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REVIEW

Advanced targeted therapeutic strategies in metastatic breast cancer: from molecular drivers to clinical impact

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Metastatic breast cancer (MBC) remains a key health problem and still causes most breast cancer deaths around the world, even after big gains in treatment. The varied biology of breast cancer has made clear how limited traditional chemo is and has sped up the move toward specific, tailored treatments. Today, treating MBC depends more than ever on understanding its molecular makeup to find key targets and weak points, such as estrogen receptor (ER) activity, human epidermal growth factor receptor 2 (HER2) levels, mammalian target of rapamycin (mTOR) pathway issues, DNA repair problems, and tumor markers. In recent times, the range of options for MBC has grown quickly with the addition of new types of drugs like selective estrogen receptor degraders (SERDs), cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, and PI3K/AKT/mTOR blockers, which have shown better results in slowing disease and, in certain groups, improving overall survival (OS). The new class of antibody drug conjugates (ADCs) has been especially important, as they let doctors send very strong drugs straight to cancer cells, which has worked well in HER2-positive, low-HER2, and triple-negative types of MBC. Other recent advancements include PARP inhibitors for BRCA-related cancers, tropomyosin receptor kinase (TRK) inhibitors for rare cancer-causing gene fusions, and immune-based methods such as checkpoint drugs, bispecific antibodies, and well-planned drug combos. Even with these gains, controlling the disease for a long time is still hard because of natural and learned resistance, side effects from treatment, how some drugs do not enter the brain well, and the ongoing lack of good choices for aggressive forms like triple-negative breast cancer. This short summary covers how advanced targeted medicines work at the molecular level in MBC, highlights key new findings and ongoing studies from 2023 to 2025, gives a brief view of selected patents, and shares real-world example cases to show the true effect of these advances. Finally, it discusses how resistance is forming and future directions for making treatment even better using molecular data.

Keywords: metastatic breast cancer, targeted therapy, antibody–drug conjugate, CDK4/6 inhibitors, SERD, PIK3CA, clinical trials

Introduction

Breast cancer is a disease with many different types, and each one behaves and reacts to treatment in its own way. New treatments use the molecular markers of each tumor, like estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) positivity, PIK3CA and BRCA mutations, neurotrophic tyrosine receptor kinase (NTRK) gene fusions,

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and other changes that can be targeted, as well as tumor weaknesses like DNA repair problems or the presence of specific antigens. Targeted drugs have saved many lives in metastatic breast cancer (MBC). But many problems are still here, like resistance to treatments, brain metastases, side effects of drugs, and no good options for triple negative breast cancer. This paper looks at new advanced targeted treatments, lists the latest trials and patents from 2023 to 2025, and uses real cases to show how they help people live better (1–3).

Types of Action and Examples of Drugs

Figure 1 illustrates key oncogenic signaling pathways activated at the cell membrane and how they are pharmacologically targeted by modern precision anticancer therapies. It integrates receptor-level targets, intracellular signaling cascades, metabolic rewiring, and DNA damage repair vulnerabilities.

At the cell membrane, several receptor tyrosine kinases (RTKs) are shown as primary therapeutic targets:

1. FGFR2 (targeted by pemigatinib, infigratinib, futibatinib, erdafitinib, etc.)
2. HER2 (lapatinib, trastuzumab, pertuzumab, neratinib)
3. EGFR (erlotinib, afatinib, cetuximab, panitumumab)
4. VEGFR (vandetanib, cediranib, ramucirumab, lenvatinib)
5. ROS/NTRK signaling (entrectinib)

Activation of these receptors drives major downstream oncogenic pathways:

1. PI3K–AKT–mTOR pathway: This pathway regulates cell growth, metabolism, and survival. Aberrant activation promotes tumor proliferation and resistance to therapy.
    (a) Everolimus inhibits mTORC1, suppressing growth signaling.
2. RAS–RAF–MEK–ERK (MAPK) pathway: A central driver of tumor cell proliferation and differentiation.
    (a) RAF inhibitors (dabrafenib, regorafenib)
    (b) MEK inhibitors (selumetinib, trametinib) block signal propagation.

The diagram also highlights mitochondrial and metabolic reprogramming:

1. IDH1 and IDH2 mutations alter the citric acid cycle, producing the oncometabolite D-2-hydroxyglutarate (D-2HG).
2. Ivosidenib (IDH1) and enasidenib (IDH2) specifically inhibit these mutant enzymes, restoring normal metabolism.

In the nuclear compartment, defects in DNA damage repair (DDR)—including BAP1 mutations—create vulnerabilities exploited by PARP inhibitors such as niraparib and rucaparib, which induce synthetic lethality.

