

Emerging Targeted and Multimodal Therapeutic Strategies in Breast Cancer: A Comprehensive Review

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Abstract: Breast cancer treatment has advanced substantially with the development of targeted and multimodal strategies, yet tumor heterogeneity and therapeutic resistance continue to limit long-term outcomes. This review provides a concise and critical overview of established and emerging targeted therapies, with emphasis on resistance mechanisms, innovations in drug delivery, and integrative therapeutic approaches. Established modalities, including endocrine therapy, HER2-directed antibody and antibody–drug conjugate therapies, and chemotherapy, are summarized alongside key subtype-specific challenges. Emerging targets such as PARP, CDK4/6, WBP2, and Trop2, as well as metabolic and tumor-microenvironment–oriented strategies, are evaluated for their potential to overcome resistance. Advances in immunotherapy, including checkpoint inhibitors, bispecific antibodies, and CAR-T cell therapies, are examined with attention to mechanistic rationale and limitations across breast cancer subtypes. Progress in nanotechnology-based delivery systems, exosome-mediated transport, and multimodal predictive frameworks, including miRNA regulatory networks, is further assessed for its relevance to personalized treatment. Overall, this review synthesizes current molecular insights and therapeutic innovations to inform the development of more effective and durable targeted treatments for breast cancer.

Plain Language Summary: Breast cancer is not a single disease. Different people develop different tumor types, which respond in different ways to treatment. Because of this diversity, many women still face treatment resistance, relapse, or limited benefit from current therapies. We wrote this review to help readers understand how new scientific advances are reshaping breast cancer treatment and what these developments may mean for future care.

In this article, we explain the major treatment approaches used today, including hormone-based therapy, HER2-targeted therapy, chemotherapy, immunotherapy, and drug–antibody combinations. We also describe important new directions, such as medicines that act on DNA repair, the cell cycle, tumor metabolism, and proteins like Trop2, WBP2, and CDK4/6. We highlight how the tumor's surrounding environment, including immune cells, fibroblasts, blood vessels, and the extracellular matrix, can either support treatment or impede its effectiveness. We also summarize emerging tools such as nanomedicine, ultrasound-guided drug delivery, and exosome-based therapies. These technologies aim to deliver drugs more precisely and overcome resistance.

Our review shows that no single therapy is enough for all patients. Instead, combining targeted drugs, immunotherapy, metabolic treatments, or advanced delivery systems may offer stronger and longer-lasting effects. We also discuss early research using prediction models and microRNA networks, which may help doctors choose the best therapy for each person.

Together, these findings suggest that the future of breast cancer treatment will rely on personalized, multi-target strategies designed around the unique biology of each tumor and each patient.

Keywords: breast cancer, targeted therapy, drug resistance, tumor microenvironment, nanomedicine

Introduction

Breast cancer is a highly heterogeneous malignancy with marked variability in molecular subtypes, biological behavior, and therapeutic responsiveness. Although endocrine therapy, HER2 directed agents, chemotherapy, and antibody drug conjugates have all undergone continuous refinement, intrinsic and acquired resistance still limit treatment durability for many patients.^{1,2} These persistent challenges underscore the need to better understand breast cancer heterogeneity and to accelerate therapeutic innovation.

Previous reviews have documented advances in endocrine therapy, HER2 targeted therapeutics, or resistance mechanisms within specific subtypes, yet most discussions remain focused on isolated pathways or single categories of treatment.^{3–6} Existing literature has also separately addressed immunotherapy, nanomedicine, pathway inhibition, metabolic rewiring, or drug delivery technologies. However, few attempts have been made to integrate these rapidly developing fields into a broader multimodal framework that reflects the convergence of targeted therapy, tumor microenvironment modulation, immune based strategies, and advanced delivery systems.^{7–9} This fragmented perspective limits the ability of readers to appreciate how emerging modalities collectively reshape the therapeutic landscape.

Therefore, this review aims to provide a more unified overview of recent advances in targeted and multimodal strategies for breast cancer. By synthesizing progress in novel molecular targets, resistance related signaling networks, innovative delivery platforms such as nanoparticles and exosomes, and integrative models that incorporate immunologic and microenvironmental regulation, we aim to clarify how these approaches complement established therapies and support individualized treatment. Through this perspective, we outline evolving opportunities to overcome resistance and improve long term therapeutic outcomes across breast cancer subtypes.

Molecular Characteristics and Targetable Pathways of Breast Cancer

Breast cancer exhibits substantial molecular heterogeneity, with intrinsic subtypes defined by hormone receptor status, HER2 expression, and transcriptomic signatures.^{10–13} Hormone receptor positive disease depends on estrogen receptor (ER) and progesterone receptor (PR) signaling for tumor growth and therefore responds to therapies such as tamoxifen and aromatase inhibitors.^{14,15} HER2-positive (HER2+) tumors are driven by HER2 amplification and overexpression, and targeted agents including trastuzumab and pertuzumab significantly improve outcomes by suppressing HER2 mediated signaling.^{16,17}

Triple-negative breast cancer (TNBC) remains the most therapeutically challenging subtype because it lacks ER, PR, and HER2 expression. Efforts to identify alternative oncogenic drivers have revealed several promising targets. Gupta et al identified CXCR4 signaling as a potential vulnerability that can be inhibited by Z-cocainone.¹² Lan et al reported oncogenic circular RNAs such as circBRAF that influence DNA methylation and transcriptional regulation in TNBC.¹⁸ Additional studies have shown that proteins including CD151 regulate exosome mediated communication and contribute to metastatic progression.

Collectively, these findings broaden the spectrum of actionable biomarkers and pathways across breast cancer. Although many candidates show potential for precision treatment, most remain in preclinical or early clinical development. Continued investigation will be required to validate their therapeutic relevance and to advance them toward clinical application. [Table 1](#) presents the current targeted treatment strategies for breast cancer subtypes.

Current Treatment Strategies

Endocrine-Targeted Therapy for ER+ Breast Cancer

Endocrine therapy remains central to the management of ER-positive (ER+) breast cancer, yet intrinsic and acquired resistance continue to restrict its long-term effectiveness. Evidence shows that activation of the AKT and AMPK pathways drives metabolic reprogramming in endocrine resistant cells, supporting the role of altered energy metabolism as a contributor to therapeutic failure.⁶² Niu et al further demonstrated that high SGLT1 expression enhances glycolysis and promotes M2 macrophage polarization, thereby accelerating resistance.⁶³

Genomic alterations also influence treatment outcomes. *ESR1* mutations enable ligand independent activation of the ER pathway and are among the best-established mechanisms of aromatase inhibitor resistance.^{64–66} Their non-invasive

Table I Targeted Therapy Strategies for Breast Cancer Subtypes

Subtypes	Target	Medication	Applications and Instructions	Refs
Luminal A type: Estrogen receptor (ER) and/or progesterone receptor (PR) positive, HER2 negative, low Ki67 ^{19,20}	WWP1-PTEN		WWP1 promotes bone metastasis by polyubiquitinating PTEN and may serve as a target for inhibiting early bone metastasis.	[21]
	KAT2B/TAFIL		Potential therapeutic targets identified through bioinformatics analysis may be relevant to the development of personalized treatment strategies.	[22]
	RNF20/40		Eg5 participates in spindle assembly via its axon, is associated with tumorigenesis, and can serve as an intervention target; however, no specific drugs have been mentioned in the literature.	[23]
	c-JUN		Mediating the vicious cycle within the bone metastasis microenvironment represents a potential target for subtype-specific bone metastasis therapy.	[24]
	AKT	Jolkinolide B	Jolkinolide B also exhibits some efficacy against luminal A.	[25]
	BC200lncRNA		Overexpression promotes proliferation and migration, potentially emerging as a novel therapeutic target.	[26]
	Estrogen Receptor Alpha (ER α)	Tamoxifen	Endocrine therapy (such as tamoxifen and aromatase inhibitors) is the standard treatment.	[27,28]
	RHAMM		Potential target	[25]
Luminal B: ER/PR positive, HER2 may be positive or negative, high Ki67 ^{19,20}	CDK4/6	Palbociclib	Combining CDK4/6 inhibitors (such as palbociclib) with endocrine therapy is a key strategy.	[29]
	PI3K-Akt	Jolkinolide B	Jolkinolide B significantly inhibits the proliferation and migration activity of BT-474 cells (Luminal B subtype) by downregulating the PI3K-Akt pathway, and demonstrates superior therapeutic efficacy against the Luminal B subtype compared to the Luminal A subtype.	[30]
	SOX2-Driven Cancer Stem Cells (CSCs)	ladademstat	ladademstat selectively targets SOX2-driven CSCs in the Luminal B subtype, inhibiting their spheroid-forming capacity and reducing SOX2 expression, while remaining ineffective against the Luminal A subtype.	[31]
	RNF20/40-Eg5	RNF20/40	The RNF20/40 complex participates in breast cancer development by regulating spindle assembly, and this pathway may serve as a therapeutic target.	[23]
	HER2 (ERBB2)	Trastuzumab		[32]
	p62 (SQSTM1)		As a potential prognostic marker and therapeutic target for ALDH1-positive Luminal B cancer stem cells	[33]

(Continued)

Table I (Continued).

