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EDITORIAL

Precision immunotherapy for breast cancer: from biomarkers to clinical practice

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The landscape of breast cancer treatment has undergone a transformative shift with the integration of immunotherapy. Historically considered a "cold" tumor with limited immunogenicity, breast cancer management was dominated by surgery, chemotherapy, radiotherapy, and targeted therapies[1]. However, the advent of immune checkpoint inhibitors (ICIs) has challenged this paradigm, opening a new frontier. The initial breakthrough in triple-negative breast cancer (TNBC) demonstrated that a subset of patients could derive profound and durable clinical benefit from pembrolizumab and atezolizumab[2,3]. Today, precision immunotherapy aims to identify the patients most likely to respond, to convert immunologically silent tumors into responsive tumors, and to strategically combine immunotherapies with other modalities to overcome resistance. This evolution from empirical application to biomarker-driven strategies marks the critical juncture at which we stand, transitioning promising clinical trial data into refined, effective, and accessible clinical practice[4]. Recent key clinical studies on breast cancer immunotherapy are summarized in **Table 1**.

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Current status of immunotherapy in breast cancer

TNBC: breakthroughs in ICIs and combination strategies

TNBC accounts for 15%–20% of all breast cancers. Patients with TNBC derive limited benefit from endocrine and anti-HER2 targeted therapy due to a lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. However, TNBC exhibits a higher tumor mutational burden (TMB) and greater number of tumor-infiltrating lymphocytes (TILs) compared to other molecular subtypes, which indicates stronger immunogenicity. TNBC also has a higher expression of programmed cell death ligand-1 (PD-L1), suggesting the presence of an active but suppressed antitumor immune response[5]. These characteristics have positioned TNBC as the most intensively studied breast cancer subtype undergoing immunotherapy.

The KEYNOTE-522 study represents a landmark trial in early-stage TNBC immunotherapy. This phase III randomized controlled trial enrolled 1,174 patients with high-risk TNBC to evaluate the efficacy of pembrolizumab combined with neoadjuvant chemotherapy followed by adjuvant pembrolizumab monotherapy[6]. The results showed that the pathologic complete response (pCR) rate was significantly higher in the pembrolizumab group than the placebo group (64.8% *vs.* 51.2%; $P < 0.001$). The final survival data showed a sustained event-free survival (EFS) benefit in the pembrolizumab group [hazard ratio (HR) = 0.65, 95% confidence interval (CI): 0.51–0.83]. More importantly, the overall survival (OS) achieved statistically significant improvement for the first time (HR = 0.66, 95% CI: 0.50–0.87; $P = 0.003$)[7].

The KEYNOTE-355 study established the role of pembrolizumab as first-line treatment of advanced TNBC. This phase III trial enrolled 847 treatment-naïve patients with advanced

Table 1 Summary of key clinical trials in breast cancer immunotherapy

Study	Subtype	Setting	Design	Intervention	Year
KEYNOTE-522	TNBC	Neoadjuvant + adjuvant	Phase III RCT	Pembrolizumab + chemo *vs.* placebo + chemo	2024
KEYNOTE-355	TNBC	Advanced 1L	Phase III RCT	Pembrolizumab + chemo *vs.* placebo + chemo	2022
IMpassion130	TNBC	Advanced 1L	Phase III RCT	Atezolizumab + nab-paclitaxel *vs.* placebo + nab-paclitaxel	2020
IMpassion131	TNBC	Advanced 1L	Phase III RCT	Atezolizumab + paclitaxel *vs.* placebo + paclitaxel	2021
IMpassion132	TNBC	Advanced 1L	Phase III RCT	Atezolizumab + chemo *vs.* placebo + chemo	2024
TORCHLIGHT	TNBC	Advanced 1L	Phase III RCT	Toripalimab + nab-paclitaxel *vs.* placebo + nab-paclitaxel	2024
ASCENT-04	TNBC	Advanced 1L	Phase III RCT	Pembrolizumab + sacituzumab govitecan *vs.* pembrolizumab + chemo	2025
MEDIOLA	gBRCAm BC	Advanced	Phase II single-arm	Olaparib + durvalumab	2020
CheckMate 7FL	HR+/HER2−	Neoadjuvant	Phase III RCT	Nivolumab + chemo *vs.* placebo + chemo	2024
KEYNOTE-756	HR+/HER2−	Neoadjuvant + adjuvant	Phase III RCT	Pembrolizumab + chemo *vs.* placebo + chemo	2024
PANACEA	HER2+	Advanced	Phase II single-arm	Pembrolizumab + trastuzumab	2019
IMpassion050	HER2+	Neoadjuvant	Phase III RCT	Atezolizumab + chemo + dual anti-HER2 *vs.* placebo + chemo + dual anti-HER2	2022
DESTINY-Breast08	HER2+	Advanced 1L	Phase Ib	T-DXd + chemo/endocrine therapy/ICI	2026

1L, first-line; BC, breast cancer; chemo, chemotherapy; gBRCAm, germline BRCA mutation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICIs, immune checkpoint inhibitors; RCT, randomized controlled trial; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer.

