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Conventional and Advanced Therapeutic Approaches in Breast Cancer Treatment

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ABSTRACT

Breast cancer (BC) is the second leading cause of cancer-related deaths among women worldwide, and occasionally occurs in men. The majority of deaths related to breast cancer, over 90%, are due to delayed detection, which allows the disease to spread to other organs. The diagnostic process usually involves a biopsy, supported by imaging techniques such as MRI and CT scans, to confirm the diagnosis and guide treatment planning. This review examines various treatment strategies, including chemotherapy, hormonal therapy, and targeted therapy, which are selected based on the molecular characteristics of the breast cancer. Treatment options for breast cancer are diverse and encompass both traditional and modern therapies. Traditional approaches include oncoplastic breast surgery, radiation therapy, and adjuvant chemotherapy, while advanced treatments focus on systemic treatments, including targeted therapy, hormone therapy, and immunotherapy. These advanced treatments are designed to specifically target cancer cells, minimize side effects, and increase the overall effectiveness of the treatment. Treatment decisions are influenced by factors such as the molecular subtypes of breast cancer, the patient's overall health, personal preferences, and regular screening results.

Keywords: Advanced therapy, Breast cancer, Chemotherapy, Target therapy, Conventional therapy, Hormonal therapy

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Introduction

In 2020, breast cancer (BC) affected 2.3 million women globally, resulting in 685,000 deaths. By the end of 2020, a cumulative total of 7.8 million women had been diagnosed with BC in the preceding five years, making it the most prevalent cancer worldwide. Data from 2020 reveals that global breast cancer cases account for 0.6% of all cancers, while BC-related fatalities make up 0.9% of cancer deaths, positioning it as the second leading cause of cancer death, following lung and bronchus cancer (13.9%) [1]. The incidence and mortality of BC vary across different regions. It is the most commonly diagnosed cancer among women in the majority of countries worldwide, with 140 out of 184 nations reporting it as the most frequent type of cancer [2].

From the 1930s to the 1970s, breast cancer mortality remained relatively stable. However, since the 1980s, improvements in survival rates have been observed, particularly in countries with early detection programs and effective treatment modalities. Age-standardized breast cancer mortality in high-income countries dropped by 40% between the 1980s and 2020. Countries that successfully reduced BC mortality achieved an annual decline of 2-4% per year. If this annual reduction continues globally, an estimated 2.5 million BC deaths could be prevented between 2020 and 2040 [3].

Breast cancer is a complex, multifactorial disease influenced by various factors, including genetic mutations, reproductive history, exposure to biological carcinogens, environmental factors, chemical exposures, and obesity. It typically originates in the cells of the lobules (15%), glandular tissue (85%), or the ducts of the breast. For

patients with metastatic BC, the common sites of metastasis include the brain (4-10%), bones (30-60%), lungs (21-32%), and liver (15-32%) [4].

BC is classified into five molecular subtypes based on differences in histopathological genetic expression **(Table 1)**. These molecular alterations, including receptor overexpression, underperformance, or mutations, can trigger various signaling pathways, leading to the development of BC [5]. It is crucial to categorize each BC patient into a specific molecular subtype to predict their diagnosis and determine the most suitable treatment approach. Key factors like histological grade, which involve evaluating tumor differentiation, nuclear pleomorphism, and proliferation, are essential components of pathology reports [6].

Ongoing research in BC therapy is focusing on the creation of new treatments tailored to the sub-molecular types of BC, aiming to provide more effective, individualized options with fewer side effects to enhance survival and quality of life. This goal can be achieved through a combination of treatment strategies or by using less toxic drug regimens. This review outlines various therapeutic approaches, including chemotherapy, targeted therapy, and hormonal therapy, which are selected based on the molecular subtypes of BC.

Table 1. BC subtypes based on molecular classification

Subtypes	Characteristics
Luminal A	This subtype is characterized by the presence of hormone receptors (HR positive) while lacking HER2 expression. Estrogen receptor (ER) levels are notably elevated, whereas the proliferation marker Ki67 tends to remain at relatively low levels.
Luminal B	Identified as ER-positive and HER2 negative, this group is often associated with a less favorable response to endocrine treatment strategies when compared to Luminal A cases.
Basal-like/triple negative BC (TNBC)	This classification is marked by the absence of ER, progesterone receptor (PgR), and HER2 expression. It generally exhibits reduced gene expression activity, although cytokeratins (CK) display increased expression. TNBC is frequently observed in patients with BRCA1 gene mutations.
HER positive	Tumors within this category demonstrate amplification of the HER2 gene, located on chromosome 17q21. The HER2 protein structure comprises an extracellular ligand-binding domain, a membrane-spanning region, and an intracellular tyrosine kinase domain responsible for catalytic activity.
Normal like (HR-positive and HER2 negative)	This rare subtype of breast cancer resembles non-cancerous breast tissue and fibroadenomas. It is HR and HER2 negative and also lacks expression of CK5 and the endothelial growth factor receptor (EGFR). Importantly, it is distinct from the basal-like subtype and shows limited responsiveness to neoadjuvant chemotherapy.

Results and Discussion

Targeted therapy in breast cancer (BC)

Targeted therapies (TTs) for breast cancer (BC) involve the use of specific drugs or compounds designed to recognize and interfere with molecules that play a critical role in the development, proliferation, and survival of cancer cells [7]. These therapeutic agents function by selectively binding to particular targets within cancer cells, disrupting their activity, and subsequently inhibiting tumor progression and uncontrolled cell division. Unlike traditional chemotherapy, which often affects both cancerous and healthy cells, TTs primarily act on cancer-specific or cancer-related cells, thereby minimizing damage to normal tissues and resulting in fewer intense side effects. Targeted treatments may be administered either orally or through intravenous infusion. A comparison highlighting the key distinctions between targeted therapies and conventional chemotherapy is presented in **Table 2**.

Table 2. Major differences between TTs and conventional chemotherapy

S/N	Targeted therapy	Conventional chemotherapy
1	Specifically binds to certain molecules and cellular components that drive cancer progression	Acts broadly on rapidly dividing cells, affecting both malignant and healthy cells
2	Associated with comparatively mild or less intense side effects	Often results in more severe and widespread side effects
3	Exhibits cytostatic properties — functions by halting or suppressing tumor cell growth and multiplication	Exhibits cytotoxic properties — aims to eliminate and destroy cancer cells

The integration of various targeted therapies (TTs) or the identification of novel TT agents in breast cancer (BC) could significantly contribute to expanding knowledge about alternative or compensatory signaling pathways. Although TT has initiated progress in uncovering mechanisms responsible for therapeutic resistance, certain BC subtypes, such as triple-negative breast cancer (TNBC), seem to rely on distinct proliferation pathways that still require urgent investigation and clarification [8].

The clinical performance of targeted drugs in BC is often restricted due to the rapid emergence of resistance, which may result from genetic mutations or oncogenic modifications within cellular signaling pathways. Consequently, implementing strategies that involve simultaneous inhibition of multiple pathways should be emphasized to achieve more effective and durable therapeutic outcomes [9].

Standard treatment options for BC currently include chemotherapy, immunotherapy, radiotherapy, and surgical intervention [10]. Given the molecular heterogeneity of BC, including HER2-positive, HER2-negative, hormone receptor-positive, and triple-negative breast cancer (TNBC), the application of customized targeted therapies has become a critical element of modern treatment protocols. In particular, personalized approaches for hormone receptor-positive BC have gained clinical approval, involving selective estrogen receptor degraders and modulators (SERDs and SERMs), endocrine-based therapies, and aromatase inhibitors (AIs) [11].

Among the notable TT drugs are monoclonal antibodies, which can exert anti-cancer effects through multiple mechanisms. These agents not only interfere with cancer cell growth but can also stimulate immune system activity, positioning them within the scope of immunotherapy. **Table 3** provides a summary of currently available targeted therapeutic drugs with specific activity against distinct molecular pathways.

Targeted therapy in HER2-positive breast cancer

Around 20% of women diagnosed with breast cancer (BC) overexpress a protein called Human Epidermal Growth Factor Receptor 2 (HER2), which is crucial in driving cancer growth. HER2 is a transmembrane receptor protein belonging to the EGFR/ERBB family of tyrosine kinase receptors [12]. It is recognized as a primary biomarker in BC since its overexpression is commonly observed in these cancers, making it both a diagnostic and prognostic marker [13]. This proto-oncogene is notably overexpressed in 10-12% of more than 2,500 BC cases and correlates with a higher risk of malignant spread and poor survival, particularly in cases involving lymph node metastasis [14].

The HER2 gene is located on chromosome 17 (17q12) and is classified within the EGFR family of tyrosine kinase receptors [15]. This family includes EGFR/HER1, ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4. These receptors share structural similarities, including a transmembrane domain, a juxtamembrane region, a kinase domain, and a cytoplasmic tail with multiple tyrosine phosphorylation sites [16]. Estrogen is known to activate HER2, a process facilitated by the estrogen receptor located on the cell's nuclear surface [17].

HER2 is critical in the formation of both homo- and heterodimers with other receptors, such as EGFR, HER3, and HER4. These interactions enable ligand binding at the extracellular domains, which activate kinase functions. The most frequent event among these receptors is the formation of a HER2/HER3 heterodimer. The HER3 component then triggers the activation of the AKT/PI3K signaling pathway through its six docking sites for the p85 adapter subunit of PI3K. This pathway plays a vital role in maintaining the survival of cells dependent on HER2 signaling. If HER3 is lost, the survival of HER2-overexpressing BC cells is compromised [18]. For patients with HER2-positive metastatic BC, targeting the HER2 gene with a combination of targeted therapy and chemotherapy offers an effective treatment option.

Monoclonal antibodies (MAs)

Monoclonal antibodies are lab-engineered proteins designed to replicate the function of natural antibodies. These antibodies can attach to specific molecules to treat a range of diseases, including cancer. In BC, monoclonal antibodies bind to the HER2 protein, blocking its role in cancer cell growth and proliferation [19]. They can function independently or deliver additional agents, such as toxins or radioactive substances, directly to cancer cells. As a result, monoclonal antibodies are often combined with chemotherapy as part of an adjunctive treatment strategy. The development of anti-HER2 monoclonal antibodies has significantly transformed the clinical outlook for HER2-positive BC patients, dramatically improving the management of metastatic cases in this subgroup [20].

Antibody-drug conjugates (ADCs)

Antibody-drug conjugates (ADCs) are innovative therapies that combine monoclonal antibodies (MAs) with cytotoxic chemotherapy agents. The anti-HER2 antibody in ADCs specifically targets HER2 on the surface of cancer cells, delivering chemotherapy directly to the tumor. The development of ADCs combines the cell-targeting capabilities of MAs with the potent cytotoxic properties of chemotherapeutic agents, which work in tandem to destroy cancer cells [21]. From a molecular perspective, ADCs consist of a monoclonal antibody that targets specific cancer cells, linked to a cytotoxic compound via a specialized drug linker. This method has shown considerable promise in treating HER2-positive BC, especially with the introduction of TDM-1. Several ADCs are currently under clinical and preclinical investigation, yielding encouraging outcomes [22].

Trastuzumab is a recombinant monoclonal antibody that effectively targets the HER2 protein and blocks its signaling. As the first FDA-approved drug for HER2-positive BC, Trastuzumab (branded as Herceptin, Herzuma, Kanjinti, Ogivri, and Ontruzant) was approved in 1998. It is commonly used in combination with other chemotherapies such as carboplatin, doxorubicin, docetaxel, paclitaxel, and cyclophosphamide to treat HER2-positive BC [23]. Trastuzumab is effective for both early and advanced BC stages, typically administered intravenously over 6 months before or after surgery. However, the drug can cause heart-related side effects, so cardiac monitoring is essential during treatment [24].

Pertuzumab (Perjeta) is another monoclonal antibody approved by the FDA on December 20, 2017. It is often used alongside Trastuzumab and other chemotherapy agents in the first-line treatment of HER2-positive metastatic BC [25]. Pertuzumab can be administered intravenously before or following surgery to treat early or advanced-stage BC, including locally advanced or inflammatory types. While it has mild side effects like diarrhea and rashes, when combined with Trastuzumab and hyaluronidase (Physio), it is given subcutaneously, with potential severe side effects such as reduced red blood cell counts, hair loss, nausea, and fatigue [26].

Margetuximab, approved by the FDA on December 16, 2020, is another monoclonal antibody designed to treat advanced HER2-positive BC. Marketed as Metgena, it is typically used for patients who have received at least two prior HER2-targeted therapies. Margetuximab is administered intravenously every three weeks and can cause heart complications, necessitating regular echocardiogram monitoring [27].

Fam-trastuzumab deruxtecan (Tukysa) is an ADC combining two distinct anti-cancer drugs: Trastuzumab, which targets HER2 receptors, and Deruxtecan, which is delivered directly into cancer cells to cause cell death. This ADC is used to treat metastatic BC that cannot be surgically removed, particularly in patients who have already undergone at least two HER2-targeted therapies. It is given via intravenous infusion every three weeks. However, the drug can lead to interstitial lung disease (ILD), which damages the lungs and causes symptoms such as coughing and difficulty breathing [28].

Ado-trastuzumab emtansine (Kadcyla) is an antibody-drug conjugate that links a monoclonal antibody to the chemotherapy drug emtansine, a paclitaxel-like agent. This combination is used for both early-stage HER2-positive BC and for treating cancer that has metastasized or recurred. The antibody targets HER2 receptors, while the emtansine portion disrupts microtubules inside cancer cells to halt their growth. Ado-trastuzumab emtansine is administered intravenously at a dose of 3.6 mg/kg every three weeks until the cancer progresses or severe side effects occur. It is approved for patients who have previously received trastuzumab and paclitaxel or docetaxel-based chemotherapy [29].

Tyrosine kinase inhibitors (TKIs)

Tyrosine kinases are critical enzymes that relay signals from receptors on the cell surface to trigger vital cellular processes, such as growth, differentiation, migration, and programmed cell death (apoptosis). Tyrosine kinase inhibitors (TKIs) are a class of therapeutic agents designed to block the activity of these enzymes, offering life-prolonging benefits for cancer patients. These inhibitors can be used in conjunction with other anticancer drugs as part of an adjuvant treatment regimen. TKIs have gained significant popularity recently due to several advantages over monoclonal antibodies, such as their oral administration, lower cardiovascular toxicity, and ability to target multiple molecular pathways [30].

Lapatinib is an oral tyrosine kinase inhibitor that targets and blocks HER2 and other proteins, preventing their role in tumor growth. It is primarily used for the treatment of advanced HER2-positive breast cancer that has not responded to previous therapies. Lapatinib is often combined with other treatments, such as trastuzumab and capecitabine, depending on the patient's specific condition. Notably, lapatinib is capable of crossing the blood-brain barrier, making it a useful option for treating HER2-positive breast cancer that has spread to the brain. However, this drug can lead to liver toxicity and gastrointestinal side effects, including diarrhea [31, 32].

Neratinib is another TKI that targets HER2, HER4, and EGFR receptors, inhibiting their function to prevent tumor cell growth. This drug is typically used as a follow-up treatment after a year of trastuzumab therapy for early-stage HER2-positive breast cancer and is also approved for advanced or metastatic HER2-positive breast cancer, particularly in patients who have undergone at least two prior anti-HER2 treatments. Neratinib is taken orally once daily with food and may cause side effects such as diarrhea and liver damage [33].

Approved by the FDA in 2020, tucatinib is used alongside trastuzumab and capecitabine to treat advanced HER2-positive breast cancer. It works by blocking HER2 signaling, helping to slow the progression of cancer, especially in cases where the cancer is inoperable or has spread to distant organs, including the brain. Tucatinib is administered orally, twice a day, and may lead to diarrhea and liver-related issues as common side effects [34].

Targeted therapy for metastatic HER2-negative breast cancer and hormone receptor-positive cancer

Nearly 75% of breast cancer cases are classified as hormone receptor-positive, with estrogen and progesterone playing a crucial role in cancer progression. For these types of cancers, hormone therapy (HT) is typically effective. In addition to traditional hormone therapies, targeted treatments that inhibit downstream signaling pathways like RAS/MEK/ERK and PI3K/AKT/mTOR, as well as agents targeting tyrosine kinases such as SRC, IGF, IGFR, PARP inhibitors, and MMPs, are now used to address cancer metastasis and invasion [35].

Cyclin-dependent kinase inhibitors

These molecules that inhibit cyclin-dependent kinases (CDKs) work by preventing tumor growth, targeting the CDKs involved in processes such as cell cycle regulation, gene transcription, metabolism, apoptosis, and other critical functions like insulin secretion and brain communication [36]. When used in combination with hormone therapy, CDK4/6 inhibitors can be an effective treatment for advanced hormone receptor-positive HER2-negative breast cancer (BC). The FDA has approved CDK inhibitors, particularly for treating metastatic hormone receptor-positive BC with disruptions in CDK4 and CDK6 enzymatic activities [37]. These inhibitors work by affecting the G1-to-S phase of the cell cycle and regulating checkpoints [38]. When used together with estrogen therapy, CDK4/6 inhibitors have significantly improved survival rates [38]. The activation of CDK4 and CDK6 by cyclins leads to the phosphorylation of retinoblastoma protein (pRb), which inhibits the E2F transcription factor family, enabling the cell to continue its division and cycle [39]. As the G1-to-S checkpoint is often dysregulated in HR-positive BC, CDK4/6 inhibitors are used to block this phase and promote cancer cell death [39]. In the human genome, there are 21 CDKs and 5 CDK-like genes identified based on sequence homology [40], with CDK1 being vital for mitotic progression and CDK2 for DNA replication.

Palbociclib, an oral CDK4/6 inhibitor, targets and blocks CDK4/6, which are essential for the proliferation and division of cancer cells. It was FDA-approved in 2015 to be used with aromatase inhibitors such as letrozole or anastrozole as a first-line therapy for postmenopausal women with ER-positive, HER2-negative metastatic BC [41]. Palbociclib can also be paired with fulvestrant for patients whose cancer has relapsed or progressed after treatment with an aromatase inhibitor. This drug carries a low risk of severe adverse effects but can reduce white blood cell counts [42].

Ribociclib is another CDK inhibitor that, in combination with letrozole, is used to treat HR-positive and HER2-negative BC that has recurred or metastasized. It follows a 21-day treatment cycle [43]. It can also be used with fulvestrant in postmenopausal women with metastatic HR-positive and HER2-negative BC [43].

Abemaciclib is approved for use as a first-line treatment in combination with aromatase inhibitors like letrozole or anastrozole for postmenopausal women with ER-positive, HER2-negative metastatic BC. In cases where the cancer has relapsed after being treated with an aromatase inhibitor, it can also be used alongside fulvestrant. A common side effect of abemaciclib is diarrhea, which can be severe. Additionally, gonadotropin-releasing hormone analogs or ovarian suppression may be necessary for premenopausal women or male BC patients when used in combination with aromatase inhibitors and CDK4/6 inhibitors.

Mammalian target of rapamycin (mTOR) inhibitors

The inhibition of mTOR plays a critical role in limiting cancer cell proliferation and preventing the development of new blood vessels (neo-angiogenesis). mTOR is involved in multiple cellular signaling pathways that regulate key processes such as cell growth, autophagy, and programmed cell death. Recent studies have highlighted the association of the mTOR pathway with conditions like cancer, arthritis, insulin resistance, and osteoporosis [44]. The mTOR pathway impacts cancer by controlling transcription factors, protein synthesis, cell proliferation,

immune cell differentiation, and metabolic activities within tumors [45]. Present in most mammalian cells, mTOR belongs to the phosphoinositide 3-kinase-related kinase (PIKK) family of proteins. It functions as a nutrient sensor within cells, stimulating cellular growth and protein accumulation while simultaneously inhibiting autophagy [46]. Everolimus (Afinitor) is an mTOR inhibitor that was approved for treating advanced renal cell carcinoma in 2009 and was later authorized in 2010 for preventing organ rejection in kidney transplants [47]. In 2012, the FDA approved Everolimus in combination with the aromatase inhibitor exemestane (Aromasin) for treating advanced HR-positive, HER2-negative metastatic breast cancer in postmenopausal women who had previously received therapy [48]. The drug works by binding to the FK506-binding protein 12, which interacts with mTOR, preventing further progression of the cell cycle and halting cell division and growth [48]. This interaction improves the effectiveness of hormone therapy. Side effects associated with Everolimus include mouth ulcers, diarrhea, rash, nausea, fatigue, low red blood cell counts, difficulty in breathing, as well as coughing. Furthermore, Everolimus may elevate blood lipid and glucose levels, requiring ongoing monitoring of patients for potential complications [49].

Poly (ADP-ribose) polymerase (PARP) inhibitors

PARP enzymes play an essential role in maintaining DNA replication, repair mechanisms, and cellular development. Cancer cells exploit this function to repair DNA damage and promote their survival [50]. This insight has led to the creation of a new category of anticancer drugs known as PARP inhibitors, which aim to hinder the DNA repair process within cancer cells. Research is ongoing into their use for treating triple-negative breast cancer (TNBC) and as an adjunct in patients with HER2-negative early-stage breast cancer who carry BRCA1 or BRCA2 mutations. There are 18 members in the PARP family, ranging from PARP-1 to PARP-3, classified as DNA damage-dependent [51]. Currently, only 2 PARP inhibitors are approved for use in breast cancer: olaparib and talazoparib, though others have been authorized for ovarian cancer treatment [52]. Recent studies have shown that olaparib can improve progression-free survival and distant disease-free survival in gBRCAm patients with HER2-negative high-risk early breast cancer [52].

Olaparib is a PARP inhibitor that targets patients with HER2-negative breast cancer and mutations in the BRCA1 or BRCA2 genes, particularly those whose tumors have spread or progressed to other regions.

Talazoparib is another PARP inhibitor approved for treating HER2-negative breast cancer in patients with BRCA1 or BRCA2 gene mutations whose disease has metastasized.

Veliparib is still under investigation for its effectiveness in treating HER2-negative, gBRCA-mutated metastatic or locally advanced breast cancer, when combined with platinum-based chemotherapy. This drug targets both PARP1 and PARP2 but has limited PARP-trapping abilities [53].

Niraparib is a PARP1 and PARP2 inhibitor, currently being explored in phase 1 clinical trials for its ability to reduce tumor size in HER2-negative, gBRCA-mutated breast cancer when used as neoadjuvant chemotherapy. It is also employed as a maintenance therapy to prevent relapse.

Rucaparib inhibits the activity of PARP1 and PARP2. While primarily used for ovarian, fallopian tube, and primary peritoneal cancer, it is now being tested in phase 2 trials for use in BRCA-mutated metastatic breast cancer. It is also under evaluation in a phase 1b/2 trial alongside other treatments for TNBC or BRCA-mutated breast cancer to assess safety and efficacy [53, 54].

Pamiparib, which targets PARP1 and PARP2, is being tested as a single-agent therapy in patients with metastatic or locally advanced TNBC, BRCA-mutated breast cancer, or HER2-negative BRCA-mutated breast cancer, in phase 2 trials [55].

Phosphoinositide 3-kinase (PI3K) inhibitors

PI3K inhibitors work by targeting enzymes involved in critical signaling cascades such as the PI3K/AKT/mTOR pathway. In breast cancer (BC), dysregulation of the PI3K pathway is frequently observed, contributing to enhanced cell proliferation and survival [56]. This pathway plays a pivotal role in the initiation, progression, and development of resistance to hormonal therapies and chemotherapy in BC, influencing glucose uptake, cellular growth, and longevity [57]. The Class I PI3K isoform is most commonly implicated in BC, composed of a p85 regulatory subunit and a p110 catalytic subunit [58]. The activation of AKT leads to the activation of several downstream pathways, including mTOR, which controls various cellular processes such as translation, transcription, and growth [59]. PTEN and INPP4B act as negative regulators of this pathway, dephosphorylating PIP3 back to PIP2. Several genetic mutations affecting the genes in the PI3K pathway have been identified [60].

Alterations in the PIK3CA gene, which encodes the p110 subunit, are found in approximately 40% of HR-positive/HER2-negative and HER2-positive metastatic BC cases, as well as in around 9% of TNBC tumors [61]. In 2019, the FDA approved Alpelisib (Piqray and Vijoice) as a targeted therapy that inhibits the abnormal PI3K protein in cancer cells, particularly for HR-positive, HER2-negative metastatic BC with PIK3CA mutations in postmenopausal women and men [62]. Mutations in the PIK3CA gene occur in 20-50% of breast cancer cases, and Alpelisib can be used in combination with fulvestrant and aromatase inhibitors [63]. A blood test to identify this mutation is recommended before treatment. Possible side effects include rashes, elevated blood sugar, symptoms related to kidney, liver, or pancreatic issues, diarrhea, reduced RBC counts, and bleeding problems.

Angiogenesis inhibitors (vascular endothelial growth factor (VEGF))

Cancer growth and metastasis often rely on the formation of new blood vessels, a process known as angiogenesis, which is regulated by VEGF. Inhibiting VEGF can effectively hinder breast cancer progression by preventing new blood vessel formation. VEGF binds to its receptors, VEGFR-1 and VEGFR-2, to regulate angiogenesis. VEGFR-2 promotes endothelial cell proliferation and migration, crucial for neovascularization, while VEGFR-1 helps maintain blood vessel integrity during later stages of cancer development [64].

Targeted therapies aimed at blocking VEGF have been developed, with Bevacizumab (Avastin, Zirabev, Mvasi, and Alymsys) being one such treatment. This therapy prevents VEGF from binding to its receptors, thereby inhibiting the formation of new blood vessels essential for tumor growth and sustenance [65]. When used in combination with chemotherapy agents like paclitaxel or docetaxel, bevacizumab has shown effectiveness in treating advanced metastatic breast cancer [66].

Therapeutic approaches for BRCA gene mutations

The BRCA1 and BRCA2 genes are crucial for maintaining DNA integrity as they help repair damaged DNA. When these genes are mutated, the DNA repair process is compromised, and such mutations can be inherited from one or both parents [67]. While the majority of breast cancer (BC) cases are not linked to inherited mutations, a smaller portion of patients have defective BRCA genes from birth. In cases where individuals with metastatic hormone receptor-positive, HER2-negative BC with BRCA1 or BRCA2 mutations do not respond to hormonal therapy, the American Society of Clinical Oncology (ASCO) suggests considering PARP inhibitors as a replacement for chemotherapy. Additionally, ASCO recommends that patients with metastatic TNBC who have undergone previous chemotherapy may be given oral PARP inhibitors as an alternative treatment.

Olaparib is a PARP inhibitor used to treat metastatic HER2-negative BC in patients with BRCA1 or BRCA2 mutations. It works by interfering with the cancer cell's ability to repair DNA, thus preventing the cancer from progressing [68]. This drug is also beneficial for women with early-stage HER2-negative BC and a BRCA mutation who are at a higher risk of recurrence. It can be administered either before or after chemotherapy [69]. Olaparib may also be an option for HR-positive BC patients who have previously undergone hormonal therapy. Its common side effects include fatigue, nausea, headaches, vomiting, loss of appetite, and low blood cell counts. Talazoparib is another PARP inhibitor that can serve as an alternative to chemotherapy for metastatic HER2-negative BC patients with BRCA1 or BRCA2 mutations. It is associated with side effects similar to those of olaparib, including fatigue, nausea, and vomiting.

Therapy for triple-negative breast cancer (TNBC)

TNBC is characterized by the absence of estrogen, progesterone, and HER2 receptors on tumor cells. This form of BC responds to PARP1 inhibitors, and there is evidence suggesting that HER1 inhibitors could be effective in treating certain subtypes. A phase II trial demonstrated that a combination of cetuximab, a monoclonal antibody, and cisplatin showed promising results, indicating that some TNBC subtypes may respond well to EGFR inhibition [70]. Despite newer therapies, the standard approach for treating TNBC remains the use of taxane derivatives and anthracycline chemotherapy [71]. Additionally, the combination of ixabepilone, a microtubule stabilizer, and capecitabine is currently being evaluated for its effectiveness in TNBC resistant to traditional therapies, with the PACS08 phase III trial ongoing to test this strategy [72].

In 2020, the FDA approved Trodelvy (sacituzumab govitecan-hziy) for patients with metastatic or unresectable TNBC who have received at least two prior therapies. This drug is an antibody-drug conjugate (ADC), which means it uses an antibody to target cancer cells and deliver an anticancer drug directly to them. The monoclonal antibody in Trodelvy targets the Trop-2 protein on BC cells, delivering irinotecan, a chemotherapy agent, directly

into the tumor cells. It is given intravenously every 21 days on days 1 and 8. Common side effects include nausea, vomiting, diarrhea, constipation, fatigue, rashes, loss of appetite, and hair loss. Severe side effects may involve low RBC counts, and preventive medications are often given to reduce the risk of allergic reactions [73].

Table 3. List of available target therapies, along with combined therapy based on BC sub-types

Targeted therapy	Combined therapy	Delivered to BC type	Reference
Trastuzumab	Administered alone or in combination with carboplatin, doxorubicin, docetaxel, paclitaxel, or cyclophosphamide	HER2-positive BC, applicable to both early and advanced stages	[24]
Pertuzumab	Combined with trastuzumab and a chemotherapy agent	Metastatic HER2-positive BC	[25]
Fam trastuzumab deruxtecan	Includes irinotecan as a chemotherapy agent	Inoperable metastatic BC, particularly after at least two prior HER2-targeted treatments	[28]
Ado-trastuzumab emtansine	Paclitaxel-like agent, emtansine	HER2-positive BC with progression or recurrence	[29]
Lapatinib	Combined with trastuzumab and capecitabine	Metastatic HER2-positive BC following treatment with trastuzumab and paclitaxel or docetaxel-based chemotherapy	[31]
Neratinib	Post-trastuzumab therapy with capecitabine	Advanced or metastatic HER2-positive BC in patients who have had two or more HER2-targeted therapies	[31]
Tucatinib	Used alongside trastuzumab and capecitabine	HER2-positive BC, either resectable or with progression to other areas, including the brain	[31]
Palbociclib	Combined with letrozole, anastrozole, or another aromatase inhibitor	Postmenopausal women with ER-positive, HER2-negative metastatic BC	[38]
Ribociclib	Combined with letrozole	Hormone receptor-positive, HER2-negative metastatic or recurrent BC	[43]
Abemaciclib	Combined with letrozole or anastrozole	Postmenopausal women with ER-positive, HER2-negative metastatic BC	[43]
Alpelisib	Used with fulvestrant	HR-positive, HER2-negative BC with a specific PIK3CA gene alteration	[60]
Everolimus	Combined with exemestane	HER2-negative metastatic BC in postmenopausal women	[49]
Veliparib	Given platinum-based chemotherapy	HER2-negative, metastatic, or locally advanced BC	[53]
Niraparib	Combined with neoadjuvant chemotherapy	HER2-negative BC	[53]
Olaparib	Used alongside chemotherapy agents	Metastatic HER2-negative BC with a BRCA1 or BRCA2 mutation	[69]
Bevacizumab	In combination with taxanes or paclitaxel or docetaxel	HER2-negative BC	[66]

Chemotherapy

Chemotherapy remains a primary therapeutic approach for breast cancer (BC), utilizing either single agents or a combination of chemical compounds to eliminate rapidly dividing cancerous cells. These chemotherapeutic drugs are commonly administered through intravenous infusion or oral intake. In recent developments, both adjuvant and neoadjuvant chemotherapy strategies have been widely applied, particularly in cases of triple-negative breast cancer (TNBC) and HER-2 positive BC [74].

Extensive clinical investigations have revealed that the prognosis and therapeutic response to chemotherapy in BC significantly vary according to immunohistochemistry (IHC) subtypes. Specifically, HER2 negative tumors that are estrogen receptor (ER) and progesterone receptor (PgR) positive often respond favorably to hormone

therapy and exhibit a better prognosis. In contrast, HER2 positive and TNBC subtypes generally demonstrate an unfavorable prognosis; however, they exhibit enhanced responsiveness to chemotherapy and targeted therapeutic interventions [75]. Typically, chemotherapy is provided following surgical procedures, referred to as adjuvant chemotherapy, while in neoadjuvant chemotherapy, patients receive treatment before surgical intervention.

Chemotherapy for TNBC

In cases of low-stage triple-negative breast cancer (TNBC), surgical intervention followed by adjuvant chemotherapy remains the standard treatment approach. However, patients diagnosed with advanced-stage TNBC often face a higher likelihood of recurrence, with most relapses reported within two years post-surgical resection [74]. TNBC is characterized by a notable chemosensitivity, often achieving pathological complete remission (pCR) through the administration of neoadjuvant chemotherapy. The incorporation of carboplatin into the treatment protocol has been found to increase the probability of attaining pCR by up to 45% [74].

A meta-analysis conducted by Pathak *et al*. [75] revealed that the addition of carboplatin to neoadjuvant chemotherapy regimens led to significant improvements in both disease-free survival (DFS) and overall survival (OS). However, their findings also emphasized the necessity for identifying suitable biomarkers to guide the use of platinum-based therapies. Interestingly, neither germline BRCA mutations nor PD-L1 expression were found to reliably predict the response to platinum-containing agents [75, 76].

Further investigations have shown that the TP regimen, involving a combination of docetaxel or paclitaxel with carboplatin, demonstrated non-inferiority in therapeutic efficacy when compared to the EC-T regimen, which consists of epirubicin and cyclophosphamide followed by either docetaxel or paclitaxel. These results suggest a limited role of platinum-based adjuvant chemotherapy in TNBC treatment. Additionally, the TP regimen was associated with higher patient compliance and reduced treatment-related toxicities [77].

Carboplatin, a platinum-based alkylating agent, acts by inducing cytotoxic DNA damage through the formation of DNA cross-links, ultimately triggering apoptosis. Although the drug has shown promise in clinical trials, conclusive evidence supporting its widespread effectiveness in TNBC treatment remains insufficient. Carboplatin lacks tumor specificity and exerts cytotoxic effects on both malignant and rapidly proliferating normal cells. Therefore, identifying predictive biomarkers is essential to optimize patient selection for platinum-based therapies [78]. Adverse effects of carboplatin may include bleeding, reduced levels of red and white blood cells, increased susceptibility to infections, and potential hepatic and renal complications.

Anthracyclines function by intercalating into DNA and inhibiting topoisomerase II, which disrupts DNA and RNA synthesis, leading to apoptosis. These agents are employed in both adjuvant and neoadjuvant chemotherapy regimens. However, their toxic effects may involve bone marrow suppression, cardiotoxicity, and an elevated risk of secondary cancers [79].

Taxanes, on the other hand, stabilize microtubules, thereby inhibiting cell division and essential cellular functions. Widely used in adjuvant and neoadjuvant chemotherapy, taxanes can cause adverse effects such as bone marrow suppression, peripheral neuropathy, and muscle pain (myalgia) [79].

Chemotherapy for BRCA1 and BRCA2 mutations

In breast cancers harboring BRCA1 or BRCA2 mutations, platinum-based compounds are the most frequently utilized chemotherapeutic agents. These alkylating agents exert their cytotoxic effects by binding to DNA, leading to the formation of single-strand breaks that eventually accumulate and trigger cell death. The interaction between DNA damage induced by platinum compounds and the impaired double-strand break repair mechanism associated with BRCA mutations gives rise to a phenomenon known as synthetic lethality in clinical oncology [80].

Poly ADP-ribose polymerase (PARP) is a family of proteins essential for repairing single-strand breaks in DNA. The use of PARP inhibitors (PARPis) prevents the repair of such DNA damage, intensifying the synthetic lethality effect in BRCA-mutated (BRCAmut) cancer cells. While platinum agents are effective, their use is limited by the intravenous mode of administration and notable adverse effects, including nausea, neurotoxicity, blood-related toxicities, and hearing impairment (ototoxicity). In contrast, PARP inhibitors offer the advantage of oral administration, making them a more patient-friendly option in this context [80].

Olaparib, an orally administered PARP inhibitor, is available in two dosage forms: tablets and capsules. Its anticancer activity is directly related to its ability to induce DNA strand breaks. The Olympia clinical trial conducted by Tutt *et al*. [69] demonstrated that Olaparib provided significant benefit as adjuvant chemotherapy for individuals with early-stage breast cancer associated with germline BRCA1/2 mutations, particularly those

with HER2-negative primary tumors or at high risk of developing them. The study validated the role of germline BRCA1/2 mutations as a critical biomarker for selecting appropriate systemic treatment in early breast cancer management [69].

Chemotherapy for HER2-positive breast cancer

In the treatment of HER2-positive breast cancer (BC) and triple-negative breast cancer (TNBC), the application of multigene diagnostic assays remains limited. Consequently, clinical decisions largely depend on conventional methods, utilizing pathological parameters such as tumor size, lymph node involvement, and distant metastasis to guide therapeutic strategies. HER2-positive breast tumors are characterized by the overexpression of genes linked to cell differentiation, cell cycle regulation, and proliferation processes.

Patients diagnosed with HER2-positive BC are commonly treated with regimens that incorporate targeted therapies such as trastuzumab and pertuzumab to effectively manage the disease [81].

Paclitaxel in combination with trastuzumab

According to the evaluation by Leon-Ferre *et al*. [81], four primary neoadjuvant therapeutic strategies have been identified for HER2-positive breast cancer. These include the combination of trastuzumab with docetaxel (a taxane agent), the pairing of pertuzumab with docetaxel (TP), the triple regimen involving trastuzumab, pertuzumab, and docetaxel (THP), and the use of trastuzumab alongside pertuzumab without accompanying chemotherapy (HP). The use of anthracycline-based regimens has been gradually reduced due to their association with specific toxicities, notably cardiotoxicity and the risk of secondary leukemia. This concern has led many oncologists to exclude anthracyclines from standard treatment protocols.

Additionally, Leon-Ferre *et al*. [81] highlighted a shift in treatment sequencing where chemotherapy is now more commonly administered in the preoperative phase (neoadjuvant setting), replacing the older ‘sandwich’ approach, which involved chemotherapy both before and after surgical intervention.

Further analysis indicated that the combined use of weekly paclitaxel with dual anti-HER2 targeted agents — trastuzumab and pertuzumab — demonstrates a favorable cardiac safety profile in treated patients [82].

Sacituzumab govitecan (SG)

Trophoblast cell surface antigen 2 (Trop-2), commonly found in epithelial tumors, functions as a transmembrane glycoprotein involved in calcium signal transduction and is typically overexpressed in various malignancies. Sacituzumab Govitecan (SG) is an antibody-drug conjugate (ADC) that targets Trop-2. This drug delivers SN-38, an active cytotoxic metabolite derived from irinotecan, through its monoclonal antibody (mAb) component. However, treatment with SG is often associated with adverse effects such as nausea, diarrhea, fatigue, neutropenia, and anemia [83].

Trastuzumab deruxtecan (T-Dxd)

Trastuzumab Deruxtecan (T-Dxd) is a targeted anti-HER2 therapeutic agent composed of a trastuzumab immunoglobulin G1 (IgG1) monoclonal antibody linked to a topoisomerase I inhibitor payload via a cleavable tetrapeptide-based linker. Although this drug has received FDA approval, its clinical use is associated with a potential risk of interstitial lung disease (ILD) or pneumonitis. Patients receiving T-Dxd may experience respiratory symptoms such as shortness of breath (dyspnoea), coughing, fever, or other exacerbated pulmonary conditions [83].

Docetaxel

Docetaxel is a chemotherapeutic agent categorized under taxanes, exhibiting potent antineoplastic activity by interfering with the cell cycle, specifically inducing arrest at the G2/M checkpoint. This disruption promotes cytotoxicity and culminates in programmed cell death (apoptosis). Additionally, it has been observed that docetaxel may reduce CD8+ T-cell expression in certain patient populations [84]. In contemporary treatment regimens, docetaxel is incorporated into first-line combination therapies for HER2-positive breast cancer, particularly in conjunction with pertuzumab.

Chemotherapeutic approach for HR-positive HER2-negative breast cancer

Methotrexate (MTX)

Methotrexate (MTX), previously referred to as amethopterin, is a folate antagonist widely recognized for its antineoplastic and immunosuppressive properties. Structurally, the presence of two carboxylic acid groups within the MTX molecule facilitates the attachment of additional chemical entities, enabling the development of prodrug forms. While MTX is frequently employed in combination regimens with other therapeutic agents, it is noteworthy that such conjugation can hinder its albumin-binding capacity, thereby influencing its pharmacokinetics.

Although MTX does not hold a position as a first-line chemotherapeutic agent for breast cancer (BC), it continues to retain therapeutic relevance in clinical practice. In a study conducted by Dastjerd *et al*. [85], MTX was incorporated into liposomal delivery systems to form MTX/Lip nanoparticles. These engineered nanoparticles were subsequently tested on the BT-474 breast cancer cell line, where the results demonstrated enhanced therapeutic efficacy compared to the conventional form of the drug.

Mitomycin C (MMC)

Mitomycin C (MMC) is a chemotherapeutic compound with potent anti-cancer activity, primarily exerting its effect by inhibiting DNA synthesis. This agent disrupts DNA by inducing cross-linking, particularly targeting the N6 position of adenine residues. MMC demonstrates its most significant cytotoxic effects during the late G1 phase transitioning into the early S phase of the cell division cycle [86]. Both MMC and Methotrexate (MTX) have shown considerable efficacy across multiple breast cancer (BC) subtypes, making them valuable components in specific therapeutic protocols.

Pixantrone

Pixantrone, classified as an aza-anthracene-dione compound, belongs to the anthracycline family and is employed as a monotherapeutic agent. Its mechanism involves intercalating into both the major and minor grooves of the DNA helix, leading to the formation of stable DNA adducts. The alkylating action of Pixantrone is facilitated by amino groups positioned at either end of the drug molecule, which covalently bind to DNA strands, thereby stabilizing the drug-DNA complex. Remarkably, studies indicate that Pixantrone presents a lower toxicity profile compared to conventional anthracycline-based chemotherapies, offering a safer alternative for certain patient groups [87].

Hormonal therapy

Hormonal therapy, often referred to as endocrine therapy, is a treatment approach designed to inhibit or slow down the progression of hormone-dependent breast cancers (BC) by either suppressing the body's hormone production or obstructing the hormones' interaction with breast cancer cells [71]. In premenopausal women, hormones such as estrogen and progesterone are predominantly produced by the ovaries, while in both premenopausal and postmenopausal women, as well as in men, these hormones are also synthesized in peripheral tissues, including adipose tissue and skin [71]. Certain breast cancer types rely on these hormones for growth and survival, classifying them as hormone-sensitive or hormone-dependent BC. In these cases, hormone receptors present on the cancer cells bind to circulating hormones, initiating a cascade that activates specific gene expression and consequently promotes cellular proliferation [88].

Hormonal therapy for hormone-positive breast cancer

In premenopausal women, ovarian function is the primary source of estrogen production, and this can be reduced through ovarian ablation. Permanent ovarian ablation can be achieved by surgical removal of the ovaries (oophorectomy), radiation therapy, or medication. Temporary suppression of ovarian function can be achieved using gonadotropin-releasing hormone (GnRH) agonists, also known as luteinizing hormone-releasing hormone (LHRH) agonists. Drugs such as Goserelin (Zoladex) and Leuprolide (Lupron) are FDA-approved for this purpose.

Aromatase inhibitors are used to inhibit the enzyme aromatase, which plays a key role in producing estrogen in postmenopausal women. These inhibitors can also be utilized in premenopausal women in conjunction with drugs that suppress ovarian function. The FDA has approved several aromatase inhibitors, including anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin).

Selective estrogen receptor modulators (SERMs) are compounds that interact with estrogen receptors to block estrogen binding [89]. FDA-approved drugs, such as tamoxifen (Nolvadex) and toremifene (Fareston), fall under this category and are commonly used in the treatment of BC. By binding to estrogen receptors, these SERMs can

both prevent estrogen activity and imitate its effects in various body tissues. For instance, tamoxifen inhibits estrogen activity in the breast tissue but behaves like estrogen in the uterus and bones [89]. Another class of anti-estrogen medications, fulvestrant (Faslodex), operates differently to suppress estrogen's effects. Unlike SERMs, fulvestrant binds to the estrogen receptor to block estrogen but does not imitate its activity. Upon binding, fulvestrant leads to the degradation of the receptor [89].

Hormone therapy for early-stage BC

This therapeutic approach is used to eliminate any remaining cancer cells after surgery, and it can also be given before surgery to make the procedure easier. Adjuvant therapy is crucial in reducing the likelihood of cancer returning.

Tamoxifen is FDA-approved for the adjuvant treatment of both premenopausal and postmenopausal women, as well as men, with ER-positive early-stage BC. For postmenopausal women, the AIs anastrozole, letrozole, and exemestane are recommended. Studies suggest that women who undergo a minimum of five years of adjuvant tamoxifen treatment after surgery for early-stage ER-positive BC have a reduced chance of recurrence and improved survival outcomes [90]. The use of newer therapies, such as AIs, has become more common in clinical practice and offers additional options compared to tamoxifen.

Some common approaches to adjuvant therapy include:

1. Replacing tamoxifen with an AI for five years.
2. Continuing treatment with an AI after five years of tamoxifen.
3. Switching from tamoxifen to an AI after 2-3 years for a total of five or more years of therapy.
4. For postmenopausal women, combining adjuvant therapy with an AI has shown improved outcomes compared to tamoxifen alone.
5. Premenopausal women undergoing ovarian suppression along with an AI have a higher chance of remaining free from recurrence than those treated with tamoxifen alone.
6. In men with early-stage ER-positive BC, treatment often begins with tamoxifen, and those using an AI typically also receive a GnRH agonist.

The decision regarding the type and length of adjuvant therapy should be made on a case-by-case basis with the guidance of an oncologist.

Hormone therapy for advanced or metastatic BC

Several forms of hormone therapy are approved for treating metastatic or recurrent hormone-sensitive BC. The SERMs tamoxifen and toremifene are approved for use in metastatic BC. Fulvestrant is approved for postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic BC who have not previously received hormone therapy [91, 92]. It may also be used in premenopausal women after ovarian ablation. The AIs anastrozole and letrozole are recommended as initial treatments for postmenopausal women with metastatic or locally advanced hormone-sensitive BC. These AIs, when combined with exemestane, are approved for postmenopausal women whose cancer has progressed after tamoxifen treatment [92]. Men receiving AI therapy for advanced BC generally also require GnRH agonist therapy **(Table 4)**.

Table 4. Advanced BC treatment with a combination of hormone therapy and targeted therapies

Drug	Combining drug	Type of BC
Palbociclib (Ibrance)	Letrozole	HR-positive, HER2-negative advanced or metastatic BC in postmenopausal women.
	Fulvestrant	HR-positive, HER2-negative advanced or metastatic BC in postmenopausal women whose cancer progressed after other hormone therapy.
Abemaciclib (Verzenio)	Fulvestrant	HR-positive, HER2-negative advanced or metastatic BC in postmenopausal women with disease progression after hormone therapy.
	–	HR-positive, HER2-negative advanced or metastatic BC in men and women whose disease progressed after hormone therapy and who received prior chemotherapy for metastatic disease.
	aromatase inhibitor	First-line hormone therapy for postmenopausal women with HR-positive, HER2-negative advanced or metastatic BC.
Lapatinib (Tykerb)	Letrozole	HR-positive, HER2-positive metastatic BC in postmenopausal women eligible for hormone therapy.

Alpelisib (Piqray)	–	HR-positive, HER2-negative BC with PIK3CA gene mutation.
	Fulvestrant	Postmenopausal women and men with HR-positive, HER2-negative advanced or metastatic BC that has worsened during or after hormone therapy.

Certain women with advanced HER2-positive, HR-positive breast cancer may undergo treatment involving hormone therapy combined with trastuzumab, and in some cases, pertuzumab, with or without the latter agent [88].

Neoadjuvant treatment for breast cancer (BC)

Neoadjuvant therapy for breast cancer involves hormonal treatment aimed at shrinking the tumor before planned surgical intervention. Clinical trials suggest that neoadjuvant hormone therapy, either alone or in combination with aromatase inhibitors (AIs), can effectively reduce tumor size in postmenopausal women, though its effectiveness in premenopausal women remains uncertain [93]. Additionally, hormone therapy is utilized in the neoadjuvant treatment of HR-positive BC for postmenopausal women who are unable to undergo chemotherapy or in situations where surgery must be postponed [94].

Related research

The field of cancer therapy is in an era focused on specifically targeting cancer cells while minimizing damage to normal tissues. Treatments for breast cancer are continuously evolving as biomedicine and technology advance. BC is increasingly viewed as a systemic disease, with neoadjuvant chemotherapy playing a crucial role in the management of HER2-negative BC [95]. Advances in treatment strategies have contributed to a decline in the mortality rate from BC over recent decades. The understanding of the genetic and pathophysiological processes driving malignant transformation and carcinogenesis has spurred the development of new chemotherapeutic agents and approaches [96]. Targeting estrogen receptors (ERs) has emerged as one of the most effective strategies for managing HR-positive BC.

The success of targeted therapies (TTs), such as anti-HER2 monoclonal antibodies [97], has underscored the importance of molecular-targeted approaches in BC treatment. The progress in therapies for HER2-negative BC marks a breakthrough, with additional novel drug candidates continually improving treatment efficacy [97]. Ongoing research is emphasizing precision treatment approaches that specifically target cancer cells. More studies are required to assess the safety, effectiveness, and cost-efficiency of combining TTs with chemotherapy for treating HER2-negative BC patients, as this combination may lead to more effective treatment regimens in the future [98]. Treatment options for HER2-negative BC include drugs targeting multiple pathways such as PI3K/AKT/mTOR, PARP, CDK4/6, various kinases, and immune checkpoint inhibitors [99].

Currently, angiogenesis inhibitors are only applied in HER2-positive BC patients, and further research is necessary to evaluate their potential benefits in HER2-negative cases. CDK4/6 inhibitors have provided new hope by effectively inhibiting cell proliferation in BC patients. Multiple studies have demonstrated that combining these inhibitors with endocrine therapy can improve survival outcomes for HR-positive, HER2-negative advanced BC patients [97]. However, recent studies also highlight the challenge of BC cell resistance to CDK4/6 inhibitors. These inhibitors may also play a role in the treatment of both BC and prostate cancer [97].

In response to these challenges, many patent applications are focusing on the development of simplified bioconjugates that are cost-effective, easy to synthesize, and stable, with high yields. These advancements could offer valuable insights for researchers worldwide in creating new, economically viable treatment options for BC. This would pave the way for safe, efficient, and scalable management strategies, enhancing the overall approach to BC treatment.

Conclusion

Breast cancer (BC) remains one of the most deadly cancers, highlighting the need for continued advancement in treatment options. In this context, several patents are exploring simplified bioconjugate structures that are easier to synthesize, cost-effective, and offer high yields with excellent stability profiles. Such innovations could provide a practical direction for global developers, enabling the production of novel treatment tools and medications for BC. This would facilitate the development of cost-efficient, scalable, stable, and effective treatment strategies for

managing the disease. Existing data continue to shape the landscape of current BC therapies, while new research is driving improvements in traditional treatments and enhancing current therapeutic methods.
Future randomized clinical trials will investigate new drug combinations, guided by patient responses and residual disease, which will eventually be incorporated into standard clinical practice.

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