Subtypes	Target	Medication	Applications and Instructions	Refs
HER2+ subtype: HER2 overexpression/amplification, ER/PR typically negative ^{19,20}	HER2	Trastuzumab, Pertuzumab, T-DM1, T-DXd, Sacituzumab, govitecan	Trastuzumab is a first-line therapeutic agent that inhibits tumor growth by directly binding to the HER2 receptor. Pertuzumab targets the HER2 dimerization domain and is often used in combination with trastuzumab.	[34–38]
	TKIs	Lapatinib	By inhibiting the HER2 intracellular kinase domain	[39]
	PI3K/AKT/mTOR	Everolimus	This pathway frequently interacts with HER2 signaling, and inhibitors such as Everolimus can be used to overcome drug resistance.	[40,41]
	CDK4/6	Palbociclib	In the HR+/HER2+ subtype, agents such as Palbociclib may be combined with HER2-targeted therapy.	[42]
	PD-1/PD-L1		Exploring combination therapy with HER2-targeted treatments	[40]
	CTLA4			
	MUC4		Research has found that it induces trastuzumab resistance by masking the HER2 epitope, making it a potential target.	[43]
	LINC00589-miR		Regulating drug resistance and tumor stem cell characteristics may serve as diagnostic markers and therapeutic targets.	[44]
	IL1 α		Chronic inflammation drives the maintenance of tumor stem cells, suggesting anti-inflammatory targeting potential.	[45]
	ERK/MAPK		Cross-activation with HER2 signaling may serve as a target for combination therapy.	[46]
	Akt			
	CD44+/CD24-		Associated with tumor stem cell phenotypes, currently under investigation	[47]
Triple-negative breast cancer (TNBC): Estrogen receptor (ER)/Progesterone receptor (PR)/HER2 all negative ^{48–50}	Glucose Transporter (GLUT)	WZB117	GLUT inhibitors (such as WZB117) can suppress TNBC progression by blocking energy supply.	[51]
	EGFR	gefitinib	EGFR overexpression is a common feature of TNBC. Combining EGFR-targeted tyrosine kinase inhibitors (such as gefitinib) with Rac1 inhibitors enhances therapeutic efficacy.	[52]
	AXL Receptor Tyrosine Kinase	BGB324	AXL overexpression correlates with TNBC aggressiveness, and small-molecule inhibitors (such as BGB324) are currently under investigation.	[53]
	Notch	DLL4/Hes1	Targeting upstream ligands (such as DLL4) or downstream effector molecules (such as Hes1) may inhibit TNBC growth.	[54]
	PD-1/PD-L1 inhibitor	Pembrolizumab	Immune checkpoint inhibitors (such as pembrolizumab) have been approved for use in PD-L1-positive triple-negative breast cancer (TNBC).	[55,56]
	PARP inhibitor	Olaparib	PARP inhibitors such as olaparib can induce synthetic lethality effects in BRCA mutation patients.	[55,57]
	TROP-2	Sacituzumab govitecan	Sacituzumab govitecan (TROP-2-targeted) has demonstrated clinical benefit.	[55]
	miR-138		Downregulation of miR-138 correlates with TNBC progression; restoring its expression or targeting MMP-13 may represent potential therapeutic strategies.	[58]
	Fatty acid synthase (FASN)	TVB-2640	Fatty acid synthase (FASN) inhibitors such as TVB-2640 are currently undergoing clinical trials.	[59]
	HDAC	Vorinostat	Combining HDAC inhibitors (such as Vorinostat) with DNA methylation inhibitors can reverse the EMT process.	[60,61]

detection allows earlier identification of emerging resistance.⁶⁷ Additional regulatory mechanisms such as NR4A1-mediated suppression of ERK signaling and unfolded protein response related stress signaling further illustrate the complexity of endocrine resistance.^{68,69}

New endocrine targeted agents have been developed to counter these mechanisms. The complete ER antagonist palaezstrant (OP-1250) shows potent antitumor activity in preclinical studies and fully suppresses estrogen responsive transcriptional programs.⁷⁰ The ER directed PROTAC vepdegestrant (ARV-471) induces proteasomal degradation of ER and has demonstrated meaningful efficacy in early clinical trials.^{71,72} Studies also indicate that non coding RNAs and epithelial-mesenchymal transition (EMT) related signaling shape responses to aromatase inhibitors and provide opportunities for combination strategies.⁷³

Despite these advances, resistance remains frequent and reliable biomarkers for predicting response are still lacking. Continued research is needed to develop rational combination approaches and to identify molecular predictors that support individualized therapy for ER+ breast cancer.

Antibody Therapy for HER2+ Breast Cancer

Antibody-based therapy remains central in HER2+ breast cancer. Trastuzumab, the first humanized anti-HER2 antibody, blocks HER2 signaling and induces antibody-dependent cellular cytotoxicity (ADCC), improving outcomes in both metastatic and early-stage disease.^{74–76} Pertuzumab enhances this effect by inhibiting HER2–HER3 dimerization, forming the standard dual blockade.^{77–79} Nonetheless, resistance driven by HER3 reactivation, inadequate modulation of the tumor microenvironment (TME), and treatment-related toxicities remains common.^{79–81}

Enhancing immune engagement has emerged as an important strategy. ADCC and antibody-dependent cellular phagocytosis (ADCP) are key components of trastuzumab activity, and CD47 blockade strengthens macrophage-mediated ADCP, improving responses in resistant models.^{82–87} Antibody-drug conjugates (ADCs) extend HER2 targeting by delivering cytotoxic payloads. T-DM1 (trastuzumab emtansine) provides clinical benefit in metastatic disease, although HER2 down-regulation, impaired endocytosis, and compensatory pathway activation increasingly limit its efficacy.^{88–92}

Emerging ADCs aim to overcome these limitations. ARX788, a site-specific trastuzumab–AS269 conjugate, shows robust activity in preclinical and early clinical studies, including T-DM1–resistant models.⁹³ T-DXd (trastuzumab deruxtecan), incorporates a cleavable linker and a topoisomerase I inhibitor payload, demonstrating potent activity even in HER2-low cancers and benefiting patients with prior T-DM1 exposure.⁹⁴ Disitamab vedotin, composed of an anti-HER2 monoclonal antibody and monomethyl auristatin E (MMAE), has produced encouraging results in prospective clinical studies, including in trastuzumab-resistant disease.^{95,96}

Importantly, HER2 spatial heterogeneity profoundly influences treatment response. Tumors with heterogeneous amplification show markedly reduced pathological complete response (pCR) rates, with neoadjuvant data reporting 55% pCR in homogeneous tumors versus 0% in heterogeneous tumors treated with T-DM1 plus pertuzumab.^{97–101} This highlights the need for strategies that maintain efficacy despite intratumoral variability. Radionuclide-augmented ADCs such as ¹⁷⁷Lu-labeled HER2 or TROP2 conjugates offer improved tumor control in heterogeneous and refractory models by enhancing intratumoral penetration and sustaining cytotoxicity.¹⁰²

Despite their promise, ADCs carry safety concerns. Interstitial lung disease, particularly associated with T-DXd, requires close monitoring and prompt management.^{103–108} Toxicity profiles differ across ADC platforms, and long-term safety data remain limited. Advances in spatial proteomics and molecular profiling may refine biomarker development and patient selection. Continued investigation into resistance mechanisms, heterogeneity, and toxicity will be essential to optimize future HER2-targeted antibody and ADC therapies.

Chemotherapy and Its Auxiliary Role in Targeted Therapy

Chemotherapy remains a fundamental component of breast cancer treatment and continues to play an irreplaceable role despite advances in targeted and immune-based therapies. Cytotoxic agents exert antitumor effects by interfering with DNA replication and repair, disrupting mitotic spindle assembly, and inhibiting nucleic acid synthesis.^{109–112} Although targeted strategies are expanding rapidly, none can fully substitute for chemotherapy, which therefore remains widely integrated into multimodal regimens alongside surgery, radiotherapy, endocrine therapy, and targeted therapy.^{113,114}

Chemotherapy is increasingly combined with targeted agents to enhance efficacy and delay resistance. ADCs such as T-DM1 illustrate how targeted delivery of cytotoxic payloads can strengthen antitumor activity beyond that achieved by chemotherapy alone. Improving intratumoral drug penetration has also become a priority, as abnormal vasculature contributes to chemoresistance. Strategies that promote vascular normalization, including HER2-directed antibodies and the VEGFR2 inhibitor apatinib, improve perfusion and alleviate hypoxia, thereby enhancing the distribution and activity of chemotherapeutic agents.^{115,116}

Clinical evidence supports the auxiliary role of chemotherapy within targeted regimens. In HER2-positive patients with small node-negative tumors (≤ 2 cm), chemotherapy combined with HER2-targeted therapy reduces recurrence risk by roughly 30% and yields five-year survival exceeding 60%.¹¹⁷ In metastatic settings, dual HER2 blockade with endocrine therapy shows superior efficacy compared with chemotherapy alone, with response rates of 86–91% versus 62%–81%.¹¹⁸ For ER-negative (ER-) tumors, activation of the IRF7/IFN- β /IFNAR axis drives immune dormancy and chemoresistance, and inhibition of this pathway restores sensitivity and correlates with improved metastasis-free survival.¹¹⁹

Despite its central role, chemotherapy has important limitations. In TNBC, systemic chemotherapy remains primary, yet responses are often limited and recurrence is frequent.^{120–122} In hormone receptor-positive disease, chemotherapy serves mainly as an adjunct to endocrine therapy, with anti-angiogenic agents offering potential enhancement of chemosensitivity.^{116,123} Toxicities such as neurotoxicity, cardiotoxicity, myelosuppression, and immune suppression restrict dose intensity and may influence subsequent response to targeted or immune-based therapies. Chemotherapy also remodels the tumor microenvironment, contributing to immune suppression and altered stromal architecture, which can limit the effectiveness of later treatments.^{124,125} Practical and logistical barriers also influence real-world outcomes, as older adults or patients with comorbidities often tolerate standard multi-drug regimens poorly, leading to incomplete therapy and suboptimal survival benefits.

