Cancer Biol Med 2025. doi: 10.20892/j.issn.2095-3941.2024.0510

REVIEW

The treatment of breast cancer in the era of precision medicine

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ABSTRACT The management of breast cancer, one of the most common and heterogeneous malignancies, has transformed with the advent of precision medicine. This review explores current developments in genetic profiling, molecular diagnostics, and targeted therapies that have revolutionized breast cancer treatment. Key innovations, such as cyclin-dependent kinases 4/6 (CDK4/6) inhibitors, antibody-drug conjugates (ADCs), and immune checkpoint inhibitors (ICIs), have improved outcomes for hormone receptor-positive (HR+), HER2-positive (HER2+), and triple-negative breast cancer (TNBC) subtypes remarkably. Additionally, emerging treatments, such as PI3K inhibitors, poly (ADP-ribose) polymerase (PARP) inhibitors, and mRNA-based therapies, offer new avenues for targeting specific genetic mutations and improving treatment response, particularly in difficult-to-treat breast cancer subtypes. The integration of liquid biopsy technologies provides a non-invasive approach for real-time monitoring of tumor evolution and treatment response, thus enabling dynamic adjustments to therapy. Molecular imaging and artificial intelligence (AI) are increasingly crucial in enhancing diagnostic precision, personalizing treatment plans, and predicting therapeutic outcomes. As precision medicine continues to evolve, it has the potential to significantly improve survival rates, decrease recurrence, and enhance quality of life for patients with breast cancer. By combining cutting-edge diagnostics, personalized therapies, and emerging treatments, precision medicine can transform breast cancer care by offering more effective, individualized, and less invasive treatment options.

KEYWORDS Breast cancer; precision medicine; diagnostic precision; personalized therapy

Introduction

Breast cancer is among the most prevalent and biologically diverse malignancies globally, and accounts for a substantial portion of cancer diagnoses and deaths among women[1]. Despite decades of research and advancements in screening and treatment, breast cancer remains a leading cause of cancer-related mortality in women[1]. The disease is characterized by its heterogeneity, including various subtypes with differing tumor biology, prognosis, and response to treatment. In 2000, Perou et al.[2] introduced molecular subtyping, classifying breast cancer into luminal-like, HER2-enriched, basal-like, and normal-like types. This landmark discovery facilitated the development of subtype-specific therapies, such as endocrine therapy (ET) for luminal-like tumors and anti-HER2 therapy for HER2-enriched tumors. Subsequently, gene expression analysis by Sørlie et al.[3] further refined the luminal-like subtype by dividing it into 2 distinct subgroups, luminal A and luminal B, on the basis of differences in prognosis and treatment response. The 2011 St. Gallen Conference built on these findings by establishing an immunohistochemical classification system for streamlining clinical application, on the basis of markers such as estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67[4]. Historically, breast cancer treatment was relatively uniform, relying on standard protocols such as surgery, chemotherapy (ChT), and radiotherapy, with limited consideration of individual tumor biology. This "one-size-fits-all" approach often resulted in suboptimal outcomes, particularly for patients with aggressive or advanced disease.

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Received November 8, 2024; accepted March 5, 2025;
published online April 23, 2025.
Available at www.cancerbiomed.org

The advent of precision medicine has revolutionized breast cancer treatment by offering a personalized approach[5-7]. Precision medicine involves tailoring treatments according to the genetic, molecular, and environmental factors unique to each patient's cancer[8]. This approach transcends the traditional "one-size-fits-all" approach to therapy, by using specific biomarkers, genetic testing, and advanced technologies to guide treatment decisions. The shift from conventional treatment paradigms to precision-based strategies has significantly improved patient outcomes, particularly regarding survival and quality of life[9]. Advances in molecular diagnostics[10] and genetic profiling[11] have been central to this transformation, by enabling the identification of key biomarkers and actionable mutations that can guide treatment decisions. In particular, the ability to classify tumors according to specific genetic and molecular features, such as HER2-low expression[12] and mutations in BRCA1/2[13-15], has expanded therapeutic options and enabled more targeted interventions.

Recent breakthroughs in technologies such as next-generation sequencing (NGS) have facilitated deeper understanding of tumor biology and enabled the identification of novel molecular targets[16]. These discoveries led to the development of targeted therapies, including cyclin-dependent kinases 4/6 (CDK4/6) inhibitors[17], antibody-drug conjugates (ADCs)[18], and immune checkpoint inhibitors (ICIs)[19], which have shown considerable promise in overcoming treatment resistance and improving outcomes in advanced and metastatic breast cancer. For example, CDK4/6 inhibitors have been shown to delay disease progression in hormone receptor-positive (HR+) breast cancer[20]. Simultaneously, ADCs such as trastuzumab deruxtecan have demonstrated efficacy in HER2-low and HER2-ultralow breast cancer[21,22], a subtype that previously had limited treatment options. ICIs, particularly in triple-negative breast cancer (TNBC), are also opening new avenues for treatment[23,24] and offering hope for patients with a subtype historically associated with poor prognosis.

The integration of diagnostic tools, such as genetic profiling and liquid biopsies, has markedly enhanced the precision medicine approach in breast cancer care. Genetic profiling assays, including Oncotype DX[25,26] and MammaPrint[27,28], offer valuable insights into recurrence risk and potential ChT benefits, and empower clinicians to make more informed treatment decisions. Liquid biopsies provide critical information through analysis of circulating tumor cells (CTCs)[29] and circulating tumor-derived materials such as circulating tumor DNA (ctDNA)[30], circulating miRNA[31], and extracellular vesicles[32]. Together, these tools enhance personalized treatment strategies, support the early detection of therapeutic resistance, and increase the likelihood of timely and effective interventions.

This review explores the current state of precision medicine and therapies for female breast cancer, focusing on advanced treatments and diagnostics and future developments in this field.

Precision medicine in early breast cancer (EBC)

In recent years, breast cancer mortality rates have declined in many countries, particularly among younger populations, primarily because of advancements in earlier detection and precision therapy strategies[33]. However, despite these improvements, breast cancer remains the leading cause of cancer-related deaths among women worldwide[1], including in China[34]. Most patients with breast cancer are diagnosed in early stages (stage I–III) and undergo potentially curative treatments. These treatments typically include surgery followed by systemic treatments such as neoadjuvant and/or adjuvant ChT, ET, radiotherapy, or combinations of these approaches. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a comprehensive analysis of patients with EBC diagnosed between 1990 and 2009, on the basis of their extensive database[35]. The risk of distant recurrence among patients with EBC diagnosed after the year 2000 was approximately 20% lower than the risk of those diagnosed in the 1990s. This improvement is attributed to advancements in diagnostic and treatment methods, particularly the development of adjuvant therapies. Next, we discuss recent advancements in systemic treatment for EBC.

HR+/HER2-negative (HER2–) EBC

HR+/HER2– breast cancer, the most common subtype, represents approximately 60%–70% of all breast cancer cases[36]. This subtype responds well to ET, and ChT may be used in high-risk patients. In the past decade, substantial advancements in precision medicine have reshaped the treatment landscape for HR+/HER2– EBC by providing new therapeutic options aligned with patients' tumor biology and individual risk factors. These options include extended ET, CDK4/6 inhibitors, and poly (ADP-ribose) polymerase (PARP)

inhibitors, all of which decrease recurrence and improve overall survival (OS)[37].

ET is the essential treatment for HR+/HER2– EBC

ET, a core treatment approach for HR+/HER2– EBC, leverages the hormone dependence of these tumors to curb growth and decrease recurrence risk. This therapy targets hormonal pathways that drive tumor proliferation and has been found to significantly improve long-term outcomes for patients[38].

For premenopausal women with HR+/HER2– EBC at low risk, the ER selective modulator tamoxifen is often used as the primary ET without ChT[39-41]. However, for high-risk patients with HR+/HER2– EBC, tamoxifen alone might have diminished effectiveness in patients who have retained ovarian function, because their ovaries continue to produce estrogen. In these patients, ovarian function suppression (OFS) with gonadotropin-releasing hormone analogues, such as leuprolide, can help decrease estrogen production and enhance tamoxifen's effects[42,43]. The Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) evaluated OFS combined with tamoxifen or exemestane in premenopausal women[44,45]. The SOFT trial found that tamoxifen with OFS, compared with tamoxifen alone, improved outcomes, particularly in high-risk women. The TEXT trial showed that exemestane plus OFS achieved better outcomes than tamoxifen plus OFS among high-risk premenopausal women, thereby supporting the use of aromatase inhibitors (AIs) in this group. For postmenopausal women, ET often includes AIs such as anastrozole, letrozole, and exemestane. AIs block aromatase, an enzyme responsible for converting androgens into estrogen, and thereby effectively decrease estrogen levels in the body and consequently the stimulation of HR+ breast cancer cells, which depend on estrogen for growth[46]. AIs therapy has been shown to decrease recurrence rates, particularly in postmenopausal women with high recurrence risk, and to have greater efficacy than tamoxifen[47,48].

Extending ET beyond the standard 5 years has been another key strategy for decreasing long-term recurrence risk in patients with HR+/HER2– EBC. Trials such as MA.1R have shown that extending AIs therapy beyond 5 years significantly decreases recurrence, particularly in high-risk patients, such as those with lymph node involvement[49]. However, this benefit must be weighed against the potential for adverse effects, including bone density loss and increased fracture risk. Consequently, extended ET is considered on a case-by-case basis, through shared decision-making between clinicians and patients to balance the benefits and risks. Interestingly, a multigene prognostic genomic assay, Breast Cancer Index (BCI), helps predict recurrence risk and guide the duration of ET in patients with HR+ EBC with high hormone receptor/insulin-like growth factor (H/I) ratios, who significantly benefit from extended treatment[50].

