 and MTHFD2, selectively inducing cell death in cancer cells. Our findings indicate that TH9619 specifically targets nuclear MTHFD2 while leaving mitochondrial MTHFD2 unaffected. Consequently, formate continues to overflow from the mitochondria even in the presence of TH9619. The compound inhibits MTHFD1 activity, which is downstream of mitochondrial formate release, resulting in the buildup of 10-formyl-tetrahydrofolate, a phenomenon we refer to as a ‘folate trap’. This accumulation leads to a depletion of thymidylate and ultimately the death of cancer cells expressing MTHFD2. This novel folate trapping mechanism is intensified by physiological levels of hypoxanthine, which obstruct the de novo purine synthesis pathway and further inhibit the utilization of 10-formyl-tetrahydrofolate for purine synthesis. The folate trapping mechanism associated with TH9619 is distinct from other inhibitors of MTHFD1/2 and antifolate agents. TH9619 serves as a strong inhibitor of the enzyme MTHFD2, playing a crucial role in folate metabolism. Research indicates that TH9619 selectively targets and eliminates cancer cells, demonstrating its ability to hinder cancer progression in animal studies. Nevertheless, it is essential to recognize that TH9619 remains in the preliminary phases of development and has not yet received approval for human use (67, 68).

**Other Pathways of Interest in ER+ Breast Cancer**

The molecular chaperone HSP90 is critical for ensuring the correct folding and structural stability of key client proteins involved in cancer cell pathways, including HER2(61). Preclinical studies have demonstrated that inhibiting HSP90 can lead to the degradation of HER2, resulting in tumor cell apoptosis and growth suppression. A phase I trial combining trastuzumab with the HSP90 inhibitor alvespimycin showed one confirmed partial response and seven cases of stable disease in heavily pretreated metastatic HER2+ breast

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cancer patients. A subsequent phase II trial using the HSP90 inhibitor tanespimycin in combination with trastuzumab in HER2+ metastatic breast cancer patients who had progressed on trastuzumab showed an overall response rate of 22% and a median progression-free survival of 6 months, indicating the potential efficacy of HSP90 inhibitors in HER2+ breast cancer. Despite the promising results, further clinical development of tanespimycin was halted, and ongoing research is now focusing on other novel heat shock protein inhibitors (62, 69).

Trastuzumab is a monoclonal antibody designed to target the human epidermal growth factor receptor 2 (HER2) tyrosine kinase receptor, which is overexpressed in about 25% of invasive breast cancer cases. However, most patients with metastatic breast cancer who initially respond to trastuzumab experience disease progression within a year of starting treatment. Preclinical research has identified various molecular mechanisms that may lead to resistance against trastuzumab. Enhanced signaling through the phosphatidylinositol 3-kinase/Akt pathway may play a role in this resistance, as it activates multiple receptor pathways, including those related to HER2 and other receptors like the insulin-like growth factor 1 receptor, which seems to interact with HER2 in resistant cells. Furthermore, the loss of function of the PTEN tumor suppressor gene, which negatively regulates Akt, results in increased Akt signaling and reduced sensitivity to trastuzumab. Additionally, reduced binding between trastuzumab and its target receptor HER2, caused by a steric hindrance from cell-surface proteins such as mucin-4 (MUC4), may inhibit the drug's effectiveness. Innovative therapies aimed at these disrupted molecular pathways hold promise for enhancing the efficacy and duration of response to trastuzumab.

The majority of these mutations in ERBB2 were shown to enhance kinase activity, leading to in vitro cell transformation and xenograft tumor growth upon overexpression. Notably, these mutations responded well to neratinib, while specific presented resistance to lapatinib. Certain mutations located in the extracellular domain were identified as oncogenic and were sensitive to neratinib in preclinical trials. These findings suggest that somatic mutation serves as a substitute path to activate HER2 in breast cancer, in the absence of ERBB2 gene amplification. A phase II trial involving multiple institutions is currently underway to assess the effectiveness of neratinib in metastatic ERBB2 mutant but no amplified breast cancer patients (NCT01670877) (62).

The clinical trial investigated the efficacy of combining bevacizumab with various chemotherapy regimens as a second-line treatment for metastatic HER2-negative breast cancer. Although the trial showed an improvement in progression-free survival, it did not demonstrate a significant effect on OS. In a subgroup analysis involving 159 triple-negative breast cancer patients, the inclusion of bevacizumab resulted in a significant enhancement in overall response rate and PFS when compared to chemotherapy alone, with a trend suggesting better OS. In neoadjuvant studies, results were inconsistent regarding the addition of bevacizumab to chemotherapy. The GeparQuinto trial indicated a higher pathologic complete response rate in TNBC patients receiving bevacizumab, whereas the NSABP B-40 trial failed to confirm these results. The advantages of bevacizumab were particularly evident in the hormone receptor-positive subset in the NSABP B-40 trial (70, 71).