Together, these findings highlight the enduring importance of chemotherapy in breast cancer while emphasizing the need for strategies that enhance delivery, mitigate toxicity, and overcome microenvironmental and biological resistance. Figure 1 summarizes the current systemic treatment strategies.

Advanced Therapeutic Targets in Breast Cancer Management

Application of PARP Inhibitors in *BRCA*-Mutated Breast Cancer

Poly (ADP-ribose) polymerase (PARP) participates in multiple processes relevant to breast cancer progression, including chromatin remodeling, DNA single-strand break repair, TGF β -driven EMT, and JAK/STAT3-mediated metabolic regulation.^{126–128} PARP inhibitors represent a major advance in precision oncology. By exploiting homologous recombination repair (HRR) defects caused by *BRCA* mutations, they induce synthetic lethality and significantly improve progression-free survival (PFS) in appropriately selected patients.^{129–132} Olaparib, the first approved PARP inhibitor for germline *BRCA*-mutated breast cancer, inhibits PARP1 and PARP2 and disrupts DNA repair. In the Phase III OlympiAD trial, olaparib prolonged PFS in *gBRCA*-mutated, HER2-negative metastatic breast cancer compared with physician's-choice chemotherapy (19.3 vs 8.2 months).^{130,133–135} Other agents such as talazoparib have shown comparable efficacy in early- and late-phase clinical trials.^{133,136}

Importantly, recent evidence indicates that PARP inhibitors are also effective in tumors with somatic *BRCA* mutations or broader HRR impairment. This phenotype, termed “*BRCAness*”, arises from alterations in HR-related genes beyond *BRCA1/2* and confers sensitivity to PARP inhibition.¹³⁷ Accordingly, potential beneficiaries extend beyond germline *BRCA* carriers.

PARP inhibitors are particularly relevant in TNBC with *BRCA1/2* loss. PARP blockade prevents single-strand break repair, causing replication fork collapse and double-strand breaks. Tumor cells lacking *BRCA*-mediated HRR cannot repair such lesions, leading to apoptosis.^{129,138,139} However, prolonged inhibition may promote cancer stem cell-like phenotypes and activate compensatory repair pathways, attenuating long-term responsiveness.^{140–142}

Consequently, combination strategies have therefore become a central focus. Preclinical studies show that combining PARP inhibitors with platinum agents enhances synthetic lethality in *BRCA*-like TNBC by simultaneously inducing double- and single-strand DNA damage.^{139,143} Combinations with EZH2, CDK4/6, WEE1, and c-MET inhibitors are

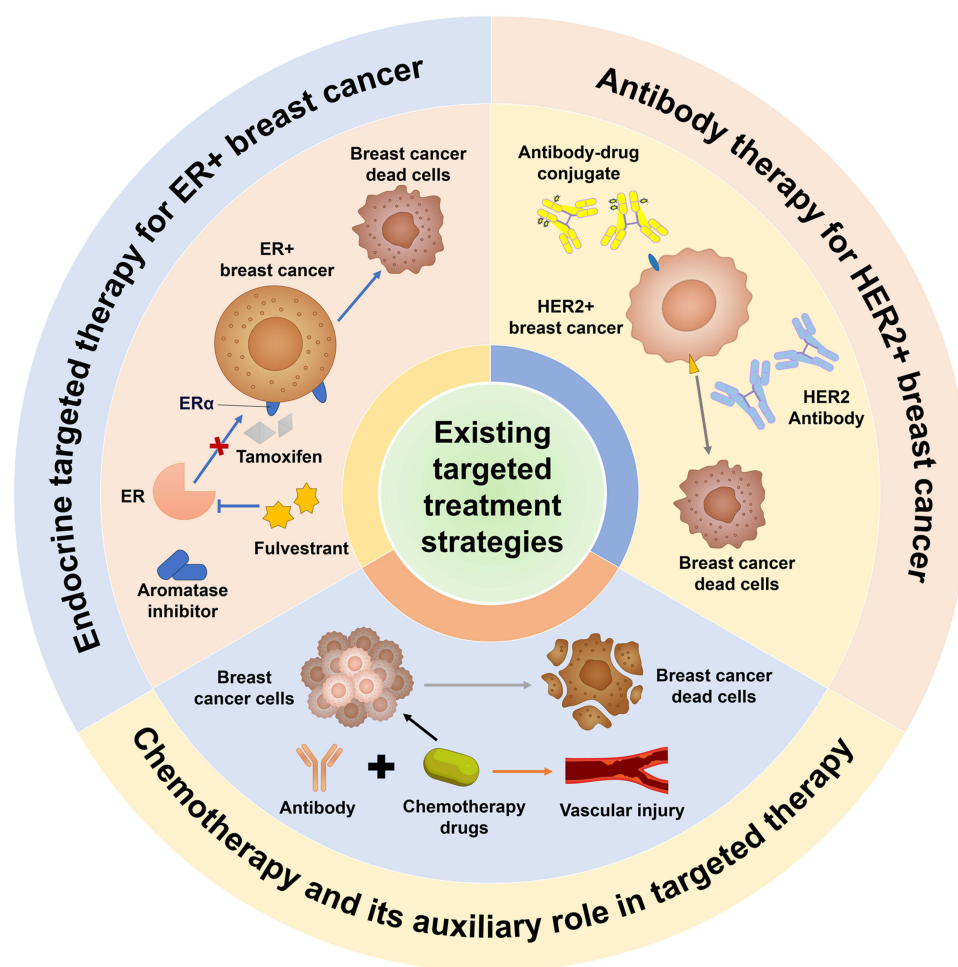


Figure 1 Overview of current systemic treatment strategies for breast cancer. This schematic summarizes the major systemic therapies used in breast cancer management, including endocrine therapy for ER+ tumors, HER2-targeted antibody therapy and antibody-drug conjugates for HER2+ tumors, and chemotherapy as a foundational modality across subtypes. Endocrine targeted therapy: In ER+ breast cancer, agents including tamoxifen, fulvestrant, and aromatase inhibitors block ER α signaling, leading to BCDC; Antibody therapy: In HER2+ breast cancer, HER2-targeted antibodies and antibody-drug conjugates inhibit tumor growth; Chemotherapy: Chemotherapy combined with antibody therapy induces BCDC but may also cause vascular damage.

Abbreviations: BCDC, Breast cancer dead cells; ER, Estrogen Receptor; HER2, Human Epidermal growth factor Receptor 2; ER α , Estrogen Receptor alpha.

under active investigation and exhibit promising synergy, potentially benefiting *BRCA*-wild-type but HRD-positive (HRD+) tumors.^{144–150}

Despite these advances, limitations remain. Common toxicities include anemia, neutropenia, fatigue, and gastrointestinal reactions, and long-term safety data are still evolving.¹⁵¹ Clinical benefit is largely confined to *BRCA*-mutated or HRD-positive populations, and variability among HRD testing platforms complicates patient selection. Moreover, the overall survival benefit remains inconsistent across studies, and resistance mechanisms such as partial restoration of homologous recombination repair or increased drug efflux further restrict the durability of treatment responses.^{152,153}

Future priorities include establishing reliable biomarkers for HRD, optimizing combination therapy while minimizing toxicity, and developing improved delivery systems to enhance tumor specificity. These efforts are essential to expand the clinical utility of PARP inhibitors and improve outcomes for both *BRCA*-mutated and HRD+ breast cancer.

Application of CDK4/6 Inhibitors in ER+ Breast Cancer

Cyclin-dependent kinase 4/6 (CDK4/6) is central to ER+ breast cancer biology through its interaction with cyclin D1, a key downstream target of ER signaling. ER activation increases cyclin D1 expression, promoting CDK4/6-mediated phosphorylation of retinoblastoma (Rb) protein and driving the G1–S transition.^{154–156} CDK4/6 inhibitors block this phosphorylation, induce G1 arrest, and effectively suppress tumor proliferation.^{157,158}

Beyond classical ER+ disease, CDK4/6 inhibition may also benefit HER2-low breast cancer. Although HER2 expression is reduced, downstream signaling may still activate CDK4/6 via Rb phosphorylation. Elevated pRb levels observed in HER2+ and HER2-low tumors suggest increased cell cycle activity and potential sensitivity to CDK4/6 blockade.¹⁵⁹

Resistance remains a major challenge. Mechanisms include RB1 alterations, activation of alternative ER pathways, and aberrant PI3K/AKT/mTOR signaling.^{160–163} Preclinical data indicate that combining PI3K or mTOR inhibitors with emerging CDK7 inhibitors may overcome resistance and enhance antitumor efficacy.^{160,164}

CDK4/6 inhibitors are especially valuable in endocrine-resistant disease. Endocrine therapy suppresses estrogen-driven transcription, while CDK4/6 inhibitors block downstream cell cycle progression, generating synergistic dual inhibition. This combination is now the first-line standard for metastatic ER+ breast cancer, with trials showing that palbociclib, ribociclib, and abemaciclib combined with endocrine therapy significantly prolong PFS across diverse clinical subgroups.^{165–168} Ongoing studies are evaluating their role in the adjuvant setting for high-risk early breast cancer.^{166,169}

Although CDK4/6 inhibitors have achieved clinical success by extending progression-free survival in metastatic ER+ breast cancer, several challenges remain in real-world practice. Common toxicities such as neutropenia, fatigue, and gastrointestinal discomfort often necessitate dose reduction or treatment interruption.^{170,171} The presence of RB1 loss, activation of downstream pathways, or altered cyclin D1 expression can markedly reduce drug sensitivity, and potential indicators remain under investigation and require prospective validation.¹⁷² Trials in the adjuvant or early-stage setting have not consistently demonstrated an improvement in overall survival, highlighting the need for careful patient selection. Future work should focus on clarifying resistance mechanisms, developing reliable biomarkers, and optimizing combination strategies, while also considering the long-term costs and follow-up requirements associated with extended combination therapy.