Ongoing studies are also exploring selective estrogen receptor degraders[51], such as fulvestrant[52] and elacestrant[53,54], which have shown promise in metastatic HR+ breast cancer and are currently being tested in high-risk early-stage disease.

These advancements highlight the importance of personalized ET in improving outcomes in patients with in HR+/HER2– EBC by tailoring treatments to specific tumor characteristics and patient profiles.

CDK4/6 inhibitors improve prognosis for HR+/HER2– EBC with high recurrence risk

Despite the effectiveness of ET, many patients with HR+/HER2– EBC experience recurrence, particularly those with high-risk features, such as large tumors or multiple lymph node involvement[55]. Genetic profiling has revealed that these patients almost always maintain retinoblastoma function; therefore, the primary pathway targeted by CDK4/6 inhibitors remains intact[56]. In addition, CCND1, which encodes cyclin D1, is a direct target gene of the ER and consequently is frequently overexpressed in ER-positive cancers[57]. Therefore, the addition of CDK4/6 inhibitors has been a major advancement. CDK4/6 inhibitors, primarily palbociclib, abemaciclib, ribociclib, and dalpiciclib, inhibit CDK4/6's activity and halt cancer cell growth at a critical point in the cell cycle, thus preventing proliferation.

Palbociclib

The first CDK4/6 inhibitor approved for HR+/HER2– advanced breast cancer (ABC), palbociclib, has become standard in metastatic settings[20,37]. However, in the early-stage setting, the PALLAS trial, evaluating palbociclib with ET in stage II or III HR+/HER2– EBC, has indicated that this therapy has no significant benefit over ET alone in preventing recurrence[58] (**Table 1**). Similarly, the PENELOPE-B trial, assessing palbociclib plus ET in patients with high-risk HR+/HER2– EBC with residual disease after neoadjuvant ChT, compared with ET alone, did not improve invasive disease-free survival (iDFS)[59] (**Table 1**). Despite these early-stage setbacks, palbociclib remains promising in metastatic settings, and ongoing research is exploring its full potential in EBC.

Table 1 Trials on CDK4/6 inhibitors in patients with HR+/HER2– EBC

Trial	Intervention	Outcomes	Percentage of patients with selected any-grade adverse events (grade ≥ 3 events)
PENELOPE-B (NCT01864746)[59]	Patients without pCR after taxane-containing NACT and at high risk of relapse (clinical pathological staging-ER grading score ≥ 3 or 2 and ypN+) randomized (1:1) to 13 cycles of palbociclib *vs.* placebo in addition to ET	3-year iDFS 81.2% *vs.* 77.7% (*HR* 0.93, *95% CI* 0.74–1.17; *P* = 0.525)	Anemia 73.9% (0.3%) *vs.* 30.3% (0.2%); leukopenia 99.2% (56.1%) *vs.* 69.9% (0.7%); neutropenia 95.7% (70.0%) *vs.* 23.4% (1.0%); thrombocytopenia 56.6% (0.8%) *vs.* 16.2% (0.3%); fatigue 66.4% (2.7%) *vs.* 51.1% (1.5%); infection 59.9% (3.2%) *vs.* 51.1% (3.9%); hot flushes 43.8% (0.8%) *vs.* 50.9% (1.0%); arthralgia 41.2% (0.8%) *vs.* 46.8% (1.5%)
PALLAS (NCT02513394)[58]	Patients with stage II or III disease randomized (1:1) to 2 years of palbociclib plus standard ET *vs.* standard ET	4-year iDFS 84.2% *vs.* 84.5% (*HR* 0.96, *95% CI* 0.81–1.14; *P* = 0.65)	Neutropenia 82.8% (61.3%) *vs.* 4.9% (0.4%); leukopenia 54.6% (30.2%) *vs.* 7.5% (0.1%); fatigue 40.5% (2.1%) *vs.* 19.3% (0.3%); 42.2% of patients in the experimental arm discontinued treatment
MONARCH-E (NCT03155997)[60]	Patients with ≥ 4 positive nodes or 1–3 positive nodes and tumor size ≥ 5 cm/ histologic grade 3/central Ki-67 ≥ 20% randomized (1:1) to 2 years of adjuvant abemaciclib plus standard ET *vs.* standard ET	2-year iDFS 92.2% *vs.* 88.7% (*HR* 0.75; *95% CI* 0.60–0.93; *P* = 0.01)	Diarrhea 83.5% (7.8%) *vs.* 8.7% (0.2%); neutropenia 46.0% (19.7%) *vs.* 6.5% (0.8%); leukopenia 37.7% (11.4%) *vs.* 6.3% (0.4%); fatigue 40.9% (2.9%) *vs.* 17.9% (0.1%); 18.0% of patients in the experimental arm discontinued treatment
NATALEE (NCT03701334)[61]	Patients with stage II or III disease randomized (1:1) to 3 years of adjuvant ribociclib plus a NSAI *vs.* an NSAI alone	3-year iDFS 90.4% *vs.* 87.1% (*HR* 0.75; *95% CI* 0.62–0.91; *P* = 0.003)	Neutropenia 62.2% (43.8%) *vs.* 4.5% (1.0%); arthralgia 36.5% (1.0%) *vs.* 42.5% (1.0%); liver dysfunction 25.4% (8.3%) *vs.* 10.6% (2.0%)
DARLING-02 (NCT06107673)[62,63]	Patients randomized (1:1) to dalpiciclib plus letrozole *vs.* standard intervention	Ongoing	Ongoing

pCR, pathological complete response; NACT, neoadjuvant chemotherapy; ER, estrogen receptor; ET, endocrine therapy; iDFS, invasive disease-free survival; HR, hazard ratio; CI, confidence interval; NSAI, non-steroidal aromatase inhibitors.

Ribociclib

Ribociclib has shown efficacy in both metastatic and early-stage HR+/HER2– breast cancer. The NATALEE trial demonstrated significant improvements in iDFS with the addition of ribociclib to ET for early-stage HR+/HER2– breast cancer, including node-positive cases[61] (**Table 1**). With a favorable safety profile, including low rates of neutropenia and gastrointestinal adverse effects, ribociclib has broad applicability, including for patients with low-risk disease, and therefore may benefit a wide population.

Abemaciclib

The most recent CDK4/6 inhibitor approved for adjuvant treatment in HR+/HER2– EBC, abemaciclib, has achieved significant improvements in iDFS for high-risk patients. In the MONARCH-E trial, abemaciclib decreased the risk of distant recurrence by 30.4%, and was found to benefit patients with high-risk features such as elevated Ki-67 levels or large tumors[60,64,65] (**Table 1**). Continuous administration of abemaciclib, in contrast to other CDK4/6 inhibitors, enhances treatment efficacy but also increases the incidence of gastrointestinal adverse effects, notably diarrhea, which requires careful management[64,66]. Despite these challenges, abemaciclib remains a critical treatment option for patients with high-risk HR+/HER2– EBC, particularly those with node-positive or aggressive disease.

Dalpiciclib

Dalpiciclib, although widely used in regions such as Asia for advanced HR+/HER2– breast cancer, is not currently approved for EBC treatment in many areas. Studies in metastatic settings have demonstrated its efficacy in prolonging progression-free survival (PFS) when combined with ET, similarly to the other CDK4/6 inhibitors[67,68]. Its potential use in EBC remains under exploration in clinical trials aimed at determining its efficacy in preventing recurrence and improving outcomes in patients with high-risk EBC[62,63] (**Table 1**). The distinct characteristics of dalpiciclib, such as its lower rates of gastrointestinal adverse effects than abemaciclib, may make it a future candidate for broader applications in metastatic and early-stage settings.

Each CDK4/6 inhibitor offers unique benefits and challenges in treating HR+/HER2– breast cancer. Abemaciclib

is currently a leading candidate because of its effectiveness in patients with high-risk early-stage tumors, particularly those with aggressive biology. Ribociclib provides a favorable balance of efficacy and safety, and therefore is suitable for a broader patient population. Although palbociclib and dalpiciclib remain under evaluation in early-stage disease, both remain crucial in the management of metastatic HR+/HER2− breast cancer.

Exploration of immunotherapy for high-risk HR+/HER2− EBC

Immunotherapy, which was traditionally focused on treating TNBC, is currently being explored in HR+/HER2− breast cancer, particularly for high-risk patients. ICIs are being tested with standard therapies to improve immune responses in patients with HR+/HER2− tumors, which typically exhibit relatively low immune activity.

Key trials, including KEYNOTE-756 and CheckMate 7FL, have shown promising results. KEYNOTE-756, a phase III trial evaluating pembrolizumab combined with neoadjuvant ET and ChT, has demonstrated improved pathological complete response (pCR) rates[69] (**Table 2**). Similarly, the CheckMate 7FL trial, investigating nivolumab with neoadjuvant ChT followed by adjuvant ET, has shown improvements in pCR and decreases in residual cancer burden, and offered hope for patients with high-risk HR+/HER2− tumors[70] (**Table 2**). Although immunotherapy for HR+/HER2− breast cancer remains in its early stages, these trials suggest that ICIs might enhance the effectiveness of existing therapies; therefore, further research is warranted to identify the optimal combinations and the patient populations that would benefit most.

PARP inhibitors are recommended for high-risk BRCA1/2-mutated EBC

For patients with germline BRCA1 or BRCA2 mutations, PARP inhibitors, such as olaparib, provide an effective adjuvant treatment option. The OlympiA trial has demonstrated that olaparib decreases recurrence risk and improves OS in patients with high-risk BRCA-mutated EBC, thus reaffirming its role in precision medicine for this subgroup[76-78].