TNBC who were randomized to receive pembrolizumab or placebo combined with chemotherapy[8]. The pembrolizumab group in the population with a combined positive score (CPS) ≥ 10 had a significantly prolonged median progression-free survival [PFS] (9.7 months *vs.* 5.6 months, HR = 0.65) and improved median OS (23.0 months *vs.* 16.1 months, HR = 0.73)[9]. The phase 3 TORCHLIGHT trial demonstrated that adding toripalimab to nab-paclitaxel significantly improved survival outcomes with a manageable safety profile in PD-L1-positive patients with advanced TNBC[10]. However, not all ICIs have achieved positive results. The IMpassion130 study initially demonstrated that atezolizumab combined with chemotherapy improved PFS and OS in PD-L1-positive advanced TNBC but the final OS analysis failed to reach the pre-specified statistical threshold[11]. The IMpassion131 study also yielded negative results, failing to demonstrate a PFS or OS benefit. This finding in the IMpassion131 study might represent replacement of the chemotherapy backbone drug with solvent-based paclitaxel and pre-treatment corticosteroids, which might have weakened initiation of anti-tumor immunity and the effect of PD-L1 blockade[12]. The IMpassion131 results were in contrast to the IMpassion130 results, which was based on albumin-bound paclitaxel. IMpassion132 involved a biologically unfavorable, early recurrent TNBC population. Atezolizumab combined with chemotherapy failed to improve OS, even in the PD-L1 positive population (median OS: 15.4 months *vs.* 15.9 months, HR = 1.10). This finding might be because the population is rich in treatment option heterogeneity and immune exclusion/exhaustion phenotypes[13]. In such cases, PD-L1 status alone is insufficient to capture the microenvironment responsive to ICIs.

Metronomic chemotherapy combined with ICIs represents a promising treatment approach. Metronomic chemotherapy (low-dose, high-frequency, continuous administration) can induce immunogenic cell death (ICD) and promote tumor vascular normalization, thereby improving immune cell infiltration. A phase II randomized study evaluated metronomic chemotherapy combined with anti-PD-1 therapy in metastatic breast cancer with preliminary results demonstrating encouraging antitumor activity[14]. Antibody-drug conjugates (ADCs) combined with ICIs represent another strategy of considerable interest. ADCs induce ICD through intracellular release of cytotoxic payloads, thereby promoting tumor antigen release and dendritic cell (DC) maturation, theoretically enhancing ICI efficacy. In the phase III ASCENT-04 study, sacituzumab govitecan combined with pembrolizumab as first-line

treatment for patients with advanced PD-L1-positive TNBC significantly reduced the risk of disease progression or death by 35% compared to chemotherapy combined with pembrolizumab with a manageable safety profile[15]. Poly ADP-ribose polymerase (PARP) inhibitors combined with ICIs also represent an important area of exploration. PARP inhibitors can enhance immunotherapy sensitivity by increasing genomic instability, upregulating tumor cell PD-L1 expression, and activating interferon signaling pathways. The MEDIOLA study evaluated olaparib combined with durvalumab in patients with germline BRCA1/2 mutation (gBRCAm) metastatic breast cancer, achieving an objective response rate (ORR) of 63.3% and a median PFS of 8.2 months[16].

HR+/HER2− breast cancer: unlocking the potential of immunotherapy

Hormone receptor (HR)+/HER2− is the most common breast cancer subtype, accounting for approximately 70% of all breast cancers. Due to a lower TMB, TIL infiltration, and PD-L1 expression, combined with significantly higher collagen deposition compared to TNBC, this subtype was traditionally considered insensitive to immunotherapy. However, recent studies have demonstrated that a subset of HR+/HER2− breast cancers may benefit from immunotherapy, particularly the prominent collagen-rich tumor microenvironment, which underscores the need for innovative strategies to overcome extracellular matrix (ECM) barriers in this subtype.

The CheckMate 7FL study enrolled 510 patients with high-risk HR+/HER2− breast cancer who were randomized to receive nivolumab or placebo combined with neoadjuvant chemotherapy[17]. The primary endpoint analysis showed that the pCR rate was significantly higher in the nivolumab group than the placebo group [24.5% *vs.* 13.8%, odds ratio (OR) = 2.05; $P = 0.0021$]. The KEYNOTE-756 study adopted a similar design, enrolling 1,278 patients with high-risk HR+/HER2− breast cancer to evaluate the efficacy of pembrolizumab combined with neoadjuvant chemotherapy[18]. The pCR rate was also significantly higher in the pembrolizumab group than the placebo group (24.3% *vs.* 15.6%; $P = 0.00005$). These studies demonstrated for the first time that adding ICIs to neoadjuvant chemotherapy for high-risk HR+/HER2− breast cancer can significantly improve pCR rates. However, whether improvements in pCR rates translate into long-term EFS and OS benefits