The Oncogenic Role and Therapeutic Potential of WBP2 in Breast Cancer

WW-binding protein 2 (WBP2) acts as an oncogenic transcriptional co-activator integrating multiple signaling cascades, including ER/PR, EGFR, PI3K, Hippo, and Wnt pathways.¹⁷³ By interacting with β -catenin and YAP/TAZ complexes, WBP2 enhances tumor proliferation, invasion, and progression, and regulates key effectors such as c-Myc and cell-cycle proteins.^{174–178}

Mechanistically, WBP2 translocates to the nucleus upon Wnt3A stimulation, binds β -catenin, and activates TCF-dependent transcription to promote invasive behavior. Its protein levels are regulated by the E3 ubiquitin ligase ITCH, which targets WBP2 for proteasomal degradation. In TNBC, impaired ITCH-mediated degradation leads to WBP2 accumulation, enhanced ER α binding, and upregulation of multidrug resistance protein 1 (MDR1), contributing to chemotherapy resistance.^{174,179,180} Restoration of ITCH function via the AMOTL2/c-JUN axis re-establishes WBP2 degradation and reverses chemoresistant phenotypes, highlighting a potential therapeutic strategy.

Given its functional link with YAP/TAZ, WBP2 is also modulated by upstream Hippo signaling. Activation of the Hippo/MST pathway suppresses WBP2 through Dicer-mediated miRNA processing, affecting HER2 expression and cell-cycle arrest during trastuzumab treatment.¹⁷⁸ Conversely, elevated WBP2 enhances trastuzumab-induced HER2 internalization and cyclin D-dependent cell-cycle arrest, particularly in younger patients (<50 years old), supporting its role as both a functional effector and potential predictive biomarker for HER2-targeted therapy.¹⁷⁶

Collectively, WBP2 serves as a central node connecting oncogenic pathways and influencing drug sensitivity, HER2-targeted therapy response, and ubiquitin-dependent degradation, making it a promising target for precision therapy. Most evidence derives from preclinical models, and clinical translation remains limited. Key challenges include incomplete understanding of WBP2 function in normal tissues, potential compensatory mechanisms, and lack of consistent biomarkers for patient selection. Future research should focus on toxicology, pharmacokinetics, early-phase clinical studies, and therapeutic strategies such as miRNA modulation or restoration of ubiquitin-mediated degradation to overcome resistance and improve breast cancer outcomes.

Trop2-Targeted Therapy for Breast Cancer

Trophoblast cell surface antigen 2 (Trop2) is a type I transmembrane glycoprotein that regulates intracellular calcium and activates PI3K/AKT signaling, promoting tumor growth, migration, and survival.^{181–184} In glioblastoma, Trop2 also engages JAK2/STAT3, MAPK, and Wnt/ β -catenin pathways, indicating broad oncogenic involvement. Although it may act as a tumor suppressor in some contexts, these remain poorly understood. In breast cancer, particularly TNBC, Trop2 is widely overexpressed, making it an attractive therapeutic target.¹⁸⁵

Structurally, Trop2 comprises extracellular, transmembrane, and intracellular domains. Its extracellular domain forms dimers with more extensive inter-subunit interactions than epithelial cell adhesion molecule (EpCAM), potentially influencing interactions with IGF-1, neuromodulin-1, and $\alpha\beta$ integrins to drive tumor progression.¹⁸⁶ These structural insights have accelerated the development of Trop2-targeted therapies, especially ADCs.

Clinical progress has been notable, particularly with sacituzumab govitecan (SG), which significantly prolongs PFS and overall survival (OS) in metastatic TNBC compared with standard chemotherapy, although direct head-to-head comparisons are limited.¹⁸⁷ Building on these advances, new Trop2-directed ADCs continue to emerge. OBI-992, an anti-Trop2 antibody conjugated to the topoisomerase I inhibitor exatecan via an enzyme-cleavable hydrophilic spacer (DAR 4), demonstrates superior preclinical activity relative to existing agents such as Dato-DXd.¹⁸⁸ Given Trop2's broad expression across breast cancer subtypes, these agents may offer therapeutic utility beyond TNBC.¹⁸⁵ Figure 2 illustrates emerging targeted therapeutic strategies in breast cancer.

Despite clinical promise, Trop2-targeted therapies face challenges. Common toxicities include neutropenia, diarrhea, and fatigue, with some severe events requiring hospitalization.^{189,190} Heterogeneous Trop2 expression and functional variability contribute to differential responses, and single-target strategies may be less effective in tumors with low or heterogeneous expression.¹⁸⁹ Nevertheless, the rapid approval of SG and ongoing ADC development underscore Trop2 as a compelling target. Future research should focus on defining biomarker thresholds, optimizing dosing, monitoring toxicity, and evaluating real-world effectiveness, particularly in aggressive, receptor-negative subtypes such as TNBC.

Advanced Targeting Strategies in Breast Cancer Management

Targeted Metabolic Therapeutic Strategies for Breast Cancer

Breast cancer stem cells (BCSCs) drive tumor initiation, progression, metastasis, and therapeutic resistance. As “seed cells,” BCSCs possess self-renewal and differentiation capacity, maintain tumor heterogeneity, and display enhanced migratory and invasive potential, contributing to metastasis to brain, lungs, liver, and bone. Resistance to chemotherapy, endocrine therapy, and radiotherapy stems from enhanced DNA repair, elevated drug efflux, and distinct metabolic states.^{191–193}

BCSCs exhibit substantial metabolic plasticity. Mesenchymal-like (M-type) BCSCs rely on oxidative phosphorylation (OXPHOS), whereas epithelial-like (E-type) BCSCs depend on glycolysis, providing subtype-specific vulnerabilities. Lactate dehydrogenase A (LDHA) maintains stemness via lactate accumulation in the TME.^{194,195} Simultaneous inhibition of glycolysis and antioxidant pathways selectively eliminates dynamic BCSC populations, highlighting shared metabolic vulnerabilities.¹⁹⁶

The TME plays a decisive role in regulating BCSC behavior. Hypoxia is a major driver of stemness maintenance and can stabilize NANOG mRNA through the N6-methyladenosine (m6A) demethylase ALKBH5, thereby promoting stemness.¹⁹⁷ Metabolic crosstalk with mesenchymal stem cells activates P2X receptors on BCSCs, enhancing proliferation and metastasis, reversible by purinergic signaling inhibitors.¹⁹⁸

Developmental pathways, including Notch, Hedgehog, Hippo, and Wnt, regulate BCSC self-renewal, quiescence, and differentiation. NOTCH4 maintains quiescent M-type BCSCs through SLUG and GAS1, contributing to dormancy and therapy resistance.¹⁹⁹ Dysregulated lipid metabolism, including CD200 and CD276 expression and lipid droplet accumulation, supports immune evasion and stemness.²⁰⁰ Transcriptional regulators such as FoxQ1 promote stemness via Wnt/ β -catenin and Snail-mediated EMT, and compounds like diallyl trisulfide (DATS) can suppress FoxQ1 and BCSC proliferation.^{201–203}