HER2-positive (HER2+) EBC

Approximately 15%–20% of breast cancers are classified as HER2+[79]. This subtype is more aggressive than the HER2− subtype. In recent years, breast cancer subtypes have been found to exist not only within the traditional HER2+ and HER2− categories but also within a spectrum including HER2-low and HER2-ultra-low cancers[80]. These distinctions are aiding in further refinement of treatment strategies, particularly through the use of precision medicine-tailored treatments based on tumor molecular characteristics. Key elements of precision medicine for HER2+ EBC are described below.

Dual HER2 blockade has superior efficacy to single HER2 blockade

A significant breakthrough in treating HER2+ EBC has been dual HER2 blockade combining trastuzumab and pertuzumab. The APHINITY trial highlighted that adding pertuzumab to trastuzumab and ChT significantly improves iDFS, particularly in patients with high-risk, lymph node-positive tumors[81]. At 6-year follow-up, patients treated with this dual blockade experienced 4.5% greater iDFS and 24% lower recurrence risk or death rates than those who did not receive pertuzumab (*HR* 0.76)[82]. Furthermore, the third interim OS of the APHINITY trial, updated in 2024[83], showed that pertuzumab addition resulted in an absolute 4.9% improvement in 8-year iDFS in the node-positive cohort, whereas no iDFS benefit from pertuzumab was observed in the node-negative cohort. Additionally, no evidence of late-onset cardiac toxicity associated with pertuzumab addition was found, thus providing critical clinical insights for the management of patients with HER2+ EBC.

Additionally, the FDChina study further refined dual HER2 blockade by evaluating a fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection[84]. This approach achieved the same efficacy as intravenous administration in total pCR rates while simplifying the treatment process, decreasing patient burden, and maintaining a similar safety profile[84]. This innovation offers patients a more convenient treatment option without compromising outcomes.

ADCs are recommended for patients with HER2+ EBC who do not achieve pCR

Trastuzumab emtansine (T-DM1) has become a foundational therapy for patients with HER2+ EBC who do not achieve pCR after neoadjuvant treatment (**Table 3**). The critical KATHERINE trial has shown that T-DM1, compared with trastuzumab, significantly decreases the risk of invasive disease recurrence or death by 50.0%, achieving a 3-year iDFS rate of 88.3% for T-DM1 *vs.* 77.0% for trastuzumab alone[85]. In 2024, 8.4-year follow-up data further confirmed T-DM1's sustained benefit, with an iDFS rate of approximately 81.0%,

Table 2 Trials on ICIs in early breast cancer

Trial	Target	Intervention	Outcomes	Selected adverse events of any grade (grade ≥ 3 events)
KEYNOTE-756 (NCT03725059)[69]	PD-1	Early-stage high-risk ER+/HER2− breast cancer randomized (1:1) to neoadjuvant pembrolizumab *vs.* placebo plus ChT followed by adjuvant pembrolizumab *vs.* placebo plus ET	pCR 24.3% *vs.* 15.6%; (P = 0.00005)	Any adverse event (52.5%) *vs.* (46.4%)
CheckMate 7FL (NCT04109066)[70]	PD-1	Early-stage high-risk ER+/HER2− breast cancer randomized (1:1) to NACT plus nivolumab *vs.* placebo	pCR 24.5% *vs.* 13.8% (P = 0.0021)	Any adverse event (35.0%) *vs.* (32.0%)
KEYNOTE-522 (NCT03036488)[71-73]	PD-1	Previously untreated early-stage high-risk TNBC randomized (2:1) to neoadjuvant pembrolizumab *vs.* placebo plus paclitaxel and carboplatin followed by pembrolizumab *vs.* placebo	pCR 64.8% *vs.* 51.2% (P < 0.001); estimated EFS 84.5% *vs.* 76.8%; estimated OS 89.7% *vs.* 86.9%; 5-year OS 86.6% *vs.* 81.7%	Nausea 62.7% (3.3%) *vs.* 63.2% (1.3%); alopecia 60.3% (1.8%) *vs.* 56.6% (2.1%); anemia 55.1% (18.2%) *vs.* 55.3% (14.9%); neutropenia 46.7% (34.6%) *vs.* 47.0% (33.2%); fatigue 41.1% (3.5%) *vs.* 37.8% (1.5%)
IMpassion031 (NCT03197935)[74]	PD-L1	Previously untreated early-stage TNBC randomized (1:1) to atezolizumab *vs.* placebo plus ChT	pCR 58% *vs.* 41% (P = 0.0044)	Nausea 65.0% (1.0%) *vs.* 67.0% (4.0%); diarrhea 41.0% (2.0%) *vs.* 44.0% (1.0%); anemia 38.0% (9.0%) *vs.* 38.0% (7.0%); fatigue 36.0% (4.0%) *vs.* 38.0% (3.0%); neutropenia 36.0% (23.0%) *vs.* 35.0% (22.0%); vomiting 35.0% (1.0%) *vs.* 31.0% (1.0%); peripheral sensory neuropathy 33.0% (3.0%) *vs.* 27.0% (2.0%)
A-BRAVE[75]	PD-L1	Early TNBC at high recurrence risk randomized (1:1) to for 1 year as adjuvant treatment or observation	DFS 68.3% *vs.* 63.4% (*HR* 0.82, *95% CI* 0.61–1.11; P = 0.193); OS 85.2% *vs.* 78.2% (*HR* 0.66, *95% CI* 0.44–0.98; P = 0.041)	Continue to be evaluated

ChT, chemotherapy; ET, endocrine therapy; pCR, pathological complete response; NACT, neoadjuvant ChT; TNBC, triple negative breast cancer; EFS, event-free survival; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval.

Table 3 Currently approved ADCs for HER2-positive breast cancer

ADC	Trade name	Target antigen	Antibody	Payload	Linker	Average DAR	Developer	Approval date	Approved indications
Trastuzumab emtansine (adotrastuzumab ematansine; T-DM1)	KADCYLA®	HER2	Humanized IgG1 (trastuzumab)	DM1	Non-cleavable (SMCC)	3.5	Genentech	February 2013	Patients with HER2+ metastatic breast cancer who received prior treatment with trastuzumab and a taxane, separately or in combination
								May 2019	Adjuvant treatment of patients with HER2+ early breast cancer, who had residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment
Trastuzumab deruxteen (fam-trastuzumab deruxtecan-nxki; T-DXd; DS8201a)	ENHERTU®	HER2	Humanized IgG1 (MAAL-9001)	DXd	Cleavable (maleimide CGFG peptide)	7.0–8.0	Daiichi Sankyo	December 2019	Adult patients with unresectable or metastatic HER2+ breast cancer who received 2 or more prior anti-HER2-based regimens in the metastatic setting (accelerated approval)
								May 2022	Adult patients with unresectable or metastatic HER2+ breast cancer who received a prior anti-HER2-based regimen in either the metastatic setting or the neoadjuvant or adjuvant setting, and developed disease recurrence during or within 6 months of completing therapy

ADC, antibody-drug conjugate.

compared with 67.0% for trastuzumab[86]. This benefit extends across various subgroups, including patients with differing nodal and HR status. Additionally, updated OS data have shown a 34% decrease in mortality risk of patients treated with T-DM1[86].

Moreover, trastuzumab deruxtecan (T-DXd) has shown substantial potential in HER2-low EBC. The TALENT trial, designed to evaluate the neoadjuvant use of T-DXd, either alone or in combination with ET, reported highly promising early results in 2023[21]. The overall response rate was 75% in patients receiving T-DXd monotherapy and 63.2% in those receiving T-DXd combined with anastrozole[21]. Additionally, neoadjuvant administration of T-DXd is under evaluation in the DESTINY-Breast11 trial in locally advanced or inflammatory HER2+ breast cancer (NCT05113251). Adjuvant use of T-DXd is currently being explored in the ongoing DESTINY-Breast05 trial, in which its effectiveness is being compared with that of T-DM1 in patients with residual invasive HER2+ breast cancer after neoadjuvant therapy (NCT04622319). Furthermore, the SHAMROCK study will assess the use of neoadjuvant T-DXd in early-stage HER2+ breast cancer by incorporating strategies for both escalating and de-escalating therapy[87].

These advances in ADCs, both in HER2+ and HER2-low breast cancer, reflect the growing influence of precision medicine in providing more tailored and effective treatments that improve long-term outcomes for patients across the HER2 spectrum.

Tyrosine kinase inhibitors (TKIs) are recommended for patients with HER2+ EBC at high recurrence risk after completion of standard HER2-targeted therapies

TKIs, such as lapatinib, tucatinib, and neratinib, are used primarily in the adjuvant setting for HER2+ breast cancer. However, they have also been explored in the neoadjuvant setting in some trials. Neratinib is approved for extended adjuvant therapy in HER2+ EBC, particularly in patients who have completed trastuzumab-based treatment. The ExteNET trial has demonstrated that 1 year of neratinib significantly improves iDFS, particularly in HR+ patients, and decreases the risk of distant recurrence[88]. This treatment is recommended after completion of trastuzumab in the adjuvant setting, to minimize recurrence. Although TKIs are less frequently used in the neoadjuvant setting, some studies have investigated their potential. For example, lapatinib

has been explored as a neoadjuvant option in combination with trastuzumab and ChT in HER2+ breast cancer. The NeoALTTO trial has demonstrated that adding lapatinib to trastuzumab before surgery (neoadjuvant therapy) achieves a significantly greater pCR rate than trastuzumab alone[89]. However, owing to mixed results and adverse effects, lapatinib has not gained widespread use in the neoadjuvant setting.

TNBC EBC

TNBC lacks ER, PR, and HER2 expression[90], thus limiting the effectiveness of hormonal therapies and HER2-targeted agents widely used in other breast cancer subtypes. Consequently, TNBC has been associated with poor prognosis[91,92], high risk of early recurrence[93,94], and limited treatment options. However, recent advances in targeted therapies, immunotherapy, and personalized medicine are beginning to shift this paradigm, particularly for patients with high-risk early-stage TNBC. This movement toward individualized care, focusing on the specific biological traits of the tumor and the patient's genetic profile, has been instrumental in improving outcomes in early TNBC[95]. The rapid evolution of precision medicine in TNBC offers hope to patients with this aggressive and traditionally challenging subtype.