Initial results have been recently disclosed from the phase III trial, which included 2591 TNBC patients randomly allocated to either standard adjuvant chemotherapy alone or with bevacizumab. The research

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indicated no notable variance in invasive disease-free survival between the two cohorts. Nevertheless, individuals in the bevacizumab group encountered a heightened incidence of grade 3 hypertension during the combined therapy phase in contrast to those in the chemotherapy-only group (72, 73). Furthermore, the incidence of adverse events, including proteinuria, congestive heart failure, and left ventricular dysfunction, was higher in the bevacizumab cohort. These findings underscore the necessity of identifying predictive biomarkers to enhance treatment efficacy. Importantly, biomarker evaluations from the trial indicated that elevated baseline levels of plasma VEGF-A and VEGFR-2 correlated with better progression-free survival when treated with bevacizumab (74).

Combining bevacizumab with trastuzumab and docetaxel in the trial yielded comparable results for metastatic HER2+ breast cancer. The trial (NCT01663727) is investigating the potential of VEGF-A levels as a predictive biomarker for the benefits of bevacizumab (75). Patients were stratified according to their VEGF-A level and then randomly allocated to receive weekly paclitaxel along with either bevacizumab or a placebo. Sunitinib and sorafenib are both multitargeted inhibitors of receptor tyrosine kinases, including VEGFR. In phase III trials, sunitinib alone was shown to be less effective than capecitabine in patients with previously treated metastatic HER2— breast cancer. Additionally, combining sunitinib with docetaxel in the first-line setting or with capecitabine in previously treated metastatic HER2— breast cancer did not result in improved progression-free survival (76, 77). During a phase II trial, using only sunitinib led to a lower PFS when compared to standard treatment for patients with metastatic TNBC. There is not much research available on sorafenib for metastatic breast cancer. Nevertheless, in a phase IIb trial that was randomized, double-blind, and placebo-controlled for patients with locally advanced or metastatic HER2— breast cancer, the addition of sorafenib to capecitabine resulted in a significant increase in PFS. This enhancement was observed consistently across different subgroups, including those receiving first-line and second-line treatment, but further validation through phase III trials is required (75, 78).

In a phase II trial involving olaparib for metastatic breast cancers in individuals with BRCA mutations, a 400 mg b.i.d. dose resulted in an overall response rate (ORR) of 41%. Basal-like breast cancers often exhibit characteristics resembling BRCAness, which are traits commonly found in BRCA1 or BRCA2 mutation carriers. For instance, BRCA1-related breast cancers are typically high-grade, triple negative, and fall within the basal-like subtype based on gene expression profiling. Moreover, both sporadic basal-like and BRCA1-related breast cancers show a high frequency of TP53 mutations and significant genomic instability (79).

The variations in effectiveness and safety among PARP inhibitors (olaparib, talazoparib, veliparib, niraparib, rucaparib) could be attributed to differences in the strength of PARP trapping on DNA and the specificity of cytotoxicity. Research is being conducted on PARP inhibitors in early breast cancer, in new combinations, and in patients without inherited BRCA mutations, such as those with acquired BRCA mutations and mutations in other genes related to homologous recombination repair. Ongoing phase 2/3 trials are exploring the combination of PARP inhibitors with immune checkpoint inhibitors for the treatment of triple-negative breast cancer (Figure 4) (80, 81).

The phosphoinositide 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway has been linked to resistance against endocrine therapy, HER2-targeted therapy, and cytotoxic treatments in breast cancer. Numerous inhibitors targeting the PI3K/Akt/mTOR pathway are either in preclinical stages or

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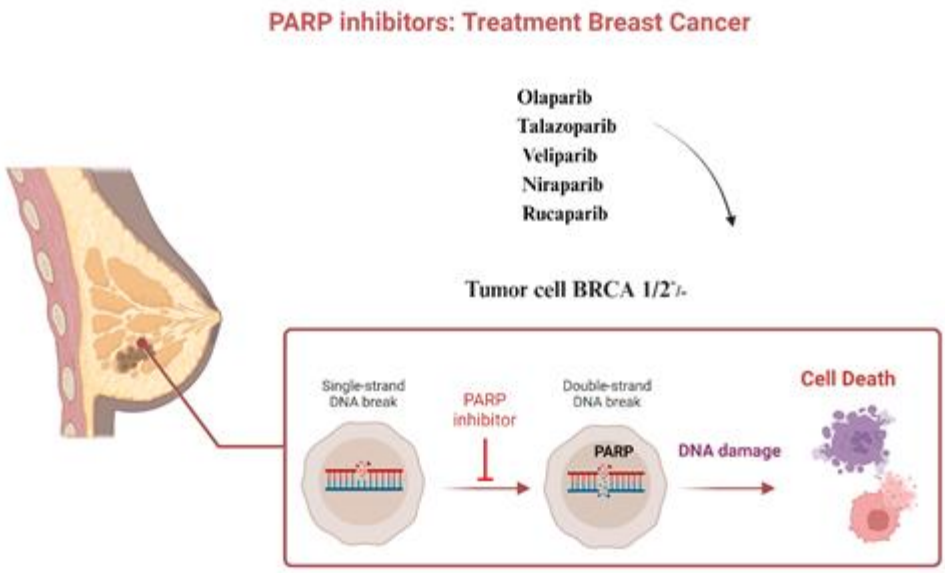


