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Clinical advancements in breast cancer research: A comprehensive review

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Abstract

Breast cancer remains the most frequently diagnosed malignancy among women worldwide, with significant morbidity and mortality rates despite advances in early detection and treatment. This review provides a comprehensive overview of recent developments in breast cancer research, spanning genetic and molecular insights, novel diagnostic techniques, and emerging therapeutic strategies. The advent of next-generation sequencing and multi-omics approaches has deepened our understanding of tumor heterogeneity, revealing key genetic drivers, epigenetic regulators, and the role of cancer stem cells in disease progression. Early detection strategies have also evolved with digital breast tomosynthesis and molecular breast imaging, offering improved sensitivity and specificity. On the therapeutic front, breakthroughs in targeted treatments—including cyclin-dependent kinase 4/6 and phosphoinositide 3-kinase inhibitors, antibody–drug conjugates, and immune checkpoint inhibitors—have transformed patient outcomes. The integration of chimeric antigen receptor T-cell therapy and mRNA-based therapeutics holds great promise in overcoming treatment resistance and improving long-term survival. However, challenges such as treatment accessibility, drug resistance, and disparities in healthcare persist, particularly in low- and middle-income regions. Emerging technologies, including artificial intelligence-driven diagnostics and risk-adapted screening, are paving the way for more precise and personalized interventions. This review highlights the latest innovations and ongoing challenges in breast cancer research, emphasizing the need for continued efforts to translate scientific advancements into clinical practice to improve patient outcomes globally.

Keywords: Breast cancer; Antibody–drug conjugates; Therapeutics; Chimeric antigen receptor T-cell therapy; Small molecule inhibitors

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1. Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide, with approximately 2.3 million new cases reported in 2022.[1-3] It originates from the uncontrolled proliferation of cells in the breast tissue, typically arising in the ducts or lobules, and, if left untreated, can progress to invasive and metastatic stages.[2,3] As the second leading cause of cancer-related mortality in women, breast cancer accounted for nearly 685,000 deaths globally in 2020.[4,5] As of 2024, breast cancer remains the most commonly diagnosed cancer among women in the United States, with

an estimated 310,720 new cases of invasive breast cancer and 56,500 cases of ductal carcinoma *in situ*. In addition, approximately 2790 men were predicted to be diagnosed with breast cancer in 2024, underscoring that the disease is not exclusive to women.[6] Breast cancer is also the second leading cause of cancer-related death among women in the United States, with a projected 42,250 female deaths and 530 male deaths in 2024 alone.[6] The lifetime risk for a woman in the United States to develop invasive breast cancer is approximately one in 8 (13.1%), with a one in 43 (2.3%) chance of dying from the disease.[7] Notably, breast cancer incidence has increased by approximately 1% per year from 2012 to 2021, and more rapidly—by 1.4% annually—among women under age 50.[8] Despite this rise, mortality rates have continued to decline, with a 44% reduction in breast cancer deaths since 1989, largely attributed to improvements in early detection and treatment strategies.[6] Globally, the burden is similarly profound. According to the World Health Organization, breast cancer accounted for 2.3 million new cases and approximately 670,000 deaths worldwide in 2022, making it the most common cancer globally and a leading cause of cancer mortality among women.[9] The International Agency for Research on Cancer projects that by 2050, the annual global incidence of breast cancer could rise to 3.2 million cases, with 1.1 million deaths, particularly affecting low- and middle-income countries due to disparities in access to screening and care.[10] These figures underscore the urgent need for continued advancements in prevention, personalized screening strategies, and equitable access to effective therapies. Despite remarkable progress in early detection, precision medicine, and multimodal therapeutic strategies, significant challenges remain in treating aggressive subtypes such as triple-negative breast cancer (TNBC) and metastatic breast cancer.[11] Recent breakthroughs, including targeted therapies such as cyclin-dependent kinase (CDK) 4/6 inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors, and antibody–drug conjugates (ADCs), have substantially improved patient outcomes. In addition, immunotherapy, particularly immune checkpoint inhibitors (ICIs) such as pembrolizumab, has demonstrated promising efficacy in TNBC.[12] However, several hurdles persist, including drug resistance, limited durability of responses, and disparities in treatment accessibility, particularly in low- and middle-income countries.[13] Advances in genomics, liquid biopsies, and artificial intelligence (AI)-driven diagnostics are paving the way for more precise, personalized interventions, offering new hope in the ongoing battle against breast cancer.[14] To understand the biological underpinnings driving breast cancer's complexity and therapeutic challenges, it is critical to explore the genetic and molecular mechanisms that contribute to its initiation and progression.

2. Genetic and molecular insights

Breast cancer is a multifactorial disease driven by genetic, environmental, and hormonal factors. While demographic variables such as gender, age, and ethnicity influence disease susceptibility, inherited mutations play a critical role in tumor initiation and progression. Germline mutations in *BRCA1* and *BRCA2* account for approximately 5–10% of breast cancer cases, significantly increasing lifetime risk.[15] These tumor suppressor genes are pivotal in DNA repair through homologous recombination, and their loss results in genomic instability, predisposing individuals to malignancy.[16] Beyond *BRCA* mutations, additional high- and moderate-penetrance genes, including *ATM, PALB2, TP53, CHEK2, PTEN, CDH1*, and *STK11,* have been implicated in hereditary breast cancer syndromes.[11,16-18] The advent of next-generation sequencing has facilitated the discovery of novel susceptibility loci through genome-wide association studies, enabling refined risk stratification through polygenic risk scores.[17] Recent studies underscore the role of epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs such as microRNAs (miRNAs) and long non-coding RNAs, in breast cancer pathogenesis.[19] Moreover, cancer stem cells (CSCs) have been identified as key drivers of tumor heterogeneity, recurrence, and resistance to therapy.[20] The epithelial-to-mesenchymal transition (EMT) program, coupled with metabolic reprogramming in CSCs, further enhances invasive potential and immune evasion. Advances in spatial transcriptomics and single-cell RNA sequencing have revealed intricate tumor microenvironment interactions that influence treatment responses.[21] Nevertheless, translating these genetic insights into clinical practice remains a challenge. The interpretation of variants of uncertain significance in genetic testing complicates patient management, whereas disparities in access to genetic testing continue to hinder widespread implementation, particularly in underserved populations. Future research should focus on integrating multi-omics data with AI-driven algorithms to refine predictive models and advance precision oncology in breast cancer care.[22] Leveraging genetic and molecular insights, advances in early detection strategies aim to identify breast cancer at its most treatable stages, thereby improving patient outcomes through timely intervention.