Immunotherapy improves pCR, EFS, and OS rates in early TNBC

Immunotherapy has emerged as a promising treatment option for TNBC. The primary focus of immunotherapy in early TNBC is on ICIs, particularly anti-PD-1 and anti-PD-L1 therapies, to enhance the immune system's ability to recognize and destroy cancer cells[96].

Pembrolizumab (Keytruda)

Pembrolizumab is among the most studied ICIs in early TNBC. The KEYNOTE-522 trial (**Table 2**), a phase III study, evaluated pembrolizumab in combination with neoadjuvant ChT in early-stage, high-risk TNBC. This treatment significant improved pCR rates (64.8% in the pembrolizumab group *vs.* 51.2% in the ChT-only group)[71]. The trial also demonstrated improved event-free survival (EFS)[72]; consequently, pembrolizumab has become a cornerstone of early TNBC treatment. The final OS results of the KEYNOTE-522 trial were presented in 2024[73]. In patients with early-stage TNBC receiving neoadjuvant therapy, adding pembrolizumab to ChT significantly improved the 5-year OS, from 81.7% to 86.6%. Moreover, long-term benefits of EFS were also observed. These findings further support the efficacy of pembrolizumab.

Atezolizumab (Tecentriq)

Another checkpoint inhibitor, atezolizumab, was evaluated in the IMpassion031 trial (**Table 2**), in combination with nab-paclitaxel, followed by doxorubicin plus cyclophosphamide as neoadjuvant treatment in early TNBC. Addition of atezolizumab achieved a higher pCR rate (58.0%) than placebo plus ChT (41.0%)[74]. Consequently, atezolizumab has been established as a potential neoadjuvant option for early-stage TNBC.

Avelumab (Bavencio)

The A-BRAVE trial (**Table 2**), a phase III study, examined avelumab in the adjuvant setting for patients with early TNBC at high recurrence risk. Although avelumab did not significantly improve DFS, it achieved a meaningful improvement in OS by decreasing the risk of death and distant metastases in high-risk patients. These findings support its potential use in selected patients' post-neoadjuvant therapy[75].

ICIs are part of a growing arsenal against early TNBC. These therapies have shown promise both in neoadjuvant and adjuvant settings, and herald a major shift toward personalized immunotherapy improving outcomes in a subtype of breast cancer with previously limited therapeutic options.

PARP inhibitors are recommended in patients with high-risk early-stage BRCA-mutated TNBC

In 2005, 2 groundbreaking studies showed that synthetic lethality can be exploited in BRCA1/2-deficient tumors: cells lacking homologous recombination are selectively killed when PARP is inhibited[97,98]. In 2009, the phase I trial of the PARP inhibitor olaparib demonstrated objective responses in patients with advanced breast, ovarian, and prostate cancers bearing germline BRCA1/2 mutations[99]. Subsequent trials also indicated substantial promise of PARP inhibitors in treating patients with early TNBC with BRCA1/2 mutations. The OlympiA trial demonstrated that 1 year of olaparib treatment significantly improved both iDFS and OS in patients with high-risk early-stage BRCA-mutated TNBC[77]. Olaparib decreased the risk of disease recurrence and death, and was the first PARP inhibitor demonstrated to achieve an OS benefit in this setting. The trial results emphasize the importance of PARP inhibitors in personalizing treatment for patients with TNBC.

Precision medicine in early TNBC has transformed the treatment landscape by incorporating immunotherapy, PARP

inhibitors, and ADCs, and surpassing traditional ChT in improving survival and recurrence. These therapies, which target the unique biology of TNBC and subgroups, are moving the field closer to personalized treatment options that extend beyond standard ChT. Although challenges remain, such as understanding resistance mechanisms and identifying optimal combination therapies, these advances provide a more hopeful outlook for patients with TNBC, particularly those at high recurrence risk.

Continued research on the tumor microenvironment, genetic mutations, and emerging biomarkers should further refine these approaches and enable greater personalization in the future. For patients with early TNBC, these precision medicine strategies signify a shift toward more effective, targeted care aimed at decreasing recurrence, improving survival, and profoundly affecting treatment for this challenging breast cancer subtype.

Precision medicine in ABC

HR+ ABC

HR+ ABC typically responds well to ETs, which are foundational in its management. However, because resistance mechanisms frequently develop over time, additional targeted therapies are frequently required.

ETs provide an initial therapy for ABC

In clinical practice, ETs are favored for their ability to manage advanced disease with a relatively favorable adverse effect profile, in contrast to ChT. These treatments are valuable for patients requiring long-term management, because they can be administered over extended periods to control disease progression.

ET is often used as a monotherapy in patients with indolent disease, or in combination with targeted therapies such as CDK4/6 inhibitors in patients with high-risk features or those who exhibit resistance to first-line therapies. Extending the duration of ET in patients who continue to benefit is a common approach, provided that the patient tolerates the treatment well.

Despite the broad application of ETs, clinical challenges arise from the development of resistance, particularly in patients with mutations, such as ESR1[100]. For such cases, novel therapies, such as oral selective estrogen receptor degraders (e.g., fulvestrant[52] and elacestrant[53,54]), provide new treatment avenues when traditional endocrine therapies fail. The EMERALD trial has demonstrated that elacestrant significantly improves PFS in patients with ESR1-mutant ABC[53]. Therefore, this treatment may provide an essential option in cases in which tumors no longer respond to standard ETs[101].

CDK4/6 inhibitors combined with ET are the standard treatment for HR+ ABC

CDK4/6 inhibitors represent a major advancement in treating HR+ ABC, particularly for patients who experience disease progression under ET. When combined with ET, these inhibitors—palbociclib, ribociclib, abemaciclib, and the emerging dalpiciclib—have achieved substantial improvements in PFS and OS[102] (**Table 4**).

Palbociclib, ribociclib, and abemaciclib are combined with ETs, particularly for patients with high-risk disease or significant tumor burdens. Clinical trials including PALOMA-2[105,106] and MONALEESA-2[109,110] have demonstrated that adding CDK4/6 inhibitors to letrozole extends PFS by 10–11 months beyond ET alone. These inhibitors have become standard care for advanced HR+ breast cancer.

Dalpiciclib, a newer addition to the CDK4/6 inhibitor class, has shown promise in improving outcomes for patients with HR+ ABC. Clinical studies such as the DAWNA-1 trial have demonstrated that, when combined with ET, this treatment significantly prolongs PFS, particularly in patients with endocrine-resistant or heavily pretreated disease[67]. Additionally, dalpiciclib exhibits a manageable safety profile, in which neutropenia is a notable but manageable adverse effect[67]. As ongoing trials evaluate its efficacy and potential applications[63,68], dalpiciclib offers another valuable option that broadens the available therapeutic strategies for managing HR+ ABC.

PI3K/AKT/mTOR inhibitors are effective options for endocrine-resistant HR+ ABC

Targeting the PI3K/AKT/mTOR pathway is critical in managing HR+ ABC, particularly for patients who develop resistance to ETs because of mutations in the PIK3CA gene[119,120]. This pathway is a central component in cellular growth, metabolism, and survival, and its dysregulation is associated with resistance mechanisms in HR+ breast cancer, thus contributing to disease progression despite standard treatments[121].

PI3K inhibitors, including alpelisib and inavolisib, have emerged as key therapeutic agents for overcoming resistance in HR+ breast cancer driven by PIK3CA mutations[122]. Alpelisib, a selective PI3K inhibitor, has notable efficacy in PIK3CA-mutant HR+ breast cancer, and its combination with

Table 4 Trials on CDK4/6 inhibitors in patients with hormone receptor-positive, HER2-negtive ABC

