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TARGETED THERAPIES AS A CORNERSTONE OF PERSONALIZED MEDICINE IN BREAST CANCER: ADVANCES, CHALLENGES, AND FUTURE DIRECTIONS

Biotechnology

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ABSTRACT

Breast cancer represents a complex and diverse group of diseases shaped by genetic, molecular, and hormonal influences. The rise of personalized medicine has shifted treatment toward approaches designed for the specific biology of each tumor. Important therapeutic advances include the use of HER2-targeted drugs, hormone receptor therapies, CDK4/6 inhibitors, PARP inhibitors, and antibody–drug conjugates, which are now applied to different breast cancer subtypes. Progress in technologies such as next-generation sequencing, companion diagnostics, and liquid biopsy has allowed detection of clinically relevant mutations and real-time evaluation of treatment response. These innovations have improved survival in many patients. Despite this progress, key barriers remain, including tumor variability, resistance to therapy, and limited access to molecular testing in resource-constrained settings. This review discusses the benefits and limitations of available targeted therapies, emphasizes the value of diagnostic tools in guiding treatment choices, and outlines future directions focused on broader accessibility, integration of novel biomarkers, and the development of next-generation therapeutic options to enhance care worldwide.

KEYWORDS

Breast Cancer, Targeted Therapies, Personalized Medicine, HER2, Precision Oncology

INTRODUCTION

The emergence of personalized medicine has revolutionized oncology by replacing conventional uniform treatments with approaches tailored to an individual's molecular and genetic tumor profile [14,15]. Breast cancer, one of the most prevalent malignancies globally, with an estimated 2.3 million new cases and 685,000 deaths annually (Table 1) [GLOBOCAN 2020], is no longer considered a single entity.

Molecular characterization plays a central role in stratifying breast cancer into clinically relevant groups [14,15]. Traditionally, this classification relies on evaluating the presence or absence of estrogen and progesterone hormone receptors, along with the overexpression or amplification of the human epidermal growth factor receptor 2 (HER2) [2,3]. Using these biomarkers, breast cancer is broadly divided into three major categories: hormone receptor–positive (HR+), HER2-enriched, and triple-negative breast cancer (TNBC). HR+ tumors are usually responsive to endocrine therapies [4–6], HER2-driven cancers benefit from HER2-targeted regimens [2,3], while TNBC—defined by the lack of all three markers—represents the most aggressive and therapeutically challenging subtype [11,18].

Despite these advances, key barriers persist. Intratumoral heterogeneity [13], acquired drug resistance [9,10], and inequitable access to molecular diagnostics—particularly in low- and middle-income countries—continue to limit the broad application of personalized oncology. This review aims to summarize current targeted treatment strategies in breast cancer, highlight the diagnostic innovations that support them, and discuss the ongoing challenges and opportunities in translating precision medicine into improved patient outcomes.

Table 1. Breast Cancer Burden and Subtype Classification: A Global Overview

Parameter	Data (Approx.)	Source
Annual new cases (worldwide)	2.3 million	GLOBOCAN 2020
Annual deaths (worldwide)	685,000	GLOBOCAN 2020
Most common cancer in women	Yes (11.7% of all new cases)	GLOBOCAN 2020
Major subtypes	HR+ (~70%), HER2+ (~15–20%), TNBC (~10–15%)	Cancer Research UK, NCI
Peak incidence age	45–65 years	WHO / IARC

2. Key Targeted Therapies and Their Personalization

A. HER2-Targeted Therapies in Breast Cancer

HER2-positive breast cancer (15–20% of cases) is identified by HER2 overexpression or ERBB2 gene amplification, confirmed through IHC or FISH [2,3]. Trastuzumab remains the backbone of therapy [3], with enhanced efficacy when combined with pertuzumab and taxane-based chemotherapy [2]. Small-molecule TKIs such as lapatinib, neratinib, and tucatinib provide further options, particularly in resistant or metastatic settings [2,3]. Antibody–drug conjugates (T-DM1, T-DXd) deliver potent cytotoxic activity, the latter effective even in HER2-low tumors [1].