3. Advances in early detection

Early detection significantly improves breast cancer survival rates by identifying malignancies at a treatable stage. Mammography remains the gold standard for breast cancer screening, with studies demonstrating a 20–40% reduction in mortality rates. However, recent advancements have refined detection methodologies, enhanced accuracy

while minimizing false positives. Among the most transformative innovations is digital breast tomosynthesis, or three-dimensional mammography, which captures multiple images from different angles to generate a three-dimensional reconstruction of breast tissue. Clinical trials, such as the Tomosynthesis Mammographic Imaging Screening Trial funded by the National Cancer Institute, have demonstrated that digital breast tomosynthesis increases cancer detection rates while reducing unnecessary recalls for additional testing.[23] For women with dense breast tissue, where traditional mammography has limited sensitivity, molecular breast imaging (MBI) has emerged as a promising alternative. MBI utilizes a radiotracer to highlight metabolically active cancerous cells, offering enhanced sensitivity and specificity. Studies indicate that MBI detects an additional 8.8 cancers per 1000 women screened compared to mammography alone, making it a valuable adjunct for high-risk populations. Beyond imaging, liquid biopsy technologies are revolutionizing early detection. The analysis of circulating tumor DNA and circulating tumor cells in blood samples provides real-time molecular insights, enabling non-invasive monitoring of tumor evolution.[24] These liquid biopsies hold the potential to detect cancer at its earliest stages, allowing for risk-adapted screening strategies. AI is also playing an increasingly critical role in breast cancer diagnostics. AI-driven algorithms, developed by institutions such as Google Health and Massachusetts Institute of Technology, have demonstrated diagnostic accuracy comparable to or exceeding that of experienced radiologists. AI-assisted mammography interpretation minimizes human error, reduces unnecessary biopsies, and streamlines clinical workflows. Despite these advancements, challenges such as overdiagnosis and false positives persist. The Women Informed to Screen Depending on Measures of Risk study is currently investigating risk-adapted screening protocols that tailor detection strategies based on genetic and lifestyle factors.[14,25,26] This precision-based approach aims to strike a balance between early detection and unnecessary interventions. Building on these early detection advancements, cutting-edge molecular profiling technologies are further elucidating tumor heterogeneity, guiding the development of targeted therapeutic strategies.

In recent years, breast cancer research has been transformed by the advent of high-resolution technologies such as single-cell RNA sequencing, which enables researchers to dissect tumors at an unprecedented level of detail.[27] Unlike bulk RNA sequencing, which averages gene expression across a cell population, single-cell approaches unravel the heterogeneity within tumors, identifying rare subpopulations such as CSCs, drug-resistant clones, or immune-evasive phenotypes that may drive recurrence and metastasis.[28] For example, single-cell RNA sequencing has revealed distinct transcriptional programs in EMT-like cells, as well as immune exhaustion signatures within tumor-infiltrating lymphocytes, offering new targets for precision immunotherapy. Complementing this, spatial transcriptomics adds a critical dimension by mapping gene expression within the tumor's architectural context, revealing how cancer cells interact with the stroma, vasculature, and immune cells. This spatial resolution helps researchers understand why certain tumor regions resist therapy and how immune exclusion or hypoxic niches contribute to treatment failure. Meanwhile, multi-omics integration, combining genomics, epigenomics, proteomics, and metabolomics, is being accelerated by AI-driven platforms to refine risk stratification, treatment prediction, and biomarker discovery.[29,30] Other key areas include the development of neoantigen-based mRNA vaccines, chimeric antigen receptor (CAR) T-cell therapy tailored to solid tumors, and the use of liquid biopsies not only for early detection but also for real-time monitoring of tumor evolution and minimal residual disease.[31,32] These technologies are not just academic—they are increasingly entering clinical pipelines and trials, reshaping how breast cancer is understood, diagnosed, and treated (Table 1) at a truly personalized level. As these innovations mature, their integration into routine oncology practice will be key to overcoming existing therapeutic limitations and delivering on the promise of precision oncology. While these molecular and diagnostic advances pave the way for precision oncology, significant challenges in treatment, particularly drug resistance, continue to impede progress in managing aggressive breast cancer subtypes.

4. Challenges in breast cancer treatment: Molecular mechanisms of drug resistance and therapeutic barriers

Despite notable advancements in breast cancer diagnostics and therapeutics (Table 1), several persistent challenges limit treatment efficacy, particularly in aggressive and metastatic subtypes. One of the most critical barriers is drug resistance, which can be intrinsic (present before therapy) or acquired (developed during therapy), and is often driven by complex molecular and cellular adaptations. In hormone receptor-positive (HR^+) breast cancers, resistance to endocrine therapy arises through multiple mechanisms. A major contributor is the *ESR1* gene mutation, which leads to ligand-independent activation of the estrogen receptor, rendering aromatase inhibitors ineffective.[33-35] In addition, cross-talk between estrogen receptor (ER) and growth factor signaling pathways, such as PI3K/protein kinase B (AKT)/mammalian target of rapamycin and human epidermal growth factor receptor 2 (HER2),

Table 1. List of Food and Drug Administration-approved breast cancer drugs from 2023 to 2024

Drug name	Brand name	Diseases/conditions
Abemaciclib	Verzenio	Breast cancer that is hormone receptor-positive (HR$^+$) and HER2-negative; used in adults with metastatic disease.
Ado-trastuzumab emtansine	Kadcyla	HER2-positive breast cancer treated with taxane and trastuzumab; adjuvant therapy for early-stage breast cancer with invasive cancer found during surgery.
Alpelisib	Piqray	HR $^+$and HER2-negative breast cancer with *PIK3CA* mutation; used with fulvestrant in postmenopausal women and men with metastatic disease, after hormone therapy failure.
Anastrozole	Arimidex	HR$^+$ early-stage breast cancer in postmenopausal women; used in those who have already received other treatments.
Capivasertib	Truqap	HR$^+$ and HER2-negative breast cancer with *PIK3CA, AKT1*, or *PTEN* gene mutations; used with fulvestrant in metastatic disease after hormone therapy failure.
Elacestrant dihydrochloride	Orserdu	Estrogen receptor-positive and HER2-negative breast cancer with *ESR1* mutation; used in postmenopausal women and men after hormone therapy failure in metastatic disease.
Everolimus	Afinitor	Advanced HR$^+$ and HER2-negative breast cancer; used in combination with exemestane in postmenopausal women after failure of letrozole or anastrozole treatment.
Exemestane	Aromasin	Advanced or early-stage estrogen receptor-positive breast cancer; used in postmenopausal women after tamoxifen treatment.
Fam-trastuzumab deruxtecan-nxki	Enhertu	HER2-positive or HER2-negative low breast cancer; used in patients whose cancer cannot be removed or has metastasized, after anti-HER2 treatment or chemotherapy failure.
Fulvestrant	Faslodex	HR$^+$ and HER2-negative advanced or metastatic breast cancer; used alone or with ribociclib, palbociclib, or abemaciclib.
Lapatinib ditosylate	Tykerb	HER2-positive advanced or metastatic breast cancer; used with capecitabine or letrozole.
Letrozole	Femara	HR$^+$ early-stage, advanced, or metastatic breast cancer; used as first-line treatment or after tamoxifen in postmenopausal women.
Margetuximab	Margenza	HER2-positive metastatic breast cancer; used with chemotherapy in patients previously treated with two or more anti-HER2 treatments.
Neratinib maleate	Nerlynx	HER2-positive breast cancer; used as extended adjuvant therapy or with capecitabine for advanced or metastatic disease.
Olaparib	Lynparza	HER2-negative breast cancer with *BRCA1/BRCA2* mutations; used in high-risk early-stage disease after surgery and chemotherapy.
Palbociclib	Ibrance	HR$^+$ and HER2-negative metastatic breast cancer; used with fulvestrant or aromatase inhibitor.
Pertuzumab	Perjeta	HER2-positive breast cancer; used with trastuzumab and chemotherapy for metastatic disease or as neoadjuvant/adjuvant therapy.
Pertuzumab, trastuzumab, and hyaluronidase	Phesgo	HER2-positive breast cancer; used with docetaxel or other chemotherapy in metastatic, neoadjuvant, or adjuvant settings.
Ribociclib	Kisqali	HR$^+$ and HER2-negative metastatic breast cancer; used with aromatase inhibitors or fulvestrant in postmenopausal women.
Sacituzumab govitecan	Trodelvy	Triple-negative or HR$^+$and HER2-negative metastatic breast cancer; used after failure of systemic therapies.
Talazoparib tosylate	Talzenna	HER2-negative breast cancer with *BRCA1/BRCA2* mutations; used in adults with metastatic disease.
Tamoxifen citrate	Soltamox	Breast cancer in women and men; used in metastatic disease.
Toremifene	Fareston	Estrogen receptor-positive metastatic breast cancer in postmenopausal women.
Trastuzumab	Herceptin	HER2-positive breast cancer; used alone or with chemotherapy in various treatment settings, including metastatic and high-risk early-stage disease.
Tucatinib	Tukysa	HER2-positive metastatic breast cancer, including brain metastases; used with trastuzumab and capecitabine in patients previously treated with anti-HER2 therapies.