Trial	Intervention	mPFS *vs.* placebo	mOS *vs.* placebo	Percentage of patients with selected any-grade adverse events (grade ≥ 3 events)
PALOMA-1 (NCT00721409)[103,104]	Patients randomized (1:1) to palbociclib *vs.* placebo as first-line therapy	20.2 *vs.* 10.2 months (*HR* 0.49, *95% CI* 0.32–0.75)	37.5 *vs.* 34.5 months (*HR* 0.90, *95% CI* 0.62–1.29; $P = 0.28$)	Neutropenia 75.0% (59.0%) *vs.* 5.0% (1.0%); leukopenia 43.0% (18.0%) *vs.* 4.0% (0.0%); fatigue 41.0% (7.0%) *vs.* 23.0% (1.0%)
PALOMA-2 (NCT01740427)[105,106]	Patients randomized (2:1) to palbociclib *vs.* placebo as first-line therapy	24.8 *vs.* 14.5 months (*HR* 0.56, *95% CI* 0.46–0.69; $P < 0.0001$)	53.9 *vs.* 51.2 months (*HR* 0.96, *95% CI* 0.78–1.18; $P = 0.34$)	Neutropenia 79.5% (66.5%) *vs.* 6.3% (1.4%); leukopenia 39.0% (24.8%) *vs.* 2.3% (0.0%); fatigue 37.4% (1.8%) *vs.* 27.5% (0.5%)
PALOMA-3 (NCT01942135)[107,108]	Patients randomized (2:1) to palbociclib *vs.* placebo as second or later-line therapy	9.5 *vs.* 4.6 months (*HR* 0.46, *95% CI* 0.36–0.59; $P < 0.0001$)	34.8 *vs.* 28.0 months (*HR* 0.81, *95% CI* 0.65–0.99; $P = 0.09$)	Neutropenia 80.0% (65.0%) *vs.* 45.0% (1.0%); leukopenia 50.0% (28.0%) *vs.* 35.0% (2.0%); anemia 28.0% (3.0%) *vs.* 11.0% (2.0%)
MONALEESA-2 (NCT01958021)[109,110]	Patients randomized (1:1) to ribociclib *vs.* placebo as first-line therapy	25.3 *vs.* 16.0 months (*HR* 0.57, *95% CI* 0.46–0.70; $P = 9.63 \times 10^{-8}$)	63.9 *vs.* 51.4 months (*HR* 0.76, *95% CI* 0.63–0.93; $P = 0.008$)	Neutropenia 74.3% (59.3%) *vs.* 5.2% (0.9%); nausea 51.5% (2.4%) *vs.* 28.5% (0.6%); infection 50.6% (4.2%) *vs.* 42.4% (2.4%); increased serum ALT 16.0% (6.0%) *vs.* 4.0% (1.0%)
MONALEESA-3 (NCT02422615)[111,112]	Patients randomized (2:1) to ribociclib *vs.* placebo as first-line or second-line therapy	20.5 *vs.* 12.8 months (*HR* 0.59, *95% CI* 0.48–0.73; $P < 0.001$)	53.7 *vs.* 41.5 months (*HR* 0.73, *95% CI* 0.59–0.90)	Neutropenia 69.6% (53.4%) *vs.* 2.1%; nausea 45.3% (1.4%) *vs.* 28.2% (0.8%); leukopenia 28.4% (13.5%) *vs.* 1.7% (0.0%)
MONALEESA-7 (NCT02278120)[113,114]	Patients randomized (1:1) to ribociclib *vs.* placebo as first-line or second-line therapy	23.8 *vs.* 13.0 months (*HR* 0.55, *95% CI* 0.44–0.69; $P < 0.0001$)	58.7 *vs.* 48.0 months (*HR* 0.76, *95% CI* 0.61–0.96)	Neutropenia 76.0% (61.0%) *vs.* 8.0% (4.0%); nausea 32.0% (1.0%) *vs.* 19.0% (< 1.0%); leukopenia 31.0% (14.0%) *vs.* 5.0% (1.0%); increased serum ALT 12.0% (5.0%) *vs.* 7.0% (1.0%)
MONARCH-2 (NCT02107703)[115,116]	Patients randomized (2:1) to abemaciclib *vs.* placebo as second-line therapy	16.4 *vs.* 9.3 months (*HR* 0.55, *95% CI* 0.45–0.68)	45.8 *vs.* 37.2 months (*HR* 0.78, *95% CI* 0.64–0.96; $P = 0.02$)	Diarrhea 86.4% (13.4%) *vs.* 24.7% (0.4%); neutropenia 46.0% (26.5%) *vs.* 4.0% (1.7%); nausea 45.1% (2.7%) *vs.* 22.9% (0.9%)
MONARCH-3 (NCT02246621)[117,118]	Patients randomized (2:1) to abemaciclib *vs.* placebo as first-line therapy	28.2 *vs.* 14.8 months (*HR* 0.54, *95% CI* 0.42–0.70)	67.1 *vs.* 54.5 months (*HR* 0.75, *95% CI* 0.58–0.97; $P = 0.03$)	Diarrhea 81.3% (9.5%) *vs.* 29.8% (1.2%); neutropenia 41.3% (21.1%) *vs.* 1.9% (1.2%); fatigue 40.1% (18.6%) *vs.* 31.7% (0.0%)
DAWNA-1 (NCT03927456)[67]	Patients with disease progression after ET randomized (2:1) to dalpiciclib *vs.* placebo plus fulvestrant	15.7 *vs.* 7.2 months (*HR* 0.42, *95% CI* 0.31–0.58; $P < 0.0001$)	Not observed	Neutropenia 97.9% (84.2%) *vs.* 12.5% (0.0%); leukopenia 97.1% (62.1%) *vs.* 10.0% (0.0%); anemia 61.3% (2.9%) *vs.* 11.7% (1.7%); thrombocytopenia 56.3% (5.8%) *vs.* 8.3% (0.8%)
DAWNA-2 (NCT03966898)[68]	Patients randomized (2:1) to dalpiciclib *vs.* placebo plus letrozole or anastrozole as first-line treatment	30.6 *vs.* 18.2 months (*HR* 0.51, *95% CI* 0.38–0.69; $P < 0.0001$)	Not observed	Anemia 67.0% (7.0%) *vs.* 8.0% (< 1.0%); thrombocytopenia 53.0% (4.0%) *vs.* 8.0% (< 1.0%); leukopenia 98.0% (66.0%) *vs.* 13.0% (0.0%); neutropenia 99.0% (86.0%) *vs.* 11.0% (0.0%)

mPFS, median progression-free survival; mOS, median overall survival; HR, hazard ratio; CI, confidence interval; ALT, alanine transaminase.

ET has become a common treatment approach[123]. In the seminal SOLAR-1 trial, patients with PIK3CA-mutant HR+ breast cancer who received alpelisib plus fulvestrant experienced a significant improvement in PFS over that observed in patients receiving ET alone[124]. Similarly, inavolisib, another selective PI3K inhibitor, has shown efficacy in combination with aromatase inhibitors, by significantly extending PFS in patients with PIK3CA-mutant tumors[125]. These inhibitors provide essential options for patients with endocrine-resistant disease, and offer an alternative strategy for targeting the PI3K pathway and delaying disease progression.

AKT inhibitors, such as capivasertib, offer a distinct approach targeting the PI3K/AKT/mTOR pathway[126]. Capivasertib has shown promising results in combination with ET, by improving PFS in patients with disease progression under prior treatments[127,128]. As an AKT inhibitor, capivasertib directly targets a downstream component of the PI3K pathway, thus providing an alternative therapeutic option for patients with HR+ breast cancer resistant to other treatments.

Another agent, everolimus, is an mTOR inhibitor that targets a downstream component of the PI3K/AKT/mTOR pathway, thereby offering an alternative mechanism to combat resistance to CDK4/6 inhibitor and ET[129,130]. Everolimus is frequently used alongside exemestane in advanced HR+ breast cancer, particularly in patients with disease progression under prior ETs. The BOLERO-2 trial has emphasized the clinical benefits of adding everolimus, which significantly extended PFS, particularly in heavily pretreated patients who would otherwise have had limited therapeutic options[131]. This combination is valuable for patients with advanced disease, because it not only helps manage resistance but also maintains quality of life by delaying progression.

These targeted therapies provide essential options for managing HR+ breast cancer and addressing the critical need for effective treatments in patients with endocrine-resistant disease driven by PI3K pathway mutations.

ADCs provide promising treatment options for advanced HR+ breast cancer after multiple therapies fail

For patients whose disease progresses after multiple lines of endocrine and targeted therapies, ADCs provide a new approach[132]. These therapies deliver cytotoxic ChT directly to tumor cells and consequently minimize systemic exposure[133].

T-DXd, initially developed for HER2+ breast cancer, has shown efficacy in HR+ breast cancer with low HER2 expression (**Table 3**). The DESTINY-Breast04 trial has demonstrated significant improvements in PFS for patients with advanced HR+ disease who have exhausted other treatment options[22].

Sacituzumab govitecan (SG), targeting Trop-2, has also shown promising results in heavily pretreated HR+ patients with breast cancer. The ASCENT trial has indicated extended OS and consequently brought hope to patients with few remaining therapeutic options[134,135].

ETs remain a fundamental part of managing advanced HR+ breast cancer, particularly in patients with relatively less aggressive disease or those who would benefit from long-term treatment with fewer adverse effects. When ETs are combined with targeted treatments such as CDK4/6 inhibitors, PI3K/AKT/mTOR pathway inhibitors, and ADCs, the outcomes improve significantly. New therapies, such as doruciclib and elacestrant, provide promising solutions for patients with resistant disease, by making precision medicine an essential component of ABC care. As research progresses, refining these therapies and addressing resistance mechanisms will be critical to further improving survival and quality of life for advanced patients with breast cancer.

HER2+ ABC

Since the discovery of HER2/neu[136], precision medicine for advanced HER2+ breast cancer continues to make major strides, primarily through the development of targeted therapies such as monoclonal antibodies, ADCs, and small molecule TKIs. These treatments are highly tailored to the molecular characteristics of HER2+ tumors, and have been found to improve survival rates and address resistance mechanisms.

Trastuzumab and pertuzumab provide an initial therapy for metastatic HER2+ breast cancer

Monoclonal antibodies, such as trastuzumab, have been foundational in advanced HER2-positive breast cancer treatment[137]. Trastuzumab blocks HER2 receptor signaling, and consequently prevents tumor growth and engages the immune system to destroy cancer cells[138]. Pertuzumab, a monoclonal antibody that blocks HER2 dimerization, is often combined with trastuzumab for dual HER2 blockade[139]. The CLEOPATRA trial has demonstrated that this combination, along with ChT, significantly improves PFS and OS in patients with metastatic HER2+ breast cancer[140]. This regimen remains the first-line standard of care for most patients.

ADCs provide a second-line treatment for HER2+ ABC

ADCs represent a major advancement in precision medicine by combining targeted HER2 inhibition with ChT. T-DM1, the first ADC for HER2+ breast cancer, links trastuzumab to a cytotoxic agent that specifically kills HER2+ cancer cells[141]. The EMILIA trial established T-DM1 as the preferred second-line treatment after trastuzumab, by showing significant improvements in PFS and overall safety[142] (**Table 3**).

More recently, T-DXd, a more potent ADC, has shown superior efficacy. The DESTINY-Breast03 trial has demonstrated that T-DXd achieves a median PFS longer than 25 months, as compared with 7 months for T-DM1; therefore, this treatment is the preferred second-line option[143]. Furthermore, the DESTINY-Breast04 trial extended T-DXd's use to patients with HER2-low expression, thus broadening its applicability beyond traditional HER2+ breast cancer[22,144]. The DESTINY-Breast06 trial evaluated T-DXd in patients with HER2-ultralow breast cancer, and might enable expansion of this potent ADC to a broader patient population[145] (**Table 3**).