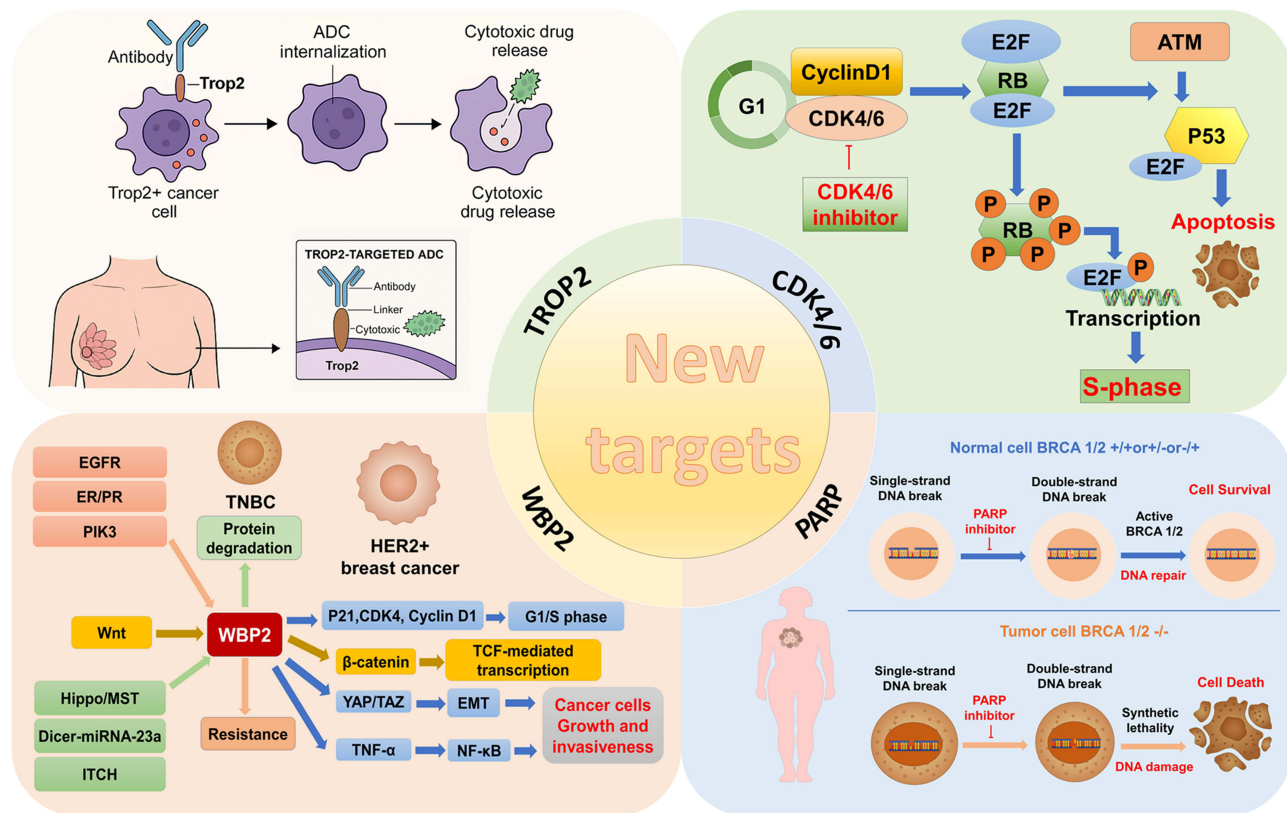


Figure 2 Schematic overview of novel target-directed strategies in breast cancer therapy. The figure is divided into four sections highlighting key molecular targets and their therapeutic implications. TROP2 (top left): Trop2-expressing cancer cells are selectively targeted by ADCs, which are internalized upon binding, undergo lysosomal degradation, and release cytotoxic payloads, inducing cancer cell death while sparing normal tissues. CDK4/6 (top right): CDK4/6 inhibitors block cell cycle progression by preventing RB phosphorylation and subsequent E2F activation, thereby arresting cells in G1 phase. These inhibitors also interact with DNA damage response pathways, such as ATM-p53 signaling, influencing therapeutic outcomes. WBP2 (bottom left): WBP2 integrates multiple upstream oncogenic signals, including Wnt/ β -catenin, EGFR, ER/PR, PI3K, Hippo/MST, and miRNA-mediated pathways, to promote cell proliferation, EMT, and tumor progression. Modulation of WBP2 protein degradation can enhance therapeutic response and overcome resistance in TNBC. PARP (bottom right): PARP inhibitors exploit synthetic lethality in BRCA1/2-deficient tumors by preventing repair of single-strand DNA breaks, leading to accumulation of double-strand breaks and selective cancer cell death, while normal cells with functional BRCA1/2 maintain genomic integrity. This multidimensional framework illustrates how targeted interventions converge to disrupt key proliferative and survival pathways across breast cancer subtypes. **Abbreviations:** ADC, Antibody-drug conjugates; Trop2, Trophoblast cell surface antigen 2; CDK4/6, Cyclin-dependent kinase 4/6; RB, Retinoblastoma protein; E2F, E2 promoter-binding factor; ATM, Ataxia Telangiectasia Mutated; ER, Estrogen receptor; SLC7A11, Solute carrier family 7 member 11; WBP2, WW domain-binding protein 2; Wnt, Wingless-related integration site; EGFR, Epidermal growth factor receptor; ER/PR, Estrogen/progesterone receptor; PI3K, Phosphoinositide 3-kinase; MST, Mammalian Ste20-like kinase; TNBC, Triple-negative breast cancer; PARP, Poly-ADP-ribose polymerase; BRCA, Breast cancer susceptibility gene; EMT, Epithelial-mesenchymal transition.

Autophagy is essential for BCSC survival under therapeutic stress. EpCAM regulates autophagy through glycosylation-dependent PI3K/Akt/mTOR signaling, with deglycosylated EpCAM promoting autophagy and cell proliferation.^{204–206}

Figure 3 illustrates the aforementioned process. These metabolic and signaling mechanisms that sustain BCSC stemness represent potential therapeutic targets.

However, translating metabolic targeting into clinical practice remains challenging. Many metabolic enzymes and pathways are active in normal tissues, raising concerns about selectivity and systemic toxicity. Evidence supporting metabolic interventions is largely preclinical, and early-phase clinical trials have yielded modest or inconsistent responses. Tumor metabolism is highly adaptive, capable of switching to compensatory pathways, and pronounced metabolic heterogeneity within and across tumors further complicates patient selection. Future progress will require reliable biomarkers, rational combination strategies to prevent metabolic escape, and rigorous clinical studies to define therapeutic windows and long-term safety.

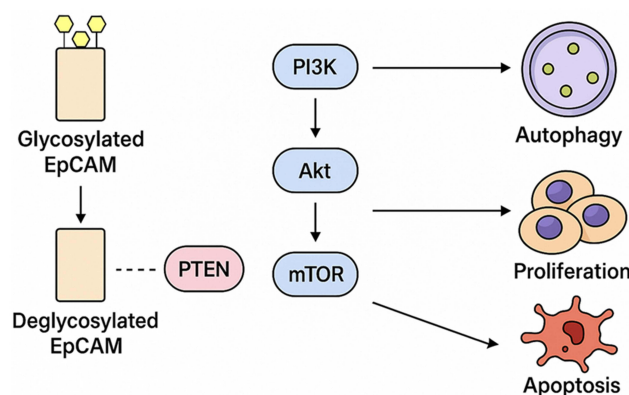


Figure 3 Mechanistic schematic of deglycosylated EpCAM in modulating breast cancer progression. Deglycosylated EpCAM exerts multifaceted effects on breast cancer cells. It promotes autophagy either directly or via inhibition of the Akt/mTOR signaling axis, and concurrently enhances apoptosis, resulting in a marked reduction in proliferative capacity. Additionally, deglycosylated EpCAM suppresses invasion and metastatic potential by downregulating MAPK and PI3K/Akt pathways, which leads to decreased expression of EMT-associated proteins, including N-cadherin and vimentin. This integrated modulation of survival, growth, and metastatic signaling highlights the critical role of deglycosylated EpCAM in restraining breast cancer progression.

Abbreviations: EpCAM, Epithelial Cell Adhesion Molecule; mTOR, mammalian target of rapamycin; AKT, Protein Kinase B; PI3K, Phosphatidylinositol 3-kinase; MAPK, Mitogen-activated protein kinase; EMT, Epithelial-mesenchymal transition.

Targeting the Tumor Immune System

Application of Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) reactivate antitumor T-cell responses by blocking inhibitory pathways such as PD-1/PD-L1 and CTLA-4. Their efficacy in breast cancer varies across subtypes, highlighting the need to understand subtype-specific immunogenic features and optimize combination strategies.

In HR+/HER2– breast cancer, low tumor-infiltrating lymphocyte (TIL) density and limited PD-L1 expression result in weak immunogenicity and poor ICI responsiveness.²⁰⁷ Combination strategies aim to sensitize these immunologically “cold” tumors. CDK4/6 inhibition with palbociclib enhances antigen presentation and T-cell priming, and when combined with pembrolizumab and the aromatase inhibitor letrozole, produces encouraging antitumor activity in HR+/HER2– metastatic disease.²⁰⁸ These findings emphasize the integration of endocrine therapy and cell cycle inhibition to improve ICI efficacy.

HER2+ tumors are more immunogenic, with higher TIL infiltration and PD-L1 expression, which enhances ICI responsiveness.^{209,210} HER2-targeted antibodies such as trastuzumab activate natural killer cells via ADCC, facilitating adaptive T-cell responses.²¹¹ Moreover, radiotherapy further amplifies HER2-specific cytotoxic T-cell infiltration, strengthening ICI activity in preclinical models.^{212,213}

TNBC exhibits the highest immunogenicity, with abundant TILs and frequent PD-L1 upregulation, making it the most responsive subtype to ICIs.²⁰⁹ Chemotherapy enhances antigen release and presentation while reducing immunosuppressive cells, synergistically improving ICI responses.^{214–217} Mechanistically, PD-L1 overexpression allows immune evasion; PD-L1 blockade with atezolizumab combined with albumin-bound paclitaxel is approved for PD-L1–positive metastatic TNBC.²¹⁸ However, therapeutic benefit remains limited to PD-L1–positive populations, and primary or acquired resistance continues to pose clinical challenges.

Emerging strategies explore ICIs in combination with anti-angiogenic agents, PARP inhibitors, or TME modulators to enhance immunogenicity and overcome resistance across subtypes.^{219,220} These combinatorial approaches aim to enhance immunogenicity, remodel suppressive microenvironments, and overcome intrinsic resistance mechanisms across breast cancer subtypes. Continued refinement of these strategies is essential for maximizing the therapeutic potential of immune checkpoint inhibitors in breast cancer.

Despite these advances, clinical benefit remains largely confined to PD-L1–positive TNBC, with limited efficacy in HR+ disease. Immune-related adverse events, including thyroid dysfunction, colitis, hepatitis, and pneumonitis, can be severe and require immunosuppressive therapy.^{221,222} Low tumor mutational burden, poor antigenicity, and immunosuppressive TME further limit response, while cost and accessibility constrain broader application. These challenges

highlight the need for predictive biomarkers, optimized combination regimens, and rigorous safety management to expand the therapeutic impact of ICIs in breast cancer.