Abbreviation: HER2: Human epidermal growth factor receptor 2.

enables cancer cells to bypass ER signaling entirely, driving resistance and promoting tumor growth.[36,37] Loss of tumor suppressors such as *PTEN* further exacerbates this resistance by hyperactivating the PI3K pathway. In HER2-positive breast cancer, resistance to HER2-targeted therapies such as trastuzumab and lapatinib often involves upregulation of alternative signaling receptors (e.g., insulin-like growth factor 1 receptor, MET) or truncated forms

of *HER2* (e.g., p95*HER2*), which lack the trastuzumab-binding domain but retain kinase activity.[38,39] Furthermore, activation of downstream survival pathways such as mitogen-activated protein kinase and PI3K/AKT confers resilience against HER2 inhibition. Tumor heterogeneity and adaptive mutations within these pathways contribute to partial responses or recurrence despite initially favorable outcomes. TNBC, lacking ER, progesterone receptor, and HER2 expression, poses an even greater therapeutic challenge due to its high heterogeneity and lack of well-defined molecular targets. Resistance to chemotherapy in TNBC is frequently associated with overexpression of drug efflux pumps such as adenosine triphosphate-binding cassette subfamily B member 1 (multidrug resistance protein 1), which actively remove cytotoxic agents from cancer cells.[40] In addition, upregulation of DNA damage repair proteins, including poly (adenosine diphosphate-ribose) polymerase (PARP) 1 and *BRCA*-reversion mutations, can restore homologous recombination repair in *BRCA*-mutated tumors, leading to resistance against PARP inhibitors such as olaparib.[41,42] CSCs play a pivotal role in drug resistance across all breast cancer subtypes. These cells exhibit quiescence, enhanced DNA repair capacity, and expression of aldehyde dehydrogenase and adenosine triphosphate-binding cassette transporters, which protect them from both cytotoxic and targeted therapies.[43,44] Furthermore, the EMT (Figure 1) enables tumor cells to acquire invasive, stem-like phenotypes

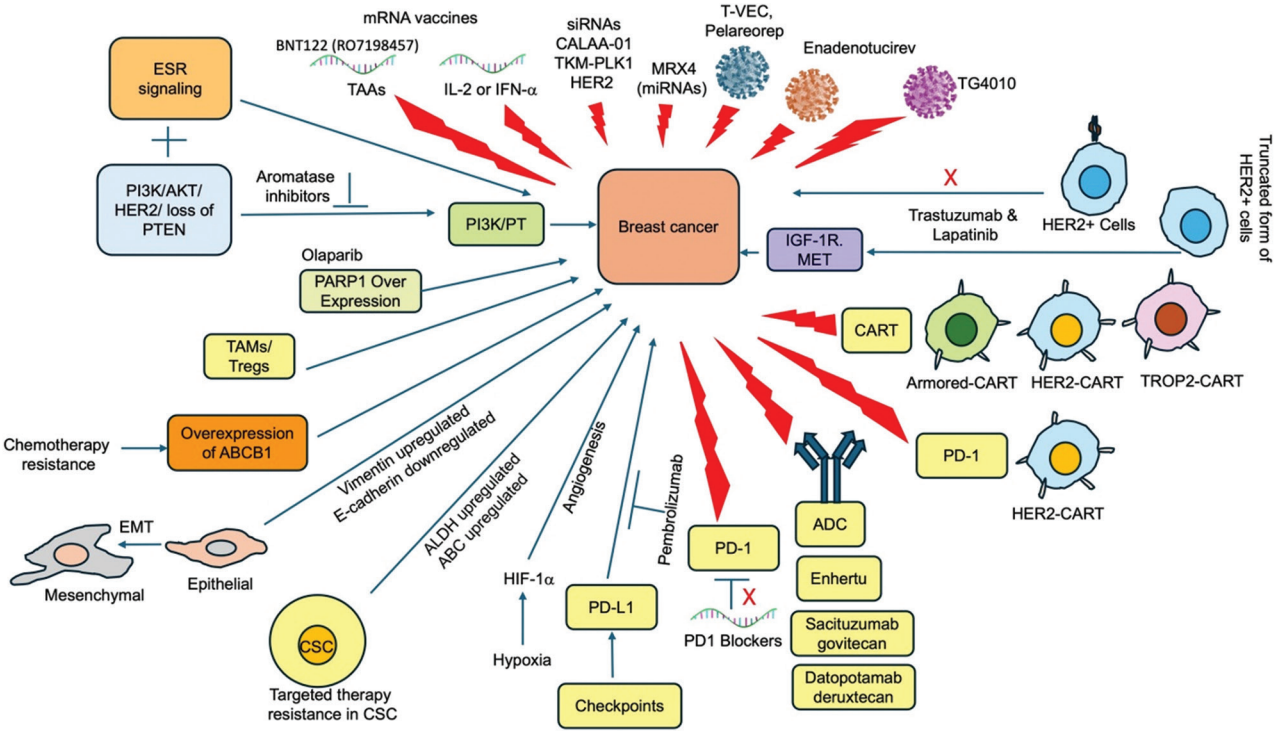


Figure 1. Schematic representation of the complex network of mechanisms driving breast cancer progression and therapeutic resistance, along with current and emerging targeted therapies. Central to the diagram is breast cancer, influenced by key oncogenic pathways such as ESR signaling, PI3K/AKT, *HER2* amplification, IGF-1R/MET signaling, and PARP1 overexpression. Resistance mechanisms include epithelial-to-mesenchymal transition (EMT), cancer stem cell (CSC) persistence, overexpression of ABCB1, immune suppression by tumor-associated macrophages (TAMs) and regulatory T cells (Tregs), and immune checkpoint signaling through PD-1/PD-L1, often exacerbated by hypoxia and HIF-1α. Therapeutic strategies include mRNA vaccines (e.g., BNT122), small interfering RNAs (siRNAs; CALAA-01, TKM-PLK1), microRNAs (miRNAs; MRX4), and oncolytic viruses (T-VEC, pelareorep, enadenotucirev, TG4010). Targeted therapies such as aromatase inhibitors, PARP inhibitors such as olaparib, and PI3K pathway inhibitors are used alongside monoclonal antibodies, antibody–drug conjugates (ADC; e.g., Sacituzumab govitecan, datopotamab deruxtecan, and Enhertu), PD-1 blockers (e.g., Pembrolizumab), and various CAR T-cell therapies, including HER2-CART, TROP2-CART, and armored-CART. The figure also notes that truncated forms of HER2 may render certain therapies, such as trastuzumab and lapatinib, ineffective. This integrative overview underscores the multifaceted nature of breast cancer and the broad spectrum of therapeutic interventions being utilized or developed to overcome tumor heterogeneity and resistance. Image created by the authors.