TKIs enhance treatment for HER2+ ABC, including brain metastases

In HER2+ ABC, TKIs have become a crucial component of treatment, particularly for patients resistant to traditional HER2-targeted therapies, such as trastuzumab or pertuzumab. TKIs are small molecules that specifically inhibit the tyrosine kinase activity of the HER2 receptor, a protein that drives tumor cell growth and proliferation in HER2+ breast cancer[146]. By blocking this activity, TKIs effectively disrupt the signaling pathways essential for tumor survival and consequently provide a more targeted therapeutic option.

Lapatinib was among the first TKIs approved for HER2+ breast cancer and is often used in combination with capecitabine[147]. However, newer TKIs, such as tucatinib, neratinib, and pyrotinib, have since expanded the treatment landscape by providing more potent options with enhanced specificity and efficacy. Tucatinib has shown particularly impressive results in patients with brain metastases common and challenging complications in HER2+ breast cancer, because of its ability to cross the blood-brain barrier more effectively than other HER2-targeted drugs[148,149]. The HER2CLIMB trial has demonstrated that the combination of tucatinib with trastuzumab and capecitabine significantly improves PFS and OS in patients with HER2+ breast cancer with or without brain metastases[150].

Pyrotinib is another potent HER2-targeted TKI that inhibits HER1 and HER4, and consequently broadly disrupts HER family signaling pathways[151]. Clinical trials such as the PERMEATE[152] and PHOEBE[153] trials have demonstrated that pyrotinib in combination with capecitabine improves PFS and response rates in patients whose disease previously progressed under other HER2-targeted therapies. This broad-spectrum activity makes pyrotinib a promising option, particularly for patients with brain metastases or those who have experienced disease progression on traditional HER2-targeted agents.

Although TKIs provide potent options, they can have adverse effects, such as diarrhea, rash, and liver enzyme elevations, which often require monitoring and management[154]. However, the clinical benefits of TKIs, particularly their ability to address CNS involvement and enhance outcomes in heavily pretreated patients, underscore their value in the HER2+ breast cancer treatment landscape. As research continues to explore new TKIs and combination strategies, TKIs are anticipated to play an increasingly prominent role in treating HER2+ ABC, by extending survival and improving quality of life for many patients.

Advanced TNBC

ChT remains a foundational treatment for advanced TNBC[155]. However, precision medicine is transforming this field by tailoring treatment strategies to the unique molecular characteristics of individual tumors. Unlike other breast cancers, TNBC lacks common therapeutic targets, and its historically restricted treatment options have contributed to its aggressive progression and higher relapse rates. Recent advances in genomics and molecular profiling have led to the discovery of distinct TNBC subtypes, thus facilitating the development of targeted therapies, immunotherapies, and novel drug delivery systems[156]. These approaches are reshaping TNBC management and bringing new hope for improved outcomes in advanced and metastatic stages.

Immunotherapy has transformed TNBC treatment

Immunotherapy has transformed TNBC treatment, particularly in tumors expressing PD-L1. ICIs, such as pembrolizumab and atezolizumab, enable the immune system to attack cancer cells by blocking the PD-1/PD-L1 pathway[157]. In the KEYNOTE-355 trial, pembrolizumab combined with ChT has been found to significantly improve PFS in PD-L1-positive metastatic TNBC (9.7 *vs.* 5.6 months)[23] (**Table 5**). Similarly,

Table 5 Trials on ICIs in ABC

Trial	Target	Intervention	mPFS *vs.* placebo	mOS *vs.* placebo	Percentage of patients with selected any-grade adverse events (grade ≥ 3 events)
KEYNOTE-355 (NCT02819518)[23]	PD-1	Previously untreated locally recurrent inoperable or metastatic TNBC randomized (2:1) to pembrolizumab plus ChT *vs.* placebo plus ChT	CPS-10 subgroup: 9.7 *vs.* 5.6 months (*HR* 0.66, *95% CI* 0.50–0.88) CPS-1 subgroup: 7.6 *vs.* 5.6 months (*HR* 0.75, *95% CI* 0.62–0.91) ITT: 7.5 *vs.* 5.6 months (*HR* 0.82, *95% CI* 0.70–0.98)	CPS-10 subgroup: 23.0 *vs.* 16.1 months (*HR* 0.73, *95% CI* 0.55–0.95; *P* = 0.0185) CPS-1 subgroup: 17.6 *vs.* 16.0 months (*HR* 0.86, *95% CI* 0.72–1.04; *P* = 0.1125) ITT: 17.2 *vs.* 15.5 months (*HR* 0.89, *95% CI* 0.76–1.05; *P* not tested)	Anemia 49.1% (16.5%) *vs.* 45.9% (14.6%); neutropenia 41.1% (29.7%) *vs.* 38.1% (29.9%); nausea 39.3% (1.6%) *vs.* 41.3% (1.4%); alopecia 33.1% (0.9%) *vs.* 33.5% (1.1%); fatigue 28.6% (2.8%) *vs.* 29.9% (2.5%); neutrophil count decreased 22.4% (17.4%) *vs.* 26.3% (20.3%); alanine aminotransferase increased 20.5% (6.0%) *vs.*16.4% (4.6%).
IMpassion130 (NCT02425891)[24]	PD-L1	Untreated metastatic TNBC randomized (1:1) to atezolizumab plus nab-paclitaxel *vs.* placebo plus nab-paclitaxel	ITT: 7.2 *vs.* 5.5 months (*HR* 0.80, *95% CI* 0.69–0.92; *P* = 0.002) PD-L1 positive: 7.5 *vs.* 5.0 months (*HR* 0.62, *95% CI* 0.49–0.78; *P* < 0.001)	ITT: 21.3 *vs.* 17.6 months (*HR* 0.84, *95% CI* 0.69–1.02; *P* = 0.08) PD-L1 positive: 25.0 *vs.* 15.5 months (*HR* 0.62, *95% CI* 0.45–0.86)	Alopecia 56.4% (0.7%) *vs.* 57.5% (0.2%); nausea 46.0% (1.1%) *vs.* 38.1% (1.8%); cough 24.8% (0.0%) *vs.* 18.9% (0.0%); peripheral neuropathy 21.7% (5.5%) *vs.* 22.1% (2.7%); neutropenia 20.8% (8.2%) *vs.* 15.3% (8.2%); pyrexia 18.8% (0.7%) *vs.* 10.7% (0.0%); hypothyroidism 13.7% (0.0%) *vs.* 3.4% (0.0%).
FUTURE-C-Plus (NCT04129996)[158]	PD-1	Previously untreated advanced immunomodulatory TNBC (CD8 IHC staining ≥ 10%) to famitinib plus camrelizumab plus nab-paclitaxel	13.6 months (*HR* 0.62, *95% CI* 0.49–0.78; *P*< 0.001)	Not reached	Neutropenia 79.2% (33.4%); anemia 20.8% (10.4%); febrile neutropenia 10.4% (10.4%); thrombocytopenia 18.8% (8.4%); fatigue 75.0% (6.3%); anorexia 81.3% (6.3%).

mPFS, median progression-free survival; mOS, median overall survival; TNBC, triple-negative breast cancer; ChT, chemotherapy; CPS, a combined positive score of PD-L1 expression of tumors; HR, hazard ratio; CI, confidence interval; ITT, intention-to-treat population.

in the IMpassion130 trial, atezolizumab combined with nab-paclitaxel has been found to improve PFS in patients with PD-L1-positive TNBC (7.5 *vs.* 5.0 months)[24]. These findings further established immunotherapy as a critical tool for TNBC treatment (**Table 5**).

Preliminary results from Future-C-PLUS have indicated promising increases in overall response rate and PFS with this therapy compared with ICI monotherapy, particularly in difficult-to-treat cases (**Table 5**)[158]. This combination strategy highlights the potential of "immune-priming" approaches to enhance checkpoint inhibitor efficacy across TNBC subtypes and to expand the benefits of immunotherapy to a broader patient population. The study exemplifies the evolving role of combination therapies in precision medicine for TNBC, and underscores the need for continued research into optimizing and individualizing immunotherapy strategies in this aggressive cancer type.

ADCs are advancing TNBC treatment, improving outcomes in advanced, resistant cases

ADCs, which combine monoclonal antibodies with ChT, have become a promising treatment for TNBC. SG, targeting Trop-2, has been particularly effective[159]. In the ASCENT trial, SG has been found to improve PFS (5.6 *vs.* 1.7 months) and OS (12.1 *vs.* 6.7 months) in patients with heavily pretreated metastatic TNBC[134]. ADCs, such as trastuzumab deruxtecan, initially used for HER2+ cancer, are being explored for HER2-low TNBC, and have shown promising early results[160] that may open new avenues for treatment.

Identifying new targets is essential for advanced TNBC

A key component of precision medicine in TNBC is identifying molecular subtypes that exhibit unique biological characteristics and therapeutic vulnerabilities. The Fudan Classification divides TNBC into 4 primary subtypes: basal-like immune-suppressed, basal-like immune-activated, mesenchymal, and luminal androgen receptor[161]. Each subtype has distinct gene expression profiles and pathways that can inform tailored treatment approaches. For example, basal-like immune-activated tumors show signs of immune activation with increased immune cell infiltration and therefore are likely to respond to immunotherapies[161]. In contrast, luminal androgen receptor subtypes express androgen receptor signaling and therefore are candidates for anti-androgen therapies[161]. By aligning treatments with the molecular characteristics of each subtype, precision medicine can maximize efficacy while minimizing unnecessary adverse effects.