Novel Immunotherapy

Bispecific antibodies (BsAbs) are engineered molecules capable of simultaneously binding tumor-associated antigens on breast cancer cells and immune effectors such as CD3 on T cells, thereby recruiting T cells to tumor cells and inducing antigen-specific cytotoxicity.^{223–225} Over 200 BsAb constructs, including BsAb drug conjugates, are under preclinical or early clinical investigation across breast cancer subtypes.^{226,227} Mechanistic studies have expanded applications beyond direct cytotoxicity; for example, IL-6/IL-8 dual-receptor–targeting BsAbs suppress migration and metastasis, while DB-1419 (B7-H3×PD-L1) BsAbs combine immune checkpoint blockade with direct tumor targeting.²²⁸ Despite these promising directions, BsAb development faces several challenges. Complex structural formats, such as asymmetric IgG-like molecules, complicate large-scale manufacturing, whereas smaller constructs, such as Fab fragments, often display reduced half-lives and suboptimal pharmacokinetic properties.²²⁹

BsAb research laid the conceptual foundation for chimeric antigen receptor T-cell (CAR-T) therapy, which genetically modifies patient T cells to express tumor antigen–binding receptors fused to activation domains such as CD3 ζ , enabling continuous T-cell activation independent of MHC presentation.^{224,230} CAR-T therapy has achieved clinical success in hematologic malignancies through standardized workflows such as viral transduction and ex vivo expansion. Solid tumors, including breast cancer, pose additional challenges due to heterogeneous antigen expression, variable target distribution, and an immunosuppressive microenvironment.^{231,232} Antigen loss through epigenetic reprogramming or clonal selection, including CD19-negative relapse in hematologic malignancies and antigen-negative outgrowth in glioblastoma, further limits CAR-T efficacy.^{233–237}

Dual-targeting strategies, exemplified by CD79a/b in B-cell malignancies, demonstrate the potential to mitigate antigen escape, yet dynamic antigen plasticity in solid tumors remains a major challenge. Emerging approaches combine CAR-T and BsAb strategies. For instance, dual-target CAR-T cells recognizing EpCAM and intercellular adhesion molecule-1 (ICAM-1) enhance antigen coverage and tumor suppression, while p95HER2-CAR-T combined with HER2/CD3 BsAbs achieved complete tumor regression in HER2-positive breast cancer models.²³⁸ Fine-tuning BsAb affinity can further guide CAR-T cells toward high-antigen tumors while minimizing off-tumor toxicity.

Despite progress, solid tumor microenvironments limit engineered immunotherapies. TGF- β and dense stroma restrict T-cell infiltration and persistence, contributing to T-cell exhaustion and antigen escape.²³⁹ Toxicities such as cytokine release syndrome and neurotoxicity further constrain treatment. BsAbs and cancer vaccines face similar obstacles, including short half-lives, on-target off-tumor activity, and limited antigenicity. Most evidence remains preclinical or early-phase, and uncertainties persist regarding feasibility, manufacturing, scalability, and long-term safety. Future research should focus on integrating BsAbs, CAR-T engineering, and microenvironment-modulating strategies to enhance tumor penetration, expand antigen coverage, and broaden the therapeutic window, thereby improving clinical efficacy and durability in breast cancer.

Targeting the Tumor Microenvironment

The breast cancer TME comprises heterogeneous cellular and non-cellular components, including suppressor myeloid cells, tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), extracellular matrix (ECM), and inflammatory mediators, collectively driving tumor progression, immune suppression, and therapeutic resistance.^{240–244} Therapeutic strategies targeting the TME aim to reverse immunosuppression, enhance intratumoral drug delivery, and overcome therapy resistance.

Reversing immune suppression is central to improving therapeutic efficacy. Tumor-derived granulocyte–macrophage colony-stimulating factor (GM-CSF) upregulates ARG1 expression in myeloid cells via STAT3, p38 MAPK, and cAMP signaling under acidic conditions, promoting local immunosuppression. Blocking GM-CSF reduces ARG1 expression, restoring antitumor immunity and enhancing T-cell–based therapies and immune checkpoint inhibitor responses.²⁴²

Structural and biophysical barriers within the TME also limit drug delivery. Dense ECM, elevated interstitial pressure, and poor perfusion impede penetration of conventional therapies, while tumor acidity can be exploited for pH-

responsive drug release. Nanotechnology-based strategies, including hypoxia- or esterase-responsive nanomicelles, functionalized liposomes, and sonodynamic therapy (SDT)-assisted delivery, enhance spatiotemporal drug release, prolong intratumoral retention, and improve therapeutic efficacy.^{240,245–252}

Given the high heterogeneity of the TME, precision oncology increasingly relies on high-resolution profiling. Eftekhari et al demonstrated that dynamic remodeling of CD4⁺ T-cell subsets (Treg, Th1, Th2, Th17), inflammatory cytokines (TNF- α , IL-6), and immune mediators (FASL, IDO, SOCS1, VEGF, CCR7) correlates with breast cancer progression.²⁵³ Single-cell RNA sequencing by Yang et al identified regulatory T cells, M2 macrophages, angiogenesis-associated mast cells, DNA-repair-deficient stem-like cells, angiogenic endothelial cells, collagen-producing fibroblasts, and proliferative epithelial cells as key drivers of a pro-tumorigenic interface zone.²⁵⁴ These findings highlight the cellular complexity that shapes tumor behavior and therapeutic response.

Despite advances in understanding the tumor microenvironment, TME-targeted therapies face substantial translational challenges. Conventional two-dimensional models inadequately recapitulate physiological conditions, emphasizing the need for advanced three-dimensional models, while integration of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, is essential to map dynamic cellular interactions and identify therapeutic vulnerabilities.^{255–259} Clinically, approaches such as ECM remodeling, CAF depletion, or vascular normalization have shown only variable or transient benefits, sometimes disrupting stromal homeostasis or producing short-lived effects. Lack of predictive biomarkers and off-tumor toxicity further limit efficacy, highlighting the need for combination strategies rather than single-target interventions.

Overall, integrating TME characterization with precision medicine offers a promising path for breast cancer therapy. Approaches that combine microenvironmental modulation, personalized therapeutic selection, and multi-omics profiling may enhance treatment efficacy and improve clinical outcomes.

Novel Drug Delivery Systems Nanotechnology Innovation

Nanotechnology has gained substantial traction in breast cancer management through diverse platforms, including liposomes, polymeric nanoparticles, and inorganic nanostructures, which function as drug carriers to overcome key limitations of conventional chemotherapy. These systems improve drug stability, enhance tumor-specific targeting, enable controlled or stimuli-responsive release, facilitate delivery of hydrophobic agents, and reduce toxicity to normal tissues.^{260–264} Increasingly, nanocarriers are being explored for combination therapies, gene silencing, and diagnostic applications.

Kahlous et al engineered gold nanoparticle-based carriers, including chitosan–citrate–tamoxifen nanocomposites and layered gold nanoparticle systems, demonstrating enhanced antiproliferative activity against MCF-7 cells, supporting potential synergy with endocrine therapy.⁷ Wang et al developed a biomimetic dual-targeted protein nanocage with three-dimensional drug-loading capacity, illustrating how rational nanoplatform design can improve delivery efficiency, enhance therapeutic synergy, and mitigate resistance.²⁶⁵

Nanocarriers have also advanced gene-silencing strategies. Yang et al designed an siRNA system targeting BCSG1, achieving effective molecular-level gene knockdown.²⁶⁶ Similarly, Alipoor et al developed DNAi peptide nanohybrids against BCL-2, inducing apoptosis in breast cancer cells.²⁶⁷ To overcome siRNA instability and poor bioavailability, hybrid systems combining liposomes with mesoporous silica nanoparticles co-delivering siRNA and doxorubicin have been proposed, enhancing intracellular accumulation and overcoming multidrug resistance.²⁶⁸

In diagnostics, nanotechnology enables sensitive detection of early disease biomarkers. Cheng et al employed surface-enhanced Raman spectroscopy (SERS) with silver nanoparticle substrates to detect serum biomarkers with high sensitivity.²⁶⁹ In addition, Heikal et al developed atorvastatin-loaded pumpkin seed oil nanovesicles delivered via microneedles, providing localized therapy while minimizing systemic toxicity.

Despite these advances, clinical translation of nanocarriers faces challenges, including reproducibility, long-term biosafety, scalable manufacturing, regulatory hurdles, and variable intratumoral distribution in heterogeneous micro-environments. Combining nanotechnology with targeted therapies or immunotherapy represents a promising direction to overcome resistance and improve precision in breast cancer treatment.

Ultrasound Delivery Technology

Ultrasound-mediated drug delivery has emerged as a promising targeted therapeutic strategy in breast cancer by leveraging acoustic energy, mechanical forces, and cavitation to enhance intratumoral drug penetration while minimizing systemic toxicity. Among these, ultrasound-targeted microbubble cavitation (UTMC) transiently disrupts tumor vasculature: upon ultrasound activation, microbubbles (MBs) or nanobubbles (NBs) undergo inertial cavitation, widening endothelial gaps, increasing vascular permeability, and promoting deeper drug distribution.^{270,271} Using microbubble/microdroplet clusters (PS101), J. Yu et al demonstrated enhanced drug accumulation and improved therapeutic outcomes in breast cancer models.²⁵²

Ultrasound also facilitates drug loading and targeted release. Italiya et al developed a microbubble-based system delivering virus-sensitized therapeutics, where ultrasonic cavitation enhanced intratumoral deposition of oncolytic agents in 4T1 breast cancer.²⁷² Beyond mechanical effects, ultrasound-generated thermal energy and transient membrane permeabilization improve drug internalization, with kinetic models confirming controllable release profiles under acoustic stimulation.^{273,274}

Recent innovations extend ultrasound applications beyond drug delivery. Wang et al engineered a system activating plant chlorophyll-based sonosensitizers (C34), generating reactive oxygen species, triggering immunogenic cell death, suppressing primary tumor growth, and reducing metastatic spread.²⁷³ Additionally, responsive nanocarriers such as ultrasound-triggered liposomes and polymeric nanoparticles enable site-specific release, reducing off-target effects. Li et al evaluated IR-780 iodide as a sonodynamic therapy agent, where ultrasound exposure induced necrotic and apoptotic cell death in 4T1 cells via reactive oxygen species.²⁷⁵ Acoustic-responsive nanobubbles further integrate diagnostic imaging and therapeutic enhancement, while approaches like acoustic droplet vaporization and phase-change nanomaterials improve spatial precision and efficacy.^{276–279}

Despite these advantages, including non-invasive activation, real-time imaging, and controllable release, clinical translation remains limited due to technical variability, incomplete long-term safety data, and lack of standardized protocols. Future directions include optimizing multimodal combinations with immunotherapy, developing intelligent acoustically responsive carriers, and establishing robust clinical validation frameworks.