B. Endocrine Therapy and CDK4/6 Inhibition in HR+ Breast Cancer

Hormone receptor–positive (HR+) breast cancer accounts for nearly 70% of cases [14,15]. Standard endocrine agents include SERMs (tamoxifen), aromatase inhibitors, and SERDs [4–6]. Resistance, particularly in metastatic disease, is frequently linked to ESR1 mutations—detectable by liquid biopsy [13]. The integration of CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) has transformed management, as these agents, when combined with endocrine therapy, substantially improve progression-free and overall survival [4–6,16,17].

C. PARP Inhibitors in BRCA-Mutated Breast Cancer

PARP inhibitors have become pivotal in BRCA1/2-mutated breast cancers by exploiting synthetic lethality [9,10]. Clinical trials (OlympiAD, EMBRACA) confirmed improved progression-free survival compared to chemotherapy [9,10]. Resistance, however, limits long-term efficacy and may arise from secondary BRCA reversion mutations, alternative repair pathway activation, or altered drug efflux [9,10]. Presently, clinical benefit is largely confined to germline BRCA-mutated, HER2-negative disease [9,10].

D. PI3K/AKT/mTOR Pathway in Breast Cancer

The PI3K/AKT/mTOR pathway plays a key role in regulating how breast cancer cells grow, adapt, and resist therapy. Among HR-positive, HER2-negative tumors, PIK3CA mutations are particularly frequent, making this signaling cascade a therapeutic focus. Alpelisib, a PI3K-α–specific inhibitor, combined with fulvestrant, demonstrated improved outcomes in the SOLAR-1 trial [7]. Everolimus, targeting mTOR, has also been useful in endocrine-resistant settings when paired with exemestane, supported by data from the BOLERO-2 trial [8]. Current research is moving toward dual PI3K/mTOR inhibitors, isoform-selective compounds, and rational combinations with CDK4/6 inhibitors or immunotherapy [7,8].

E. Antibody–Drug Conjugates (ADCs) in TNBC and HER2-Low Breast Cancer

Triple-negative breast cancer (TNBC) is among the most aggressive subtypes because it lacks both hormone receptors and HER2 expression, leaving limited targeted therapies [11,18]. Antibody–drug conjugates (ADCs) have introduced a new strategy by coupling

monoclonal antibodies with cytotoxic payloads, allowing tumor-specific delivery. Sacituzumab govitecan, directed at Trop-2, significantly improved survival in metastatic TNBC in the ASCENT trial [11]. The identification of "HER2-low" tumors (IHC 1+ or 2+/ISH–), previously considered HER2-negative, has expanded the reach of targeted therapy. In this group, trastuzumab deruxtecan (T-DXd) demonstrated strong clinical benefit in the DESTINY-Breast04 study [1].

4. Tools Supporting Personalization

Modern molecular diagnostics have reshaped breast cancer care by uncovering tumor-specific vulnerabilities. Next-generation sequencing (NGS) allows broad genomic profiling, highlighting clinically relevant alterations such as BRCA1/2, PIK3CA, and ESR1, which guide the use of targeted drugs [13]. Liquid biopsy, through the detection of circulating tumor DNA (ctDNA), provides a non-invasive tool to track tumor dynamics, therapeutic benefit, and resistance evolution [13]. In addition, validated companion diagnostics—including assays like Oncotype DX and Foundation One CDx—aid in predicting therapeutic benefit, ensuring patients receive the most appropriate interventions while avoiding ineffective options [12].