Abbreviations: ABC: Adenosine triphosphate-binding cassette; ABCB1; Adenosine triphosphate-binding cassette subfamily B member 1; AKT: Protein kinase B; ALDH: Aldehyde dehydrogenase; CART: Chimeric antigen receptor T-cell therapy; ESR: Estrogen receptor signaling; HER2: Human epidermal growth factor receptor 2; HIF-1α: Hypoxia-inducible factor 1-alpha; IGF-1R: Insulin-like growth factor 1 receptor; MET: Mesenchymal-epithelial transition; PARP: Poly(adenosine triphosphate-ribose) polymerase; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PI3K: Phosphoinositide 3-kinase; TROP2: trophoblast cell surface antigen 2; T-VEC: Talimogene laherparepvec.

that resist apoptosis and immune recognition. EMT also reduces E-cadherin expression and increases the expression of mesenchymal markers such as vimentin, contributing to both resistance and metastasis.[45] Another layer of complexity arises from the tumor microenvironment, which can shield cancer cells from therapeutic agents. Hypoxic niches within tumors reduce drug penetration and drive angiogenesis via hypoxia-inducible factor 1-alpha, whereas tumor-associated macrophages and regulatory T-cells suppress anti-tumor immunity and blunt the effects of immunotherapy.[46-48] The upregulation of immune checkpoint molecules such as programmed death-ligand 1 (PD-L1), on tumor and immune cells, also contributes to immune escape and limits the efficacy of checkpoint inhibitors such as pembrolizumab (Figure 1). Finally, genomic instability and intratumor heterogeneity result in subclonal populations with varying drug sensitivities.[49] Under selective pressure from therapy, resistant clones expand and dominate, leading to disease recurrence and progression. Liquid biopsy studies have shown that emerging mutations in *PIK3CA, ESR1*, and *TP53* during treatment correlate with therapy resistance (Figure 1) and poor outcomes.[50,51] Overcoming these challenges will require integrated approaches combining multi-omics profiling, dynamic monitoring of resistance biomarkers, and adaptive treatment strategies such as combination therapies, epigenetic reprogramming, and next-generation CAR T-cells engineered to counteract immune evasion. Personalized treatment guided by molecular diagnostics and real-time resistance tracking is essential to improving durability and depth of therapeutic responses in breast cancer. To address these resistance mechanisms, innovative treatment modalities are being developed to target cancer cells more effectively and overcome the limitations of conventional therapies.

5. Innovations in treatment modalities

5.1. Chimeric antigen receptor T-cell therapy

Chimeric antigen receptor T-cell therapy has revolutionized cancer immunotherapy, particularly in hematologic malignancies such as leukemia and lymphoma. However, its application to solid tumors, including breast cancer, presents unique challenges. Recent advancements have focused on refining CAR T-cell approaches to enhance efficacy and overcome tumor-associated barriers. A significant breakthrough in this domain is the development of CAR T-cells targeting breast cancer-specific antigens. HER2-targeted CAR T-cell therapy, for instance, has demonstrated promise in pre-clinical and early clinical studies. The HER2-CAR T-cell clinical trial (NCT03696030) reported partial responses in patients with advanced HER2-positive breast cancer, validating the feasibility of this approach.[52] In addition, trophoblast cell surface antigen 2 (TROP2)-directed CAR T-cell therapy is being actively investigated, given its overexpression in TNBC.[52-54] To enhance CAR T-cell penetration and persistence within the hostile tumor microenvironment, researchers are employing strategies such as dual-targeting CARs, which simultaneously recognize multiple tumor antigens (e.g., HER2 and PD-L1), thereby mitigating tumor escape mechanisms. Furthermore, engineered "armored" CAR T-cells that secrete cytokines such as interleukin 12 (Figure 1) have shown promise in enhancing T-cell infiltration and survival in solid tumors.[55,56] Another key innovation involves switchable CAR T-cell systems, which allow for controlled activation, thereby reducing off-tumor toxicity. The ON-switch CAR system, for example, requires the presence of a small molecule drug to activate the T-cell response, significantly improving safety profiles. In addition, ongoing clinical trials, such as NCT03932565, are investigating the synergistic effects of combining programmed cell death protein 1 (PD-1) blockade with HER2-CAR T-cells to enhance T-cell persistence and tumor eradication. Despite remaining challenges, including off-target effects, manufacturing scalability, and immune evasion, the continuous evolution of CAR T-cell therapy is advancing it toward clinical viability as a therapeutic option for breast cancer. Future research efforts will likely focus on improving persistence, minimizing toxicity, and optimizing patient selection to maximize therapeutic benefit. Beyond cellular immunotherapies, antibody–drug conjugates (ADCs) offer a complementary targeted approach, leveraging precise delivery of cytotoxic agents to improve therapeutic outcomes across breast cancer subtypes.

5.2. Antibody–drug conjugates

Antibody–drug conjugates (Figure 1) have emerged as a powerful class of targeted therapies in breast cancer, combining monoclonal antibodies with cytotoxic agents to selectively eliminate cancer cells. Recent advancements have significantly expanded the therapeutic landscape of ADCs, offering enhanced precision, efficacy, and reduced toxicity.

Enhertu (Fam-Trastuzumab Deruxtecan-nxki) has redefined HER2-targeted therapy, extending beyond HER2-positive tumors. The DESTINY-Breast04 trial demonstrated that Enhertu provides substantial survival benefits in HER2-low breast cancer, leading to its Food and Drug Administration (FDA) approval in 2023.[57,58] Its topoisomerase I inhibitor payload enhances potency and enables deeper tumor penetration. TROP2 is overexpressed in TNBC and HR^+ breast cancer. Sacituzumab govitecan (Trodelvy) has shown superior efficacy compared to

traditional chemotherapy, significantly improving progression-free and overall survival.[59,60] In addition, the novel ADC datopotamab deruxtecan (Dato-DXd) is demonstrating promising clinical trial results.[61,62]

Advances in next-generation ADC technologies include optimized linker chemistry to enhance stability and minimize off-target toxicity, the incorporation of bystander effects to enable payload diffusion to surrounding tumor cells for broader therapeutic impact, and combination therapies integrating ADCs with ICIs, such as pembrolizumab, to overcome resistance. As ADC technology continues to evolve, it is expected to reshape breast cancer treatment across subtypes, providing targeted and more effective options for both early- and advanced-stage disease. Expanding the scope of targeted therapies, mRNA-based therapeutics are emerging as a transformative tool, harnessing the immune system to combat breast cancer with unprecedented precision.