Exosome Delivery

Exosomes have emerged as versatile platforms for breast cancer diagnosis and therapy due to their unique biochemical composition, intrinsic stability, and natural capacity for intercellular communication. Carrying proteins, nucleic acids, lipids, and metabolites, exosomes reflect the molecular profile of tumor cells and enable minimally invasive biomarker detection. MUC1, a membrane-bound glycoprotein linked to breast cancer progression, is enriched on tumor-derived exosomes and correlates with metastatic potential.²⁸⁰ Rui et al developed an electrochemiluminescent aptamer sensor to quantify exosomal MUC1 across breast cancer subtypes, offering a sensitive tool for early detection and molecular monitoring.²⁸¹

Beyond diagnosis, exosomes serve as therapeutic carriers. Their lipid bilayer confers high biocompatibility, low immunogenicity, and favorable biodistribution, allowing efficient delivery of chemotherapeutics, proteins, and nucleic acids such as siRNA, circRNA, and mRNA.^{282,283} Compared with synthetic nanocarriers, exosomes exhibit superior stability and reduced off-target accumulation. Zheng et al highlighted their dual role in regulating breast cancer initiation, progression, metastasis, and treatment resistance, emphasizing their potential as both vehicles and therapeutic targets.²⁸⁴

Exosomes also modulate the tumor microenvironment (TME). Hypoxia-induced exosomes promote angiogenesis via SNHG1, while exosome-loaded siRNA against SNHG1 can reverse this effect. They enhance intracellular retention of chemotherapeutics and reduce drug efflux in resistant cells. Engineered exosomes are being explored for immunomodulation; Niu et al proposed exosomes carrying chimeric antigen receptors as a cell-free alternative to CAR-T therapy, potentially reducing cytokine toxicity and improving tumor infiltration.²⁸⁵

Despite these advantages, challenges remain, such as large-scale isolation, consistent purification, efficient cargo loading, and predictable pharmacokinetics. Continued refinement of exosome characterization and manufacturing technologies is essential for clinical translation. Their multifunctional roles as biomarkers and drug carriers position exosomes as promising components of next-generation breast cancer therapeutics. [Figure 4](#) illustrates emerging exosome-based targeted strategies.

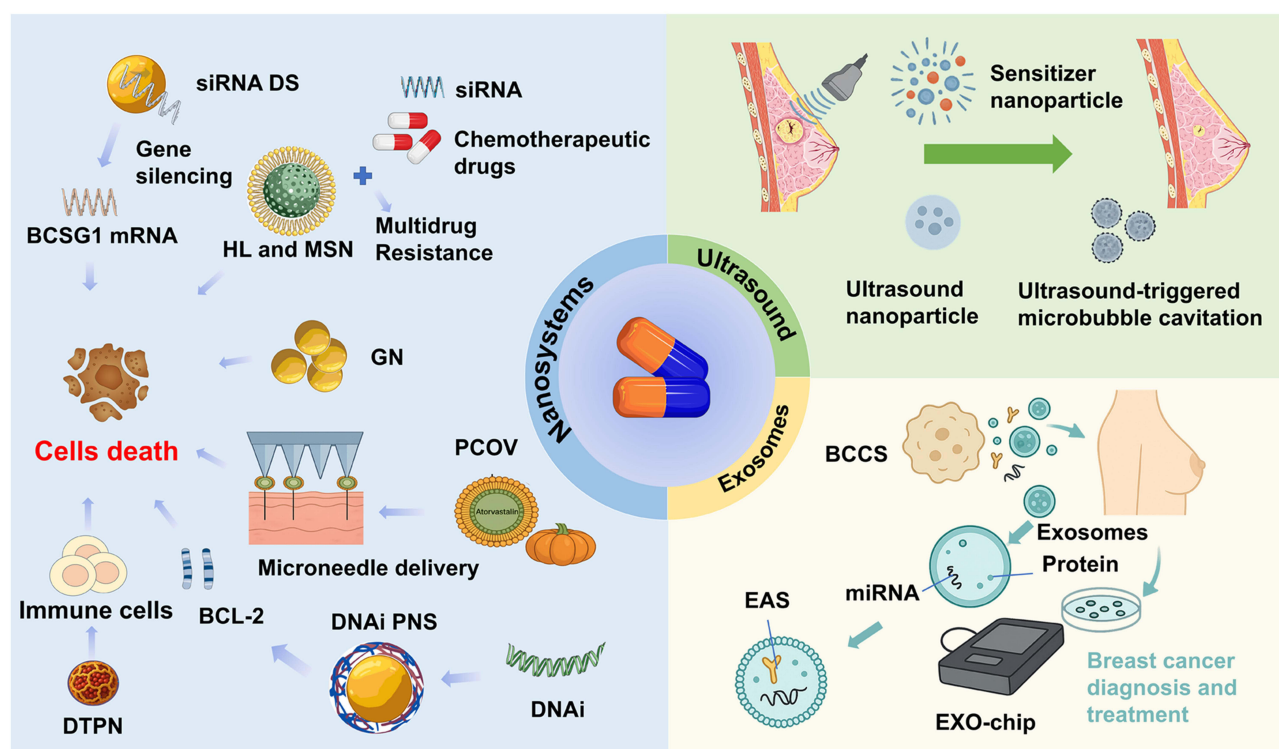


Figure 4 Schematic of emerging drug delivery platforms for breast cancer therapy. This schematic illustrates innovative strategies that enhance the precision, efficacy, and selectivity of anticancer interventions. **Nanosystems:** These include multifunctional nanoparticles that co-deliver siRNA and chemotherapeutics to overcome multidrug resistance, targeted nanoparticles such as HL, MSN, GN, and PCOV to induce selective cancer cell death, microneedle arrays enabling localized delivery of BCL-2 inhibitors and DNA interference agents, and DTPN that both elicit tumor cell apoptosis and activate antitumor immunity. **Ultrasound-assisted systems:** Techniques leveraging ultrasound-mediated microbubble cavitation enhance drug permeability and therapeutic penetration, while ultrasound-responsive nanoparticles facilitate spatiotemporal control of drug and gene delivery. **Exosome-based approaches:** Breast cancer cells secrete exosomes containing proteins and miRNAs that can serve as diagnostic biomarkers; these vesicles can be captured and analyzed via EAS or EXO chips, and engineered exosomes offer promising platforms for targeted therapeutic delivery. Collectively, these systems exemplify how advanced nanotechnology, acoustic modulation, and extracellular vesicle engineering converge to overcome biological barriers, maximize tumor-specific effects, and enable personalized breast cancer treatment.

Abbreviations: BCCS, Breast cancer cells; DTPN, Dual-targeted protein nanoparticles; EAS, Electrochemiluminescent aptamer sensor; HL, Hybrid liposomes; MSN, Mesoporous silica nanoparticles; PCOV, Pumpkin seed oil vesicles; siRNA DS, siRNA delivery systems; GN, Gold nanoparticles; DNAi PNS, DNAi peptide nanocomposites; BCL-2, B-cell lymphoma 2; DNAi, DNA interference.

Combined Treatment Strategies

Synergistic Effects of Autophagy Regulation and Targeted Therapy

Autophagy plays a context-dependent role in breast cancer, acting both as a tumor suppressor by removing damaged cellular components and as a survival mechanism that enables cancer cells to withstand metabolic and therapeutic stress.^{286,287} This duality positions autophagy as a pivotal regulator of treatment efficacy, and small-molecule modulators have shown promise. Liu et al identified LZ02/01, which suppresses breast cancer cell proliferation by impairing autophagic flux and promoting apoptosis, while You et al reported that St. John's Wort induces pro-death autophagy and apoptosis in TNBC, demonstrating dual-pathway potential.^{288,289}

Modulating autophagy can synergize with targeted therapies to overcome resistance. Paclitaxel resistance in TNBC is promoted by neddylation-activated TRIM25 driving TFEB-mediated autophagy, and inhibition of this pathway restores drug sensitivity.²⁹⁰ Autophagy also intersects with tumor immunoregulation: inhibition of glutamine metabolism elevates reactive oxygen species (ROS), inducing autophagy and enhancing antitumor immune responses, suggesting integration with immune checkpoint blockade may improve efficacy.²⁹¹ Nanotechnology offers additional avenues, as NIR-activated nanogenerators can trigger autophagy-related signaling while inducing immunogenic cell death, suppressing tumor growth and metastasis.²⁹² Epigenetic modulation further regulates autophagy-related pathways: Chidamide, a histone deacetylase inhibitor (HDACi), modulates BTG1 and FOXO1 and, in combination with androgen receptor (AR) antagonists, destabilizes AR signaling, enhancing therapeutic response in luminal androgen receptor (LAR)-type TNBC.²⁹³

Despite these advances, clinical translation faces challenges. Autophagy is highly context-dependent, and indiscriminate modulation may have pro-survival effects in tumors or normal tissues. Many findings derive from preclinical models that may not capture human breast cancer complexity, including metabolic plasticity and immune interactions. Agents often lack specificity and can affect parallel pathways, complicating toxicity and dosing, while predictive biomarkers remain limited.