5. Barriers to Personalized Targeted Therapy

Despite substantial progress, several hurdles restrict the full realization of precision medicine in breast cancer. Resistance to targeted therapies frequently emerges through secondary mutations, compensatory signaling networks, or phenotypic adaptations [9,10,13]. Both inter- and intra-tumoral heterogeneity further complicate treatment selection and contribute to variable responses [13]. Economic limitations also remain pressing, as the high costs of molecular testing and novel targeted drugs restrict availability, especially in resource-limited settings [13].

6. Emerging Directions

Future personalization in breast cancer is expected to integrate advanced technologies with innovative trial methodologies. Artificial intelligence (AI) and machine learning are being applied to combine genomic, imaging, and clinical datasets to predict therapeutic outcomes more accurately [13]. Multi-omics platforms—encompassing genomic, transcriptomic, proteomic, and metabolomic data—are refining the understanding of tumor biology and uncovering new therapeutic opportunities [14,15]. Novel clinical trial designs, such as basket and umbrella models, are accelerating the testing of drugs across biomarker-driven patient subsets [13].

7. CONCLUSION

The management of breast cancer has shifted dramatically with the rise of personalized therapy, where treatments are guided by the unique molecular profile of each patient's tumor. Targeted strategies—such as HER2-directed drugs [2,3], CDK4/6 inhibitors [4–6,16,17], PARP inhibitors [9,10], PI3K/mTOR blockers [7,8], and antibody–drug conjugates [1,11]—have already improved survival across different subtypes, including HR-positive, HER2-positive, triple-negative, HER2-low, and BRCA-mutated cancers. Modern tools like next-generation sequencing and liquid biopsies are enhancing treatment decisions by allowing real-time monitoring of tumor changes [13]. Still, major obstacles remain, including therapy resistance [9,10,13], tumor diversity [13], and unequal access to advanced diagnostics. Moving forward, greater emphasis on refining biomarkers [12–15], widening the reach of genomic testing, and integrating innovations like artificial intelligence and multi-omics technologies [13–15] will be essential to make precision oncology both effective and accessible worldwide.

REFERENCES

1. Modi S, Park H, Murthy RK, Iwata H, Tamura K, Tsurutani J, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med. 2022;387(12):9–18.
2. Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2012;366(2):109–19.
3. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer. N Engl J Med. 2001;344(11):783–92.
4. Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, et al. Palbociclib in hormone-receptor–positive advanced breast cancer. N Engl J Med. 2015;373(3):209–19.
5. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive advanced breast cancer. N Engl J Med. 2016;375(18):1738–48.
6. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 2: Abemaciclib plus fulvestrant in HR+/HER2– advanced breast cancer. J Clin Oncol. 2017;35(28):2875–84.
7. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. N Engl J Med. 2019;380(20):1929–40.
8. Hortobagyi GN, Piccart M, Rugo HS, Burris HA, Campone M, Noguchi S, et al. Everolimus plus exemestane for HR-positive breast cancer (BOLERO-2). J Clin Oncol. 2012;30(31):3194–201.
9. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation (OlympiAD). N Engl J Med. 2017;377(6):523–33.
10. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gnant M, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation (EMBRACA). N Engl J Med. 2018;379(8):753–63.
11. Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer (ASCENT). N Engl J Med. 2021;384(16):1529–41.
12. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Oncotype DX recurrence score and benefit of chemotherapy in early-stage breast cancer. N Engl J Med. 2015;373(21):2005–14.
13. Yates LR, Gerstung M, Knappskog S, Desmedt C, Gundem G, Van Loo P, et al. Subclonal diversification of primary breast cancer revealed by multiregion sequencing. Nature. 2015;518(7539):422–6.
14. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747–52.
15. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98(19):10869–74.
16. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for hormone-receptor-positive, HER2-negative metastatic breast cancer (PALOMA-3): a double-blind, phase 3 trial. Lancet Oncol. 2016;17(4):425–39.
17. Turner NC, Slamon DJ, Ro J, Bondarenko I, Im SA, Masuda N, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer (PALOMA-3). N Engl J Med. 2018;379(20):1926–36.
18. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379(22):2108–21.