5.3. mRNA therapeutics in breast cancer

Following the success of mRNA vaccines during the COVID-19 pandemic, mRNA-based therapies are rapidly emerging as transformative tools in oncology. These therapies leverage the body's cellular machinery to produce therapeutic proteins or enhance immune responses against cancer.

mRNA vaccines encode tumor-associated antigens that stimulate immune recognition of breast cancer cells. BioNTech's personalized mRNA vaccine platform, BNT122 (RO7198457), is currently in clinical trials, targeting multiple solid tumors, including breast cancer. These vaccines generate robust and durable immune responses by encoding neoantigens unique to each patient's tumor.[63,64] In addition, mRNA therapeutics are being investigated for their potential to enhance ICI efficacy. These inhibitors, which block PD-1/PD-L1 pathways, have revolutionized cancer treatment, yet many tumors remain resistant. Combining mRNA vaccines with ICIs such as pembrolizumab or nivolumab is being explored to potentiate immune responses and overcome immunotherapy resistance.[65-71]

Cytokine-encoding mRNA therapies aim to boost anti-tumor immunity by enhancing immune cell activity. For example, mRNA encoding interleukin 12 or interferon alpha has demonstrated potential in early-stage trials to stimulate immune infiltration into breast tumors, improving immunotherapy effectiveness.[72-74] Furthermore, mRNA-based therapeutics are being designed to silence or modify oncogenic gene expression in breast cancer. Small interfering (siRNA) or antisense mRNA approaches targeting *HER2* or *PIK3CA* mutations are currently in pre-clinical development, offering a novel avenue for precision oncology.[75,76]

Despite the promising potential of mRNA vaccine-based therapy for breast cancer, efficient delivery remains a challenge for mRNA therapeutics. Hence, lipid nanoparticles (LNPs), which played a critical role in mRNA COVID-19 vaccines, are being adapted for targeted delivery to breast cancer cells, ensuring optimal therapeutic efficacy while minimizing off-target effects.[77,78] Moreover, several clinical trials are currently evaluating mRNA vaccines and therapeutics for breast cancer. Companies such as Moderna and BioNTech are actively developing mRNA-based immunotherapies, exploring their potential as monotherapies or in combination with ICIs and other cancer treatments.

5.4. Small-interfering RNA and microRNA therapeutics

Complementing mRNA therapies, small RNA molecules such as siRNAs and miRNAs are being harnessed to silence oncogenic pathways, offering a highly specific approach to targeting breast cancer progression. In breast cancer therapy, siRNAs and miRNAs are being explored for their potential to silence oncogenes or restore tumor suppressor function.

siRNAs are designed to silence specific genes involved in cancer progression, such as those regulating cell proliferation, metastasis, and drug resistance. CALAA-01 is an early example of a siRNA-based therapy that entered clinical trials. CALAA-01 targets ribonucleotide reductase subunit M2, a key enzyme for DNA synthesis, which is overexpressed in several cancers, including breast cancer. Although not breast cancer-specific, the mechanism highlighted the potential of siRNAs in silencing genes critical to cancer cell survival.[79-81]

Another example is the TKM-PLK1 drug that targets polo-like kinase 1 (PLK1), an essential protein involved in cell division. Elevated PLK1 levels are associated with aggressive cancers, including breast cancer. TKM-PLK1 has demonstrated efficacy in reducing tumor growth in pre-clinical studies, and clinical trials are evaluating its role in breast cancer therapy.[82,83] In addition, HER2-positive breast cancer, a subtype with high HER2 protein expression, has been targeted by siRNAs that knock down *HER2* mRNA, thereby reducing HER2 protein levels and inhibiting tumor growth. These siRNAs are being combined with nanoparticle delivery systems to improve tumor targeting and reduce side effects.[84]

MicroRNAs are small non-coding RNAs that regulate gene expression post-transcriptionally. Dysregulation of specific miRNAs has been linked to breast cancer

development and progression, making them attractive therapeutic targets. One of the most studied miRNAs in cancer therapy is miR-34a, which acts as a tumor suppressor by targeting genes involved in cell cycle regulation and apoptosis. The restoration of miR-34a levels in breast cancer cells can inhibit tumor growth and induce cell death.[85,86] A synthetic mimic of miR-34a, called MRX34, was developed and tested in clinical trials. Although it showed promise in pre-clinical models, the trial was halted due to immune-related side effects. Nevertheless, the approach provided valuable insights into miRNA-based therapies.[87,88] Overexpression of miR-10b has been linked to breast cancer metastasis. Antagomirs (modified oligonucleotides) targeting miR-10b have been shown to reduce metastasis in pre-clinical models. Clinical trials are now underway to explore the safety and efficacy of these inhibitors in preventing breast cancer spread.[87,89,90] miR-21 is an oncogenic miRNA frequently overexpressed in breast cancer. It targets tumor suppressors such as *PTEN* and *PDCD4*, promoting cancer cell survival and proliferation. Inhibitors of miR-21 have been designed to block its oncogenic effects, and these are being evaluated in early-phase clinical trials for their ability to suppress tumor growth in breast cancer patients.[91-95]

A major challenge for siRNA and miRNA therapies is their delivery to target tissues without degradation. Several innovative delivery platforms are being tested in clinical trials, including LNPs. These are commonly used to deliver siRNAs and miRNAs to breast cancer cells. LNPs protect the RNA molecules from degradation and improve their uptake by tumor cells.[96-99] Another platform currently being explored is aptamers. Aptamers are short, single-stranded nucleic acids that can bind to specific cell surface proteins. In breast cancer, aptamers have been used to target siRNAs to HER2-positive cancer cells, increasing the specificity and efficacy of gene silencing.[100-102] In addition, combining siRNA or miRNA therapy with traditional treatments such as chemotherapy or immunotherapy is being explored to enhance treatment outcomes.[103,104] For example, siRNA targeting drug resistance genes combined with chemotherapy could improve the response in resistant breast cancer subtypes.

siRNA- and miRNA-based therapies hold significant potential for breast cancer treatment, particularly in targeting specific oncogenes or tumor suppressor genes that drive the disease. Although still in the experimental or early clinical trial phase, these therapies represent a new frontier in precision medicine, offering the possibility of highly targeted treatments with fewer side effects than conventional therapies. Successful delivery systems and reduced immune responses are key to advancing these promising therapies to routine clinical use.

5.5. Viral gene therapies in breast cancer

In parallel with RNA-based therapies, viral gene therapies are leveraging genetic engineering to directly modify cancer cells, offering innovative strategies to combat breast cancer. Viral gene therapy has emerged as a promising approach in the treatment of breast cancer, offering the potential to directly modify cancer cells at the genetic level. Several viral vectors are being explored in clinical trials, including adenoviruses, lentiviruses, and oncolytic viruses. These vectors are designed to either replace or silence faulty genes, express therapeutic proteins, or stimulate immune responses to target cancer cells.

5.5.1. Oncolytic viruses

Oncolytic viruses are engineered to selectively infect and kill cancer cells while sparing normal cells. Once inside the tumor, these viruses replicate, cause cancer cell lysis, and stimulate anti-tumor immune responses. Talimogene laherparepvec is an FDA-approved oncolytic herpes simplex virus for melanoma, and it is now being investigated in clinical trials for breast cancer.[105,106] It directly lyses tumor cells and produces granulocyte-macrophage colony-stimulating factor, a cytokine that boosts immune responses against cancer. In addition, clinical trials are testing adenoviruses that specifically replicate in and destroy breast cancer cells with particular genetic alterations. For example, enadenotucirev, a chimeric adenovirus, is currently in clinical trials for treatment against various cancers, including breast cancer, where it is being used to enhance immune infiltration into tumors.[107,108]

5.5.2. Gene transfer therapies

Gene transfer therapies introduce therapeutic genes into breast cancer cells to suppress oncogenes or restore tumor suppressor function. Adenoviruses are being used to deliver tumor-suppressing genes such as *p53*, which is often mutated in breast cancer. INGN 201, an adenoviral vector delivering *p53,* has been tested in clinical trials for various cancers, including breast cancer, to enhance cancer cell death.[109,110] Another example is lentiviral vectors. Lentiviruses are retroviruses that integrate their genetic material into the host genome. Clinical trials are evaluating lentiviral delivery of therapeutic genes, such as siRNAs or miRNAs, to silence oncogenes in breast cancer cells.