Hormone receptor drugs (ER+ cases)

Endocrine therapy is still the main type for HR+ MBC; recent focused drugs include pills called selective estrogen receptor degraders (SERDs), new selective estrogen receptor modulators (SERMs)/SERDs, and combos with cyclin-dependent kinase 4/6 (CDK4/6) (4, 5) or PI3K inhibitors. New pills like elacestrant and other investigational drugs are being made to fight ER mutations. Triple drug mixes (PI3K + CDK4/6 + fulvestrant) have shown good survival signals in certain HR+ cases with PIK3CA mutations (6, 7).

Cell-cycle targets (CDK4/6)

Palbociclib, ribociclib, and abemaciclib are still the main drugs with hormone therapy. These prevent cancer growth and can extend the time before progression and sometimes overall survival (OS); research continues to see how best to add new drugs or use earlier ones (like with the PATINA trial and others) (8, 9).

Pathway blockers (PI3K/AKT/mTOR)

In some cases, blocking the PIK3CA mutation can help. Drugs like alpelisib and protein kinase B (AKT)/mTOR blockers can benefit certain mutation-carrying patients, but side effects limit their use; newer, more selective, or combo drugs are being tested. Recent triple treatments (like inavolisib + palbociclib + fulvestrant) have shown promising survival advantages in PIK3CA mutants (6, 7, 10–12).

BRCA-targeted drugs (BRCA)

Olaparib and talazoparib are single-ring AER inhibitors that take down tumors with flaws in the main homologous recomb DNA repair job. They cause tumors to die where they have a flaw in breast cancer susceptibility gene ½ (BRCA1/2) jobs. They block the PARP job that fixes single DNA strand breaks. This makes the tumors fall apart when there are two breaks in the DNA that the cancer cell can't fix because the BRCA isn't working. These drugs have been tested in patients with a BRCA flaw and shown to help them live longer without the disease showing up. They also make the patients feel

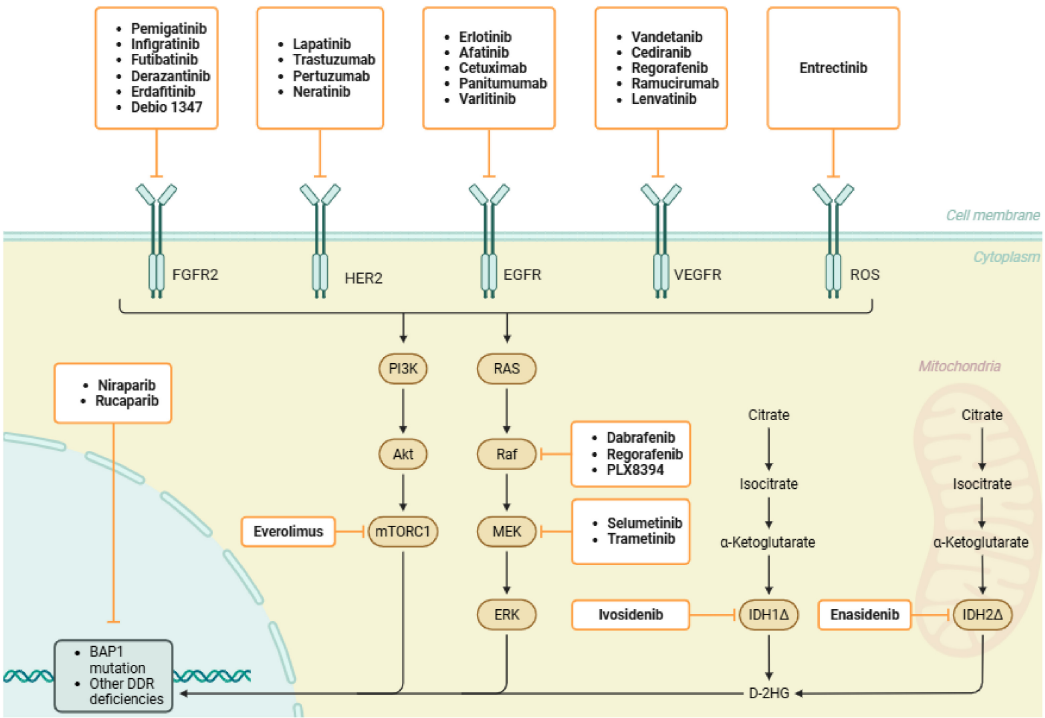

FIGURE 1 | Key oncogenic signaling pathways.

better without many bad effects. These drugs work well on the classic BRCA1/2 flaws, but we are also trying to find other flaws that work just as good as BRCA1/2. We are also testing these drugs with other drugs that block the immune system's stop signs, other drugs that aim at a specific cancer target, or drugs that cause DNA damage. These new ways may help stop tumors that are drug resistant or help more patients benefit from these drugs in a wider group of MBC (13, 14).