**Fig. 4.** The efficacy of PARP inhibitors and related drugs

undergoing clinical trials. Encouraging evidence suggests that rapalogs and PI3K/Akt inhibitors show efficacy in breast cancer cases. Everolimus, a rapamycin derivative and mTOR inhibitor is currently the sole agent approved for treating hormone receptor (HR)-positive, HER2-negative metastatic or locally advanced breast cancer. Everolimus is an oral pharmacological agent employed in the management of advanced breast carcinoma characterized by hormone receptor positivity and HER2 negativity(82). Research has demonstrated that the administration of everolimus in conjunction with other therapeutic agents can enhance clinical outcomes for various subtypes of breast cancer, particularly those that are hormone receptor-positive. It is crucial to acknowledge that this constitutes a multifaceted medical concern, and one should invariably seek the counsel of a healthcare professional for tailored recommendations. Consequently, targeting this pathway presents a viable strategy to address resistance. Therapeutic interventions aimed at inhibiting this signaling cascade involve the application of PI3K inhibitors, including pan-PI3K inhibitors like buparlisib and pictilisib(83). Activation of the PI3K pathway, often caused by the absence of negative regulators such as PTEN and INPP4B, is a common occurrence in TNBC, making it an appealing target for therapy. Notably, a patient with TNBC showed a partial response when treated with the PI3K inhibitor BKM120 in a phase I study. BKM120 is currently undergoing phase II trials in patients with metastatic TNBC (NCT01629615 and NCT01790932) (84). Furthermore, combination approaches involving PI3K pathway inhibition and PARP inhibitors (NCT01623349) are being investigated in early-phase clinical trials, based on promising preclinical data(84). In a small cohort of patients with triple-negative breast cancer, Buparlisib was linked to an extended duration of stable disease; nonetheless, no confirmed objective responses were noted. Those who achieved stable disease exhibited down regulation of significant nodes in the PI3K pathway. This indicates that targeting the PI3K pathway alone may not suffice as an effective therapeutic strategy for triple-negative breast cancer(85). Buparlisib is an orally administered pan-PI3K inhibitor and is the most clinically developed agent within this category. Its effectiveness has been validated through multiple clinical trials (NCT01339442, NCT01610284), demonstrating that the combination of buparlisib with fulvestrant in

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patients with estrogen receptor-positive breast cancer significantly enhances progression-free survival compared to fulvestrant alone (86).

Dasatinib, a strong inhibitor of Src family kinases, was evaluated as a single treatment in a phase II trial involving unselected patients with advanced TNBC. The trial showed a 4.7% response rate, indicating an antitumor effect in a specific subset of TNBC. Ongoing research is focused on identifying predictive biomarkers for dasatinib and exploring combination approaches with chemotherapy agents (NCT01676753) (87, 88).

**Future directions and highlights for research in targeted therapies for breast cancer**

Breast cancer, a multifaceted and complex group of malignancies, can be categorized into a variety of distinct subtypes that are defined by their unique origins, progression patterns, and molecular characteristics. These subtypes are not merely academic classifications but reflect significant variations in the biological behavior and clinical manifestations of the disease, which underline the necessity for precise and tailored treatment approaches. The protein-gene products that play a pivotal role in influencing the biological behaviors and clinical features of cancer cells present promising opportunities for the creation of innovative therapeutic strategies. To this end, gene signatures have emerged as potential predictors of how effectively a patient might respond to different types of therapeutic interventions. Therefore, it becomes exceedingly important to meticulously consider the various aforementioned factors to determine the most appropriate therapeutic regimen for each individual patient.