Targeted therapies have become a cornerstone of precision medicine in TNBC. Drugs inhibiting specific signaling pathways, such as the PI3K/AKT/mTOR pathway, are being developed for TNBC subgroups with mutations in genes, such as PIK3CA and PTEN[162]. For instance, PI3K inhibitors, such as alpelisib, are being studied in patients with TNBC bearing these genetic alterations[163]. Additionally, PARP inhibitors, including olaparib[164,165] and talazoparib[166,167], have shown success in patients with TNBC with BRCA1 or BRCA2 mutations. In the OlympiAD trial, olaparib, compared with standard ChT, has been found to significantly improve PFS in patients with BRCA-mutated TNBC (7.0 *vs.* 4.2 months)[165]. Similarly, in the EMBRACA trial, talazoparib extended PFS in this subgroup (8.6 *vs.* 5.6 months), thereby confirming the value of PARP inhibitors in BRCA-mutated TNBC[167]. These trials underscore the potential of targeted therapies in precision medicine to extend survival and decrease disease burden for specific TNBC subtypes.

Advancements in precision medicine have transformed the treatment of advanced TNBC, by overcoming historical limitations arising from a lack of therapeutic targets. Immunotherapy, remarkably ICIs, have improved survival in PD-L1-positive TNBC, particularly in combination with ChT. ADCs, such as SG, offer promising options for resistant or metastatic disease. Molecular profiling, such as the Fudan classification, enables tailored treatments with targeted therapies, such as PARP and PI3K inhibitors for specific subgroups. These innovations highlight the growing value of precision medicine in optimizing TNBC management and improving outcomes. Ongoing research will be critical to expanding and refining these strategies.

In conclusion, the precision diagnosis and treatment of breast cancer have made remarkable strides in recent decades (**Figure 1**). Key milestones include the discovery of ER in 1967[38], the approval of tamoxifen in 1977[40], and the identification of HER2 in 1984[136]. The 1990s brought notable breakthroughs, such as the discovery of BRCA1/BRCA2 (1994–1996)[13,14] and the approval of trastuzumab (Herceptin) in 1998[137]. The early 2000s saw the proposal of molecular subtypes in 2000[2], followed by the launch of multi-gene testing tools, such as MammaPrint in 2002[27]. In the 2010s, advancements continued with the approval of therapies such as olaparib in 2014[168] and T-DXd in 2020[144], whereas the use of NGS technology[16] and pembrolizumab[71] further personalized treatment strategies.

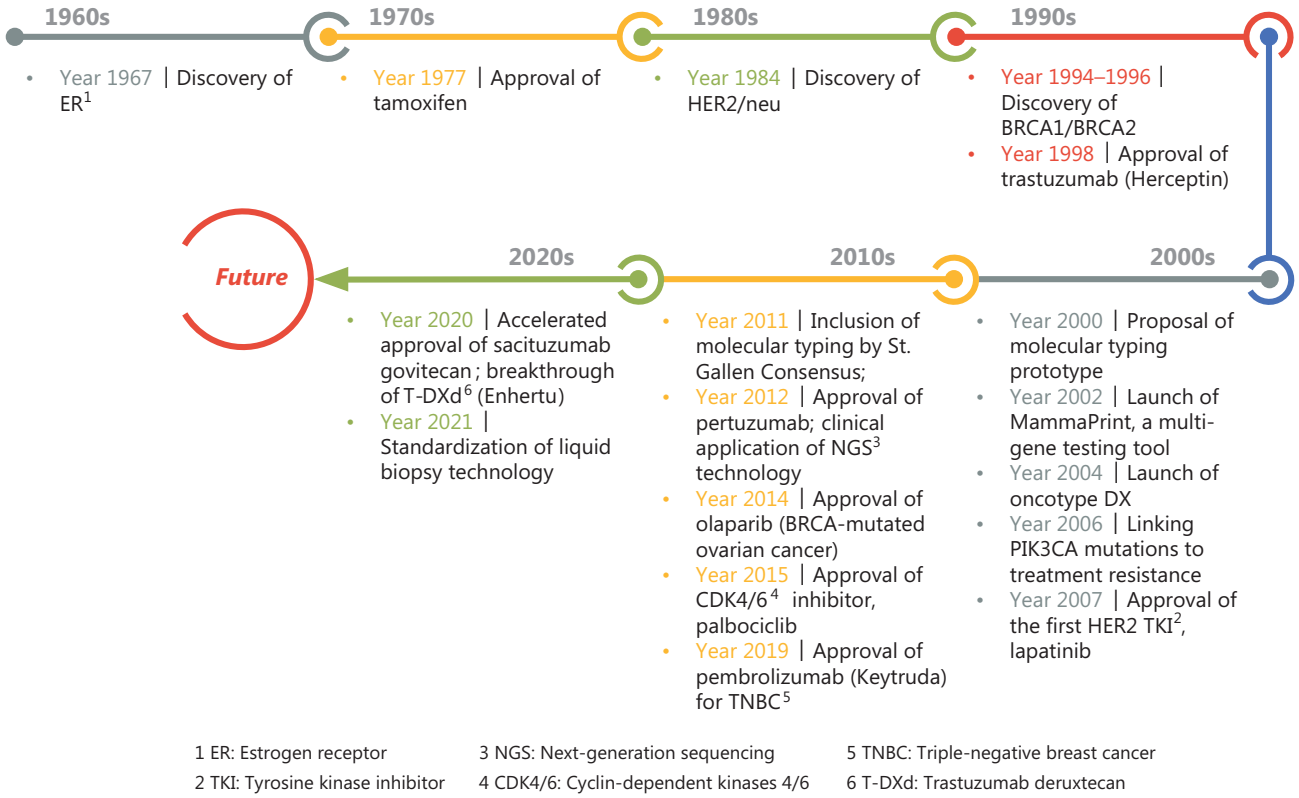

Figure 1 Key milestones in precision medicine for breast cancer.

More recently, the standardization of liquid biopsy technology in 2021[169] marked an important step in non-invasive diagnostics. In the future, emerging technologies including artificial intelligence (AI), multi-omics, molecular imaging, and cell therapy are poised to push breast cancer diagnosis and treatment to even more precise and individualized levels.

The future and emerging frontiers of precision medicine in breast cancer

Although current advancements are reshaping breast cancer diagnosis and treatment, the full potential of precision medicine continues to unfold. Emerging technologies—such as large-scale omics studies[170], AI[171], molecular imaging[172], cell-based therapies[173], and mRNA innovations[174]—are poised to drive transformative breakthroughs that may lead to the next generation of personalized therapies (**Figure 2**). Below, we explore key directions for the evolution of precision medicine in breast cancer and the exciting frontiers that could become the next breakthrough of cancer treatment.

The next breakthrough of breast cancer treatment in the era of precision medicine

Precision medicine has already revolutionized breast cancer treatment, but the next major breakthrough is likely to emerge from integrating large-scale omics data and advanced AI. Analysis of comprehensive molecular, genetic, and phenotypic data should provide unprecedented understanding of breast cancer biology and enable more precise, personalized interventions.

Large-scale omics studies

- Genomics: whole-genome sequencing and whole-exome sequencing are expected to become routinely used to uncover rare mutations, identify new driver genes, and enhance understanding of how genetic alterations (e.g., TP53, BRCA1/2, and PIK3CA) drive cancer progression[175]. These insights should fuel the development of highly targeted therapies that are more effective and less toxic.
- Proteomics and transcriptomics: mapping of protein expression[176-178], post-translational modifications[179], and