Special drugs with antibodies and ADCs

Antibody drug conjugates (ADCs) are a big leap forward for help in cancer of the breast that has spread, a form of treatment that links the precision of common and targeted medicines with the strength of chemo. These new drugs like trastuzumab emtansine T-DM1, trastuzumab deruxtecan, and sacituzumab govitecan are made to send a very strong drug to only the cancer cells that have the right markers on their surface, such as HER2 and Trop 2 (15). The precision of these drugs means they can kill the cancer cells very well while doing less harm to the rest of the body. ADCs have changed how we treat MBC that is HER2 positive and have given new hope to patients with HER2 low and triple negative forms of the disease. These drugs work very well even for patients who have been treated with many drugs before and for those who have stopped responding to chemo, showing they can beat treatment resistance. But these drugs also have different side effects that must be watched closely, including blood problems, stomach issues, and for trastuzumab deruxtecan, a higher chance of lung problems like pneumonitis. Catching and fixing these problems fast is key to giving the best treatment and keeping patients safe (16–21).

Targeted small drugs (NTRK, HER2, etc.)

Tumor-agnostic drugs like the tropomyosin receptor kinase (TRK) inhibitors larotrectinib and entrectinib have shown great and lasting effects on patients with rare NTRK fusion-positive breast cancers, which shows why we should run tests for all genes, even in unusual mutations. At the same time, HER2 treatments are progressing past the simple HER2 overexpression stage, with new tyrosine kinase inhibitors and next-generation antibodydrug combos showing strong effects on HER2 mutant and HER2 low breast cancers in the metastatic form, making targeted drugs available to more people (22, 23).

Immunotherapy and mix-and-match strategies

Drugs blocking the immune system (pembrolizumab, atezolizumab) help in some TNBC cases, especially if the immune system marker programmed death-ligand 1 (PD-L1) is high, combined with chemo. Combining these immune drugs with others (like ADCs or pathway drugs) is being studied to help immune-lacking cases react better to treatment. Ongoing/selected clinical trials (2023–2025)—(**Table 1**).

TABLE 1 | Below are representative, actively recruiting, or recently reported trials that exemplify modern targeted approaches.

Trial (NCT/name)	Population	Intervention (target)	Key objective/status
NCT05927779 (TFX06) (https://clinicaltrials.gov/study/NCT05927779)	Advanced breast cancer	TFX06 (small-molecule agent)	**Phase I/II safety, maximum tolerated dose (MTD), preliminary efficacy.**
NCT05374915 (https://clinicaltrials.gov/study/NCT05374915)	Cutaneous metastatic breast cancer (MBC)	REM-001 photodynamic therapy	**Efficacy/safety in cutaneous metastases.**
NCT02947685 (PATINA) (https://clinicaltrials.gov/study/NCT02947685)	HR+/HER2− MBC	Palbociclib ± HER2-targeted combinations	**Assessment of palbociclib in specific settings.**
NCT06383767 (ESG401) (https://clinicaltrials.gov/study/NCT06383767)	HR+/HER2− unresectable/metastatic	ESG401 (novel agent)	**Phase III evaluation.**
Multiple ASCO/NEJM trials (e.g., inavolisib+palbociclib+fulvestrant) (https://www.theguardian.com/society/2025/may/31/breakthrough-breast-cancer-therapy-can-slow-advance-of-disease-and-prolong-survival)	PIK3CA-mutant HR+ MBC	PI3K + CDK4/6 + endocrine	**Demonstrated OS benefit in 2024/25 presentations/publications.**

Recent patents and intellectual-property trends (selected examples)

Patent filings emphasize (1) new small-molecule SERDs and ER modulators, (2) ADC linker/cytotoxin optimization and new antigen targets, and (3) combinatorial claims pairing targeted agents with immunotherapy or gene therapies (**Table 2**).

Selected case studies illustrating targeted therapy impact

Case A — Dramatic response to sacituzumab govitecan in metastatic triple-negative MBC

A published case reported a complete response in a heavily pretreated patient with metastatic metaplastic (TNBC phenotype) breast cancer after sacituzumab govitecan, illustrating ADCs' capacity to overcome chemotherapy resistance in Trop-2 expressing tumors. This underscores the value of tumor profiling and ADCs in refractory metastatic settings (24).

Case B — NTRK fusion-positive metastatic breast cancer treated with larotrectinib

A case of NTRK3 fusion–positive metastatic secretory carcinoma showed substantial clinical benefit with larotrectinib, supporting tumor-agnostic targeting for rare driver alterations in MBC. Such cases validate broad genomic testing even in breast tumors with unusual histology (25).