5.5.3. Immunotherapy-boosting viruses

Viral vectors are also being used to enhance anti-tumor immunity. By introducing genes that stimulate the immune system, such as cytokines or checkpoint inhibitors, viral gene therapies aim to overcome the immunosuppressive tumor microenvironment of breast cancer.[111,112] A modified

vaccinia virus expressing CD40L (an immune-activating molecule) is under investigation for breast cancer treatment. The virus not only directly kills cancer cells but also enhances the anti-tumor immune response by activating dendritic cells and T cells.[113,114]

5.5.4. Viral gene therapy for drug resistance

Viral gene therapy is also being explored to counteract drug resistance in breast cancer. For example, viruses are used to deliver genes that silence resistance mechanisms, such as *MDR1* (a gene involved in chemotherapy resistance), thereby restoring the efficacy of standard treatments.[115]

These innovative therapies, from CAR T-cells to viral vectors, are being rigorously evaluated in clinical trials, which have yielded both breakthroughs and challenges in transforming breast cancer care.

Several clinical trials have evaluated viral gene therapies for breast cancer, either as standalone treatments or in combination with chemotherapy, immunotherapy, or radiation. Ad5/3-D24-granulocyte-macrophage colony-stimulating factor (CGTG-102), an oncolytic adenovirus expressing granulocyte-macrophage colony-stimulating factor, is being tested in metastatic breast cancer. The virus selectively replicates in cancer cells, promoting their destruction and stimulating an immune response.[116,117] Moreover, pelareorep (REOLYSIN®) is being evaluated in combination with chemotherapy and checkpoint inhibitors (e.g., pembrolizumab) for advanced breast cancer.[116] The virus preferentially infects and kills cancer cells with activated Ras signaling, a common feature in breast cancer.

Personalized viral vaccines are being developed for breast cancer patients using modified viral vectors to deliver tumor-specific antigens, thereby priming the immune system to target breast cancer cells. For example, TG4010, a modified vaccinia virus expressing *MUC1* (a breast cancer antigen), is under evaluation in metastatic breast cancer trials.[118]

While viral gene therapies show promise, challenges such as immune system clearance of viral vectors, off-target effects, and tumor heterogeneity remain. However, ongoing improvements in viral engineering, delivery systems, and combination strategies with other treatments (e.g., checkpoint inhibitors and CAR-T cells) are enhancing the safety and efficacy of these therapies. The future of viral gene therapy for breast cancer lies in combination approaches and personalized medicine, where viral vectors are tailored to target specific mutations or molecular signatures within a patient's tumor. This could lead to more effective and less toxic treatment options for breast cancer patients, particularly for those with drug-resistant or metastatic disease.

5.6. Recent clinical trials

Over the past 5 years, several clinical trials have led to the approval of new therapies for breast cancer, each with distinct mechanisms of action. Below are some notable examples:

(i) Pembrolizumab (Keytruda) for TNBC. Pembrolizumab is a PD-1 blocking antibody that enhances the immune system's ability to detect and destroy cancer cells. Inhibiting the PD-1 pathway prevents cancer cells from evading immune surveillance.[119,120] The KEYNOTE-522 trials evaluated pembrolizumab in combination with chemotherapy for early-stage TNBC. The study demonstrated a significant increase in pathologic complete response rates compared to chemotherapy alone, leading to its approval in July 2021.

(ii) Sacituzumab govitecan (Trodelvy) for Metastatic TNBC. Sacituzumab govitecan is an ADC targeting TROP2, a protein commonly overexpressed in TNBC cells. It delivers the cytotoxic agent SN-38 directly to cancer cells, enhancing tumor cell death while minimizing systemic toxicity.[121,122] The ASCENT trial assessed sacituzumab govitecan in patients with metastatic TNBC who had received at least two prior therapies. The results showed a significant improvement in progression-free survival and overall survival compared to standard chemotherapy, leading to its FDA approval in April 2020.

(iii) Olaparib (Lynparza) for HER2-negative breast cancer with *BRCA* mutations. Olaparib is a PARP inhibitor that exploits the DNA repair weaknesses in cancer cells harboring *BRCA* mutations. By inhibiting PARP, olaparib induces DNA damage accumulation, leading to cancer cell death.[123,124] The OlympiAD trial evaluated olaparib in patients with HER2-negative metastatic breast cancer and germline *BRCA* mutations. The study demonstrated a significant improvement in progression-free survival compared to standard chemotherapy, resulting in its approval for this patient population.

(iv) Trastuzumab deruxtecan (Enhertu) for HER2-positive breast cancer. Trastuzumab deruxtecan is an ADC combining trastuzumab, an anti-HER2 antibody, with a topoisomerase I inhibitor. It binds to HER2-expressing cancer cells, delivering the cytotoxic agent directly to the tumor, thereby enhancing efficacy.[125,126] The DESTINY-Breast01 trial assessed trastuzumab deruxtecan in patients with HER2-positive metastatic breast cancer who had received prior anti-HER2 therapies. The trial reported a high objective response rate and durable responses, leading to its FDA approval in December 2019.

As of February 2025, several innovative clinical trials are underway in breast cancer research, aiming to improve detection, treatment, and patient outcomes. The National Health Service in England has initiated the world's largest trial of AI for breast cancer diagnosis. This study involves approximately 700,000 mammograms and seeks to compare the effectiveness of AI systems to that of radiologists in detecting breast cancer. If successful, AI could streamline the diagnostic process, reduce the workload on radiologists, and expedite patient care.[127] In addition, the University of California, San Francisco, is conducting 116 breast cancer clinical trials, with 43 currently open to eligible participants. These studies encompass various aspects of breast cancer, including novel drug combinations, immunotherapies, and targeted treatments. For instance, one trial is exploring the efficacy of combining MDNA11, an interleukin 2 immunotherapy agent, with a checkpoint inhibitor in patients with advanced breast cancer.

The Mayo Clinic is leading a study titled "Eliminating Breast Cancer Surgery in Exceptional Responders with Neoadjuvant Systemic Therapy." The goal is to determine the feasibility of omitting surgery in patients who achieve complete remission after chemotherapy and radiation therapy. This approach could potentially reduce treatment-related morbidity and improve the quality of life for select patients.[128] The Dana–Farber Cancer Institute offers over 40 breast cancer clinical trials, many focusing on immuno-oncology. These trials aim to harness the body's immune system to combat cancer more effectively. Research includes evaluating new immunotherapeutic agents and combination therapies to enhance treatment efficacy and overcome resistance mechanisms. Moreover, the National Cancer Institute supports numerous clinical trials targeting TNBC, a particularly aggressive subtype. These studies investigate various strategies, including novel chemotherapeutic agents, targeted therapies, and immunotherapies, to improve outcomes for TNBC patients.