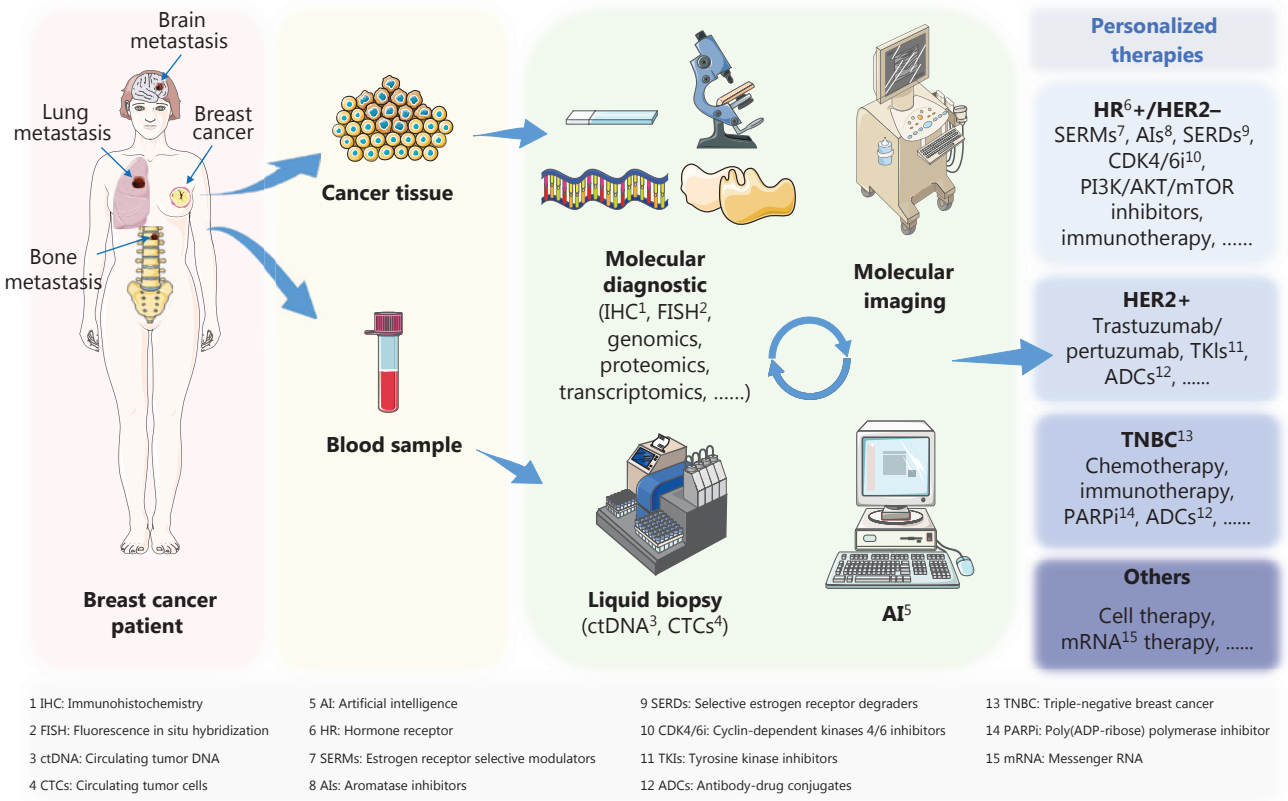

Figure 2 Precision medicine for breast cancer. This figure illustrates a personalized treatment framework that integrates diagnostic and therapeutic strategies for patients with breast cancer, regardless of metastasis presence. Tissue and blood samples are analyzed with immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), multi-omics approaches (genomics, proteomics, and transcriptomics), and liquid biopsy techniques (ctDNA/CTCs). Molecular imaging is used to visualize tumor markers, whereas artificial intelligence (AI) aids in data interpretation and decision-making. On the basis of the molecular subtypes, personalized therapies are tailored, including endocrine therapies with or without CDK4/6 inhibitors for HR+/HER2− tumors, HER2-targeted therapies (e.g., trastuzumab) for HER2+ tumors, ChT or immunotherapy for TNBC, and innovative cell/mRNA-based therapies.

gene expression profiles[180] is expected to further reveal breast cancer's heterogeneity and enable the creation of personalized treatment plans considering the dynamic proteome of a patient's cancer, rather than its genetic makeup alone.

- Metabolomics: investigating metabolic reprogramming in breast cancer cells, such as shifts in glycolysis and oxidative phosphorylation, should lead to the identification of new therapeutic targets and precision therapies tailored to the metabolic vulnerabilities of each tumor[181-184].

AI and machine learning integration

AI is expected to play a crucial role in analyzing the vast data from omics technologies, medical imaging, and patient histories, thereby providing deeper insights into cancer behavior. Key applications include the following:

- Predicting treatment response: machine learning models can predict how breast cancer subtypes will respond to specific treatments, thus enabling earlier optimization of therapy and minimizing adverse effects[185-187].
- Identifying novel targets: AI can identify novel drug targets and biomarkers by analyzing complex genetic[188,189] and proteomic data[190], and can suggest drug repurposing opportunities for specific subtypes of breast cancer[191,192].

Emerging therapies: cell therapies and mRNA innovations

Two of the most exciting frontiers in precision medicine are cell-based therapies and mRNA treatments, particularly for advanced and metastatic breast cancer.

Cell therapies

- Personalized immunotherapy: CAR-T cell therapy, which involves genetically modifying a patient's T cells to target tumor-specific antigens, has revolutionized treatment of hematological cancers[193]. For breast cancer, particularly TNBC, tumor-infiltrating lymphocyte (TIL) therapies have substantial promise[194]. Personalized TIL therapy has the potential to dramatically improve outcomes, particularly in resistant or metastatic cases[195].
- Oncolytic virus therapy: Genetically modified viruses that selectively infect and kill cancer cells are another promising approach. These oncolytic viruses can be engineered to enhance immune responses and can be paired with ICIs, thus providing a multi-pronged strategy to eliminate breast cancer cells[195-198].

mRNA therapies

The success of mRNA vaccines for COVID-19 has paved the way to treatments for cancers including breast cancer.

- mRNA cancer vaccines: These vaccines can be designed to encode tumor-specific antigens that stimulate the immune system to target and destroy cancer cells[199]. Tailoring vaccines to each patient's tumor profile offers a form of personalized immunotherapy[200,201].
- mRNA as therapeutic agents: Beyond vaccines, mRNA-based therapies can directly target cancer by delivering genetic instructions to cells, and enabling them to produce proteins that either inhibit tumor growth or trigger cancer cell death[202]. Although still in the early stages, this approach has substantial promise for treating HR+ and HER2+ breast cancer.

The road to personalized medicine: when and how will it arrive?

Although precision medicine is already influencing breast cancer treatment, fully personalized medicine might require 1 or 2 decades to mature. Key milestones include the following.

Comprehensive genomic profiling

Routine genetic testing, such as NGS of both tumor and normal tissue, is expected to become standard. This testing should help tailor therapies based on somatic mutations and germline mutations, which can influence treatment responses and predispose individuals to cancer[203].

Liquid biopsies

Advances in liquid biopsy technology, which analyzes cancer DNA in blood, should allow for non-invasive monitoring of tumor evolution and therapy response[169]. This monitoring would enable real-time treatment adjustments and early recurrence detection, even before clinical symptoms appear[204].

AI-powered personalized treatment plans

AI systems are expected to integrate genetic, molecular, and clinical data to produce fully personalized treatment plans optimizing efficacy and minimizing toxicity[205,206]. This approach could combine multiple therapies—e.g., ChT, immunotherapy, targeted therapy, and hormone therapy—according to each patient's unique tumor profile.

Molecular imaging

As precision medicine evolves, molecular imaging is expected to become more integrated into breast cancer diagnosis and treatment[207]. Advanced imaging technologies would allow for real-time visualization of tumor molecular features, such as specific receptors[208-212], mutations[213], and metabolic activity[214]. Techniques such as PET scans, magnetic resonance spectroscopy, and optical imaging are expected to enable early detection of tumors, treatment response monitoring, and tumor evolution tracking.

Precision medicine is shaping the future of breast cancer treatment, driven by breakthroughs in omics studies, AI, molecular imaging, and novel therapies, such as cell-based immunotherapies and mRNA treatments. In the coming years, therapies are expected to become increasingly personalized, through tailoring to each individual's genetic, molecular, and immune profile. Although the timeline for widespread personalized medicine is uncertain, we are on the cusp of a revolution promising more targeted, effective, and individualized treatments leading to better outcomes and fewer adverse effects for patients.

Conclusions

Precision medicine has fundamentally transformed breast cancer management by recognizing its molecular heterogeneity and tailoring therapies to distinct disease subtypes[215]. This shift has led to the identification of key mutations, such as BRCA1/2[216] and PIK3CA[217], driving the development of

highly targeted therapies that are more effective and less toxic. Advances in genetic profiling, biomarkers, and technologies, such as liquid biopsies, have significantly enhanced diagnostic accuracy and treatment personalization. Simultaneously, insights into the tumor microenvironment have informed the growth of immunotherapy strategies. These innovations have markedly improved survival rates and quality of life, particularly for patients with challenging subtypes, such as triple-negative and HER2+ breast cancer.

Key advancements in areas including CDK4/6 inhibitors, PARP inhibitors, and ADCs have precisely targeted oncogenic pathways, and improved DFS and OS. The integration of ICIs underscores the increasing importance of immunotherapy in precision oncology. However, challenges such as therapy resistance and the need for reliable predictive biomarkers remain major hurdles in fully harnessing the potential of precision medicine.

Emerging technologies are expected to drive the next wave of breakthroughs. Large-scale omics studies, including genomics, proteomics, and metabolomics, offer comprehensive understanding of breast cancer at the molecular level, and can uncover rare mutations and metabolic pathways that may become therapeutic targets. AI is expected to complement these studies by analyzing complex datasets to predict treatment responses, identify new drug targets, and personalize care for individual patients. Moreover, cell-based therapies, such as CAR-T and TIL therapies, are advancing immunotherapy, particularly for resistant or metastatic cases. Simultaneously, oncolytic viruses offer novel ways to target and destroy cancer cells directly. Moreover, mRNA innovations, inspired by the success of COVID-19 vaccines, promise breakthroughs in personalized cancer vaccines and therapeutic applications, by enabling the immune system to recognize and eliminate tumor-specific antigens[218].

Molecular imaging is likely to become increasingly important in precision medicine, by allowing real-time monitoring of tumor behavior and treatment responses[207]. This monitoring would enable dynamic treatment adjustments and enhanced personalization of therapies, particularly in detecting resistance early and tracking tumor evolution[219]. By integrating AI with molecular imaging, clinicians can create more accurate, individualized treatment plans that optimize efficacy while minimizing adverse effects.

In summary, precision medicine has become a cornerstone of modern breast cancer treatment, by offering more effective, less invasive, and highly personalized care. With the rapid evolution of omics studies, AI, cell-based therapies, mRNA technologies and molecular imaging, the field promises to deliver transformative outcomes that improve survival rates and quality of life for patients at every stage of the disease.

Grant support

This work was supported by grants from the National Natural Science Foundation of China (Grant Nos. 82103614 and 32171363) and Natural Science Foundation of Fujian Province of China (Grant No. 2021J05007). Additionally, it received funding from the start-up fund for Fujian Key Laboratory of Precision Diagnosis and Treatment in Breast Cancer and Xiamen's Key Laboratory of Precision Medicine for Endocrine-Related Cancers, as well as start-up and supporting funds from the Third Affiliated Hospital of Kunming Medical University, Yunnan Cancer Hospital for Guo-Jun Zhang and Jing-Wen Bai, Key Research and development program for social development of Yunnan Science and Technology Department (Grant No. 202403AC100014-2) and horizontal project funding from the Third Affiliated Hospital of Kunming Medical University (Grant Nos. 20233160A0866 and 20243160A0511).

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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Cite this article as: Bai J, Gao Y, Zhang G. The treatment of breast cancer in the era of precision medicine. Cancer Biol Med. 2025; 22: 322-347. doi: 10.20892/j.issn.2095-3941.2024.0510