Collectively, these findings underscore that strategic modulation of autophagy, either through inhibition or induction, can enhance the effectiveness of chemotherapy, immunotherapy, nanomedicine, and epigenetic therapies, providing a versatile framework for overcoming resistance and improving breast cancer treatment outcomes.

JAM-A/LAT1 Dual-Target Combination Therapy for Breast Cancer

Junctional adhesion molecule-A (JAM-A) is a core tight-junction protein whose expression and stability are closely linked to HER2 signaling in breast cancer.²⁹⁴ LAT1 (L-type amino acid transporter 1) mediates essential amino acid uptake, activates mTORC1, and promotes proliferation, invasion, and metastasis.²⁹⁵ Clinically, high LAT1 expression correlates with advanced stage, lymph node involvement, and poor response to trastuzumab in HER2+ metastatic patients, highlighting its role in resistance.²⁹⁶

Mounting evidence indicates a synergistic oncogenic relationship between JAM-A and LAT1. Co-expression associates with poor prognosis, especially in subtype B and HER2+ disease.^{296–298} Mechanistic studies show that JAM-A regulates mTORC1 signaling by controlling LAT1 expression, affecting protein synthesis and proliferation, particularly in estrogen-deprivation-resistant (EDR) breast cancer models.²⁹⁹ Proteomics analyses reveal that JAM-A forms a membrane complex with LAT1, enhancing amino acid uptake and tumor growth.²⁹⁸

Preclinical studies demonstrate therapeutic potential for dual targeting. JAM-A extracellular blockade reduces proliferation by >60%, and combining JAM-A inhibition with the LAT1 inhibitor JPH203 markedly enhances efficacy. In 4T1–BALB/c models, dual blockade reduced tumor volume by 72% compared with monotherapies.^{298,300,301} At the resistance level, JAM-A also stabilizes HER2/HER3, contributing to therapy resistance; combining JAM-A/LAT1 inhibition with HER2 downregulation reverses aromatase inhibitor resistance.

Dual-target intervention additionally modulates the tumor immune microenvironment. LAT1 inhibition reshapes amino-acid-dependent metabolic pathways in immune cells, enhancing PD-1 responsiveness, while JAM-A deletion reduces regulatory T-cell infiltration. In TNBC, combining the JAM-A antagonist peptide P4D with LAT1 silencing reduced lung metastasis by 89%, demonstrating strong synergy against metastatic spread.^{301–303}

Overall, JAM-A/LAT1 dual targeting holds promise for AI-resistant or trastuzumab-resistant subtype B/HER2+ breast cancer and high-tumor-mutation-burden TNBC, where junctional signaling and metabolic rewiring drive progression and immune evasion. However, translation challenges remain. Current evidence is largely preclinical, and co-dependence of JAM-A and LAT1 across heterogeneous human tumors is uncertain. Both proteins are physiologically essential, raising safety concerns. LAT1 expression varies across subtypes, and predictive biomarkers are lacking. Integrating dual targeting with endocrine therapy, HER2 blockade, or immunotherapy introduces further complexity in toxicity, sequencing, and cost. Early-phase clinical studies are needed to define therapeutic windows, long-term safety, and feasibility.

Cutting-Edge Research Directions

Multi-Target Prediction Model

Multi-target prediction models in breast cancer are designed to simultaneously forecast multiple biomarkers or clinical outcomes, integrating conventional clinical factors with advanced machine learning and multi-omics data. Compared with single-target models, these frameworks leverage diverse inputs, including pathological slides and multi-modal imaging, for a more comprehensive disease assessment. Models based on multi-modal imaging have been shown to outperform unimodal approaches.³⁰⁴ For instance, Song et al developed a multiparametric ultrasound radiomics model capable of predicting postoperative recurrence risk and molecular subtypes, providing non-invasive guidance for diagnosis and therapeutic planning.³⁰⁵

In surgical risk prediction, the Breast Cancer Surgery Risk Calculator (BCSRc) uses patient-specific factors from the NSQIP database to estimate postoperative complication probabilities, aiding preoperative risk stratification and clinical decision-making.³⁰⁶ At the molecular level, multi-target frameworks can integrate cellular and pathway-level mechanisms to identify therapeutic targets and combination strategies. Qayoom et al analyzed molecular interactions affected by Bruginin using TCGA, STRING, and AutoDock Vina, establishing a basis for predictive modeling that links molecular networks with drug-target relationships.³⁰⁷

From a technical perspective, machine learning algorithms such as random forests and naive Bayes, along with deep learning approaches like convolutional neural networks (CNNs), are commonly employed. DeepProg, proposed by Poirion et al, combines deep learning with machine learning to integrate multi-omics data and achieve robust prognostic modeling in breast cancer datasets.³⁰⁸ Additionally, Jain et al applied multivariable logistic regression and predictive margin models to identify sociodemographic predictors of treatment delays exceeding 90 days in young female patients, emphasizing the need to incorporate social determinants into predictive frameworks.³⁰⁹

Despite their promise, multi-target models face challenges for clinical translation. Most rely on retrospective datasets with limited annotation, introducing selection bias and reducing generalizability. Multi-omics integration adds complexity due to batch effects, variable data resolution, and inconsistent preprocessing. Deep learning-based models offer strong predictive performance but limited interpretability, which impedes clinical adoption and regulatory approval. Data privacy concerns, lack of cross-institutional standardization, and resource-intensive prospective validation further restrict implementation. Future advances will require harmonized data-sharing, rigorous external validation, and interpretable AI architectures that can be integrated seamlessly into clinical workflows.

miRNA Regulatory Network

In breast cancer, miRNA regulatory networks critically influence tumor progression, invasion, metastasis, and drug resistance. The EGFR-driven cell cycle pathway is central to proliferation and pathogenesis. Uhlmann et al integrated large-scale miRNA screening with proteomics to identify three novel tumor-suppressor miRNAs, miR-124, miR-147, and miR-193a-3p, which collectively target proteins in the EGFR-driven cell cycle network and demonstrate the broad regulatory impact of miRNAs on proliferation.³¹⁰

Regarding chemotherapy resistance, MDR refers to the phenomenon whereby cancer cells develop cross-resistance to multiple chemotherapeutic agents with distinct structures and mechanisms. Zhang's team showed that β -limonene reverses resistance to doxorubicin and docetaxel by regulating MDR-associated miRNAs, affecting targets such as PTEN and P-glycoprotein.³¹¹ In diagnosis and subtype classification, deep sequencing has revealed subtype-specific miRNA dysregulation. Chang et al identified 25 miRNA biomarkers distinguishing TNBC from normal tissue, while Xu et al constructed miRNA–TF–mRNA regulatory networks to classify subtypes and guide personalized therapy.^{312,313}

In prognosis, Lirussi et al reported a Let-7–SMUG1 network, with specific miRNA–mRNA interactions correlating with favorable outcomes in ER+ breast cancer.³¹⁴ Zhang et al built a lncRNA–miRNA–mRNA interaction network identifying miR-510 as a central node, and Sarkar et al applied feature selection with survival analysis to pinpoint core miRNAs associated with subtypes and prognosis.^{315,316}

Despite these advances, clinical translation is limited by context-dependent miRNA expression, intra-tumor heterogeneity, reliance on computational predictions, and challenges in therapeutic delivery due to off-target effects and pleiotropy.³¹⁷ Furthermore, the lack of standardized pipelines for miRNA detection, normalization, and network construction complicates reproducibility across studies. These limitations underscore the need for integrative multi-layer validation strategies and improved delivery platforms before miRNA-directed therapies can reach clinical applicability.

Overall, miRNAs exert multi-layered control over breast cancer initiation, progression, drug resistance, and prognosis. Integrating bioinformatics and machine learning enhances mechanistic insights and supports the development of novel miRNA-directed therapeutic strategies.

Conclusion and Prospect

Breast cancer therapeutics are converging toward a treatment paradigm in which established targeted strategies remain foundational, yet their long-term effectiveness increasingly depends on overcoming the biological constraints that limit durable responses. Endocrine therapy, HER2-directed agents, and inhibitors of CDK4/6 and PARP have produced substantial survival gains, but their efficacy is frequently compromised by tumor heterogeneity, metabolic and immune suppression within the microenvironment, and the emergence of adaptive resistance. As this review highlights, these challenges underscore an urgent need for therapeutic concepts that extend beyond single-pathway inhibition toward integrated approaches capable of modifying the tumor ecosystem as a whole.

Recent advances outline several promising directions. Metabolic targeting, regulation of cancer stem cells, and modulation of autophagy offer new routes to address refractory disease, while emerging molecular axes such as WBP2, Trop2 and the JAM A–LAT1 pathway provide additional leverage to disrupt resistance networks. Progress in drug delivery science, including nanocarriers, ultrasound-responsive formulations and engineered exosomes, further suggests that enhancing intratumoral access may be as crucial as improving intrinsic drug potency. Ultrasound-assisted nanobubbles exemplify this shift by enabling spatial and temporal control of drug release, although their translation will require rigorous validation of long-term safety, scalable production and biomarker-driven patient selection.

Taken together, the evidence reviewed in this work points toward a future in which effective breast cancer treatment relies on the coordinated use of multi omic profiling, imaging-based monitoring and artificial intelligence to align therapeutic decisions with the evolving biology of each tumor. Such convergence is expected to yield treatment strategies that are more precise, more resilient to resistance and ultimately more compatible with the complex architecture of breast cancer.

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Disclosure

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