Case C — Long-term benefit with T-DM1 biosimilar in HER2+ multisite metastases

Reports of durable disease control using T-DM1 biosimilars in recurrent HER2+ disease demonstrate biosimilars' potential to expand access while maintaining efficacy but emphasize careful long-term monitoring (3).

Resistance mechanisms and biomarkers

Common barriers include ESR1 mutations, which cause ER therapy failure, and activation of alternative PI3K/AKT pathways, which bypass suppression; in addition, loss of RB1 or amplification of cyclin E leads to resistance to CDK4/6 inhibition, while increased activity of efflux mechanisms and ADC payloads cause drug resistance, and immune escape may hinder checkpoint inhibitor success. Liquid biopsy (ctDNA) is now regularly used to monitor mutation changes over time, such as PIK3CA or ESR1, and new imaging and immune profiling tools are being adopted to help tailor treatments and select drug combinations more precisely. The reports from ASCO/NEJM on triple therapy used ctDNA to detect PIK3CA mutations for patient inclusion, underscoring the key role of molecular markers (26).

Safety, toxicities, and real-world considerations

Targeted agents improve efficacy but have class-specific toxicities: PI3K inhibitors (hyperglycemia, rash), CDK4/6 inhibitors (neutropenia, diarrhea for abemaciclib), ADCs (interstitial lung disease with some HER2-ADCs, severe neutropenia), and PARP inhibitors (hematologic toxicity). Real-world use requires patient selection, monitoring, dose

TABLE 2 | Patent activity highlights both formulation innovations and new combination claims.

Patent/publication	Focus	Relevance
US20180098963A1 (lasofoxifene) (https://patents.google.com/patent/US20180098963A1/en)	Lasofoxifene for estrogen receptor (ER)+ cancers/ESR1 mutation contexts.	Selective estrogen receptor degraders (SERD)/selective estrogen receptor modulators (SERM)-class strategy to delay endocrine resistance.
US10689457B2 (https://patents.google.com/patent/US10689457B2/en)	Human epidermal growth factor receptor 2 (HER2)-targeted combination regimens for metastatic HER2+ disease.	Protection for combination regimens and dosing claims.
USPTO grants (e.g., (Z)-endoxifen formulations) Apr 2025 (https://medcitynews.com/2025/05/latest-patent-news-in-womens-health/)	Novel oral endocrine modulators/formulations.	Emerging small molecules focused on ER modulation.
Patents on SEMA4D blockade & DC1 combos (https://pubchem.ncbi.nlm.nih.gov/patent/US-12201719-B2)	Immunomodulatory + targeted combos.	Reflects trend toward combining immune modulation with targeted therapy.

modifications, and multidisciplinary care. Cost and access remain barriers globally (4, 5, 27–30).

Future directions

Key priorities: (1) rational combinations to overcome resistance (e.g., PI3K + CDK4/6 + SERD triple regimens), (2) ADCs with novel antigens/payloads and improved therapeutic indices, (3) tumor-agnostic approaches for rare drivers, (4) integrating immunotherapy with targeted agents to sensitize tumors, (5) expanding genomic and ctDNA-guided adaptive trials (31), and (6) central nervous system (CNS)-penetrant targeted drugs for brain metastases. Patent and trial activity reflect these priorities (32).

Conclusion

Targeted treatments have greatly changed how we treat MBC; choosing the right one (molecular test), flexible treatment plans, and combination approaches now help improve results in certain groups. Still, drug resistance, side effects, access issues, and the need for drugs that work in the brain are key challenges. Many ongoing studies and new patents mean new ideas come fast, often in combinations and with a focus on biomarkers. Doctors should do broad genetic tests and think about putting suitable patients into clinical trials.

List of Abbreviations

MBC: metastatic breast cancer; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; HR+: hormone receptor–positive; TNBC: triple-negative breast cancer; P13K: phosphatidylinositol 3-kinase; AKT: protein kinase B; mTOR: mammalian target of rapamycin; CDK4/6: cyclin-dependent kinase 4/6; SERDs: selective estrogen receptor degraders; SERMs: selective estrogen receptor modulators; ADCs: antibody–drug conjugates; PARP: poly(ADP-ribose) polymerase; BRCA1/2: breast cancer susceptibility gene 1/2; NTRK: neurotrophic tyrosine receptor kinase; TRK: tropomyosin receptor kinase; PD-L1: programmed death-ligand 1; ctDNA: circulating tumor DNA; PFS: progression-free survival; OS: overall survival; MTD: maximum tolerated dose; CNS: central nervous system.

Author Contributions

Conceptualization, literature search, manuscript drafting, and final approval were performed by the author.

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