In light of the challenges posed by chemoresistance and the recurrence of breast cancer, researchers and pharmaceutical scientists have devoted significant efforts to the development of targeted pharmaceuticals aimed specifically at the management of diverse forms of breast cancer. Among these therapeutic agents, PARP inhibitors, PI3K/AKT/mTOR inhibitors, CDK4/6 inhibitors, and HER2 TKIs have surfaced as promising targeted therapies for distinct subtypes of breast cancer including those with gBRCA mutations, PIK3CA mutations, estrogen receptor positivity, and HER2 overexpression, respectively. Some of these targeted drug therapies have already achieved promising clinical outcomes, either as monotherapy or in combination with other therapeutic agents, and have received endorsement from regulatory agencies for the treatment of specific breast cancer subtypes. Nevertheless, the application of targeted therapies tailored to specific cancer subtypes does not guarantee complete clinical success, as the complexity of breast cancer often leads to challenges in achieving optimal outcomes. One of the most significant hurdles in the effective administration of current targeted agents is the emergence of drug resistance, which poses a formidable challenge to successful treatment. The incorporation of a co-drug that effectively antagonizes the mechanisms of drug resistance and mitigates potential escape pathways may represent a viable solution to this pervasive issue.

In this context, it is crucial to ensure that the disease characteristics, particularly those relating to specific clinical and genetic markers, are comprehensively understood to achieve the anticipated therapeutic success. Consequently, it is of utmost importance to elucidate the molecular, genetic, and immune signatures of tumor cells, as well as the tumor microenvironments, prior to the initiation of targeted therapeutic strategies. Numerous small molecules have demonstrated encouraging results in preclinical studies, indicating their potential for further clinical translation and application. The exploration of avant-garde methodologies,

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especially those that emphasize gene and molecular-level analyses of breast cancer subtypes within clinical environments in response to therapeutic interventions, should be prioritized in forthcoming clinical research endeavors to derive more accurate conclusions. Additionally, a meticulous examination of the adverse reactions associated with targeted therapeutics is warranted, particularly given the serious toxicities that accompany these treatments, which necessitate thorough critical interpretation. Conversely, as it currently stands, chemotherapy remains the sole treatment option available for patients suffering from triple-negative breast cancer. However, substantial advancements in the realm of immunotherapy hold the potential to foster new optimism in the management of breast cancer, particularly for those afflicted with TNBC. The integration of immune checkpoint inhibitors and other immunotherapeutic agents into the existing framework of breast cancer treatments has the capacity to enhance therapeutic responses, as evidenced by improvements in progression-free survival and overall survival rates among patients, including those diagnosed with TNBC. The approval of immune checkpoint inhibitors by regulatory bodies, particularly when used in conjunction with other therapeutic modalities, underscores the promising potential of immunotherapy in this context. Furthermore, the increasing number of clinical trials being conducted indicates that the combination of immune checkpoint inhibitors with various therapeutic agents is emerging as a potentially efficacious strategy in the management of breast cancer, especially for patients with TNBC. Despite the notable advancements represented by immune checkpoint inhibitors as a significant breakthrough in the treatment landscape for TNBC, it is important to recognize that the efficacy remains limited primarily to tumors that overexpress PD-L1. Thus, further research is essential to comprehensively address this critical issue and expand the applicability of immunotherapeutic strategies in breast cancer management.

## Discussion

In conclusion, recent developments in targeted therapy have introduced a more precise and effective approach to managing breast cancer. The primary goal of targeted therapy is to inhibit specific molecules that facilitate tumor growth and survival. Several targeted medications, either alone or in combination with other treatments, have received FDA approval for various breast cancer subtypes, with many more currently undergoing clinical trials. Nonetheless, drug resistance poses a significant challenge for these therapies. Additionally, most targeted treatments have yet to achieve clinical success in patients with triple-negative breast cancer (TNBC). Conversely, immunotherapies have shown promise as targeted treatments specifically for TNBC patients. Certain immune checkpoint inhibitors, when used in conjunction with other drugs, have already been approved by the FDA for TNBC treatment. The growing number of ongoing clinical trials reflects the increasing interest in this area. However, due to the heterogeneity of breast cancer, a comprehensive understanding of the molecular, genetic, and immunological characteristics of tumor cells and their microenvironment is crucial for achieving effective outcomes with targeted or immunotherapy. Therefore, there is an urgent need to identify and develop specific markers to enhance our understanding of breast cancer subtypes, which will aid in determining the most appropriate therapeutic strategies. On the other hand, this methodology provides highly individualized interventions, which may enhance therapeutic efficacy while reducing adverse effects. Nevertheless, such therapies frequently entail greater financial burdens relative to conventional treatment modalities. Economic factors significantly influence the

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accessibility of these therapies, given that the expenses associated with development, research, and production can be substantial. Furthermore, the extent of insurance coverage and the affordability of these treatments may serve as barriers to access for certain patient populations.

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