These ongoing trials represent the forefront of breast cancer research, striving to develop more effective and personalized treatment strategies. Patients interested in participating in clinical trials should consult with their healthcare providers to determine eligibility and potential benefits. Despite these promising trials, setbacks in clinical research reveal persistent limitations that must be addressed to fully realize the potential of novel breast cancer therapies.

6. Setbacks or limitations in breast cancer therapy

In the past 5 years, several clinical trials in breast cancer have faced failures or produced inconclusive results. AstraZeneca and Daiichi Sankyo's Dato-DXd, an ADC targeting TROP2, was evaluated in the TROPION-Breast01 Phase III trial for patients with inoperable or metastatic HR^+, HER2-low or negative breast cancer.[129,130] While the trial met the primary endpoint of progression-free survival, it did not achieve statistical significance in overall survival compared to chemotherapy. Despite improvements in PFS, the lack of a significant overall survival benefit suggests that prolonging time without disease progression may not always translate into extended survival. An alternative approach would be to combine Dato-DXd with other agents, such as ICIs, to enhance efficacy and potentially improve overall survival rates. In addition, biomarkers that predict response to Dato-DXd can be identified, enabling better patient selection and personalized treatment approaches.

Trials involving sacituzumab govitecan, an ADC targeting TROP2, have also faced challenges. Despite its effectiveness, various trials have reported mixed results regarding efficacy, particularly concerning patient subgroups. Sacituzumab govitecan has shown mixed results across different breast cancer subtypes.[131,132] The drug's effectiveness appears to vary among different breast cancer subtypes and patient populations. An alternative strategy would be to conduct trials focusing on specific breast cancer subtypes to better understand the drug's efficacy and optimize its use. In addition, combination therapy integrating sacituzumab govitecan with other therapies to enhance its effectiveness across various subtypes can be explored.

Neratinib has demonstrated significant benefit in improving invasive disease-free survival in patients with HER2-positive breast cancer after adjuvant therapy. However, the trial did not show a statistically significant improvement in overall survival. While diarrhea is a common and potentially severe side effect, it can often be managed with proactive measures.[133,134]

Trials exploring the effectiveness of ICIs, such as pembrolizumab in combination with chemotherapy for TNBC,[135,136] have had mixed results. Some trials reported insufficient improvement in overall survival rates, raising concerns about the efficacy of these combinations in certain patient populations. Utilizing biomarkers to select patients more likely to respond to immunotherapy can serve as an alternative strategy in overcoming efficacy-related challenges. Moreover, combinations with other agents, such as targeted therapies or novel immunomodulators, can be explored to improve outcomes.

Veracyte's Decipher Prostate genomic classifier,[137] which aimed to guide treatment decisions for breast cancer patients, was unable to demonstrate a significant

advantage over existing methods in clinical trials, leading to its withdrawal from consideration. The tool, originally designed for prostate cancer, was evaluated for its applicability in guiding treatment decisions for breast cancer patients. However, clinical trials did not demonstrate a significant advantage over existing methods, leading to its withdrawal from consideration in breast cancer treatment. The Decipher test is validated for prognostic use in prostate cancer, particularly in identifying high-risk patients who may benefit from intensified treatment. Its application in breast cancer may have been limited due to differences in tumor biology between prostate and breast cancers. Hence, developing genomic classifiers specifically tailored to breast cancer's unique molecular characteristics could improve predictive accuracy. Collaborative efforts between genomic researchers and oncologists are essential to design tests that address the heterogeneity of breast cancer.

The Oncotype DX test is widely used to predict recurrence in early-stage breast cancer; however, several recent studies have suggested that its predictive capabilities may not be as robust for certain patient subsets, leading to questions about its continued use.[138-140] While the Oncotype DX test provides valuable prognostic and predictive information, its utility may vary among different patient populations. For instance, its predictive power for chemotherapy benefit is well-established in HR^+, HER2-negative early-stage breast cancer, but may be less applicable in other subtypes. Thus, integrating additional genomic or molecular assays could complement the Oncotype DX test, providing a more comprehensive risk assessment. Personalized treatment plans should consider multiple factors, including tumor biology, patient preferences, and other clinical indicators.

Various trials assessing the benefits of extended hormonal therapies after initial treatment have shown limited benefits, questioning the standard practice of prolonged adjuvant endocrine therapy in certain low-risk populations.[141] These examples illustrate the complexities and challenges in breast cancer clinical research, highlighting that promising therapies can still fail to deliver the expected benefits in real-world patient populations. The failures often arise from a combination of factors, including trial design, patient selection, and the inherent heterogeneity of breast cancer itself. Trials assessing the benefits of extended hormonal therapies after initial treatment have shown limited benefits, questioning the standard practice of prolonged adjuvant endocrine therapy in certain low-risk populations. Extended endocrine therapy can reduce recurrence risk in HR^+ breast cancer. However, the absolute benefit may be minimal in patients with low-risk disease, while exposing them to potential side effects and impacting their quality of life. Instead, utilizing genomic assays to stratify patients based on recurrence risk can help identify those who would benefit most from extended therapy. Shared decision-making between clinicians and patients is crucial, weighing the risks and benefits of prolonged treatment.

Trodelvy (sacituzumab govitecanhziy) was granted accelerated approval in April 2020 for metastatic TNBC after two prior treatments.[142] While it has not been retracted, it comes with a boxed warning for potential severe side effects, including neutropenia and diarrhea, indicating careful ongoing monitoring is required. While Trodelvy offers a treatment option for a challenging cancer subtype, its toxicity profile requires vigilant management. The severity of side effects may limit its use in certain patient populations. Implementing comprehensive patient monitoring protocols can mitigate these adverse effects. Research into biomarkers predicting response and toxicity could help identify patients most likely to benefit from Trodelvy, allowing for more personalized treatment approaches.

The SONIA trial evaluated the timing of CDK4/6 inhibitors in combination with endocrine therapy for HR-positive/HER2-negative advanced breast cancer.[143-145] It found no significant difference in overall survival between first-line and second-line use, questioning the necessity of upfront administration. Alternate approaches include individualizing treatment strategies based on patient characteristics and disease progression, and identifying biomarkers that predict response to CDK4/6 inhibitors to guide treatment sequencing.

The APTneo Phase III trial investigated the combination of the ICI atezolizumab with HER2-targeted therapy and chemotherapy in high-risk, HER2-positive breast cancer patients.[146,147] Although the addition of atezolizumab increased pathologic complete response rates when combined with anthracyclines, it did provide a modest overall improvement when added to non-anthracycline regimens. The benefit of adding atezolizumab was regimen-dependent, suggesting that its efficacy may be influenced by the chemotherapy backbone used. Hence, identifying patient subgroups most likely to benefit from ICIs through biomarker analysis could refine treatment approaches. In addition, tailoring immunotherapy combinations based on individual tumor characteristics may enhance efficacy.

The INAVO120 trial compared the PI3Kα inhibitor inavolisib combined with palbociclib and fulvestrant against palbociclib and fulvestrant alone.[148-150] The results did not meet the expected efficacy benchmarks, highlighting challenges in targeting specific mutations in breast cancer. These trials underscore the complexities in breast cancer treatment and the ongoing need for research

to better identify effective therapies and combinations. Targeting the PI3K pathway has shown promise, but the complexity of signaling networks and potential compensatory mechanisms may limit the effectiveness of single-agent PI3K inhibitors. Combining PI3K inhibitors with agents targeting parallel pathways or employing adaptive trial designs to identify responsive subpopulations could improve outcomes.

In addition to the clinical trials detailed in this review, real-world case illustrations help contextualize the therapeutic efficacy of emerging treatments in breast cancer. One notable example involves a 42-year-old female with stage IIb TNBC who participated in the KEYNOTE-522 trial. She received pembrolizumab in combination with neoadjuvant chemotherapy and achieved a pathologic complete response post-surgery, remaining recurrence-free for over 3 years.[151] Similarly, a 60-year-old female with HR$^+$, HER2-low metastatic breast cancer enrolled in the DESTINY-Breast04 study and was treated with trastuzumab deruxtecan. She experienced a partial tumor response exceeding 40% shrinkage and maintained disease stability at the 1-year mark, with manageable side effects.[58,152] Another compelling case involved a 48-year-old female with heavily pre-treated metastatic TNBC who was treated with sacituzumab govitecan as part of the ASCENT trial. She achieved a marked extension in progression-free survival (5.6 months versus 1.7 months with standard chemotherapy), with side effects including manageable neutropenia and diarrhea.[153] In the case of a 37-year-old patient with a germline *BRCA1* mutation and HER2-negative breast cancer, adjuvant treatment with olaparib following surgery and chemotherapy—aligned with findings from the OlympiAD trial—resulted in durable remission over 2 years.[124] In addition, a 55-year-old female with metastatic HR$^+$/HER2-negative breast cancer and a high neoantigen burden received a personalized mRNA vaccine developed by BioNTech, in combination with a PD-1 checkpoint inhibitor.[154] This treatment induced a measurable anti-tumor immune response and early signs of tumor regression, underscoring the promise of mRNA-based immunotherapies in advanced disease settings. These clinical cases illustrate the tangible impact of targeted and personalized treatment strategies, reinforcing the potential of novel agents to improve outcomes across diverse breast cancer subtypes.

In the past 5 years, the FDA has taken significant actions regarding breast cancer treatments, including accelerated approvals (Table 1) and the ongoing monitoring of certain therapies. The FDA remains vigilant regarding the safety and efficacy of breast cancer therapies. For instance, any

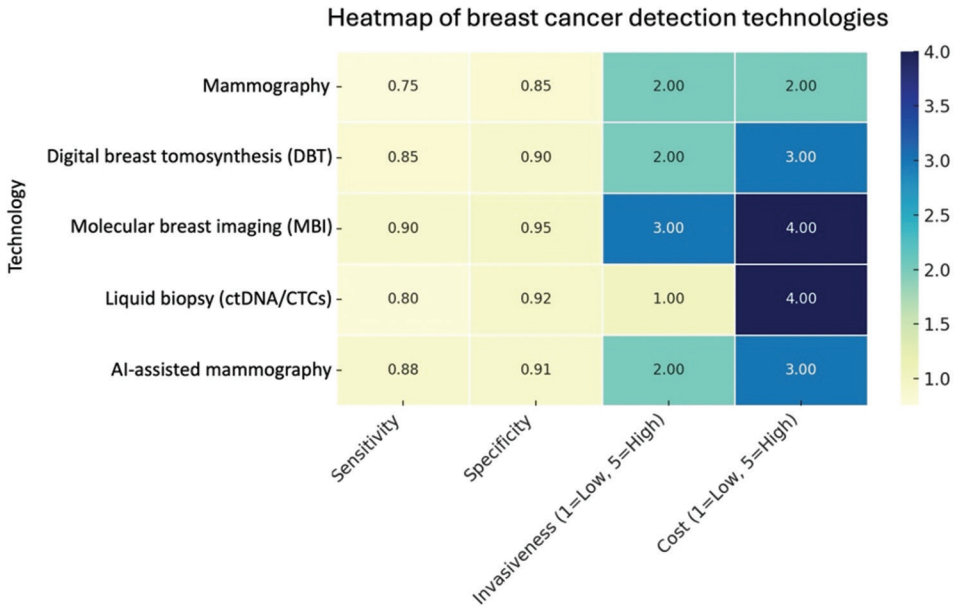


Figure 2. This heatmap compares five breast cancer detection technologies—mammography, digital breast tomosynthesis (DBT), molecular breast imaging (MBI), liquid biopsy (ctDNA/CTCs), and AI-assisted mammography—across four key parameters: sensitivity, specificity, invasiveness, and cost. Sensitivity and specificity are presented as decimal values (0–1), indicating diagnostic accuracy, whereas invasiveness and cost are ranked on a scale from 1 (low) to 5 (high). MBI shows the highest sensitivity (0.90) and specificity (0.95), but is also among the most invasive and expensive options. Liquid biopsy is the least invasive (1) and equally costly (4) while maintaining high specificity (0.92). AI-assisted mammography performs well across all metrics, with high sensitivity (0.88) and specificity (0.91), moderate invasiveness (2), and cost (3). This visualization aids in evaluating the trade-offs between accuracy, patient impact, and economic factors among different diagnostic tools. Image created by the authors using ChatGPT.
Abbreviations: AI: Artificial intelligence; CTCs: Circulating tumor cells; ctDNA: Circulating tumor DNA.

emerging safety concerns may lead to modifications in treatment recommendations or label updates, but there have been no full retractions reported in this context. While there are ongoing discussions in the scientific community about potential risks and the need for further studies on certain drugs, no drugs have been officially retracted in the specified timeframe.

7. Patients' experience and demands

Beyond the molecular complexity and therapeutic innovations, breast cancer remains a profoundly personal and life-altering diagnosis. Patients undergoing treatment often face multifaceted challenges—physical, emotional, financial (Figure 2), and social. Many experience fatigue, hair loss, nausea, and neuropathy as side effects of chemotherapy, whereas endocrine therapy can lead to joint pain, mood disturbances, and hot flashes that disrupt daily life. For patients on newer targeted therapies or immunotherapies, the burden may shift to managing immune-related adverse events, which, while clinically manageable, can be unpredictable and induce anxiety. Psychologically, the fear of recurrence, body image concerns after mastectomy, and long-term uncertainty weigh heavily. Patients with metastatic disease often speak of the emotional toll of "living scan to scan," balancing hope with the realities of chronic treatment. The need for holistic care is paramount. Patients consistently express the value of clear communication with clinicians, psychological counseling, peer support groups, and access to integrative care—including nutrition, physical therapy, and mindfulness-based stress reduction. For many, personalized medicine is not just about targeted drugs, but about feeling seen and heard—having treatment plans that reflect their life goals, comorbidities, and quality-of-life preferences. In underserved populations and low- to middle-income countries, issues such as treatment affordability, access to transportation, genetic testing, or clinical trials compound distress, making equity a critical component of effective cancer care. Incorporating patient-reported outcomes in clinical trials and care plans is essential to align scientific advancement with what matters most to those living with the disease, such as survival, dignity, autonomy, and well-being.

8. Conclusion

Significant progress has been made in breast cancer research, particularly in the areas of genetic insights, early detection, and treatment modalities. The continued development of personalized screening techniques, biomarkers, and targeted therapies offers hope for improved outcomes and survival rates. Ongoing research is critical to addressing the complexities of breast cancer and reducing the global burden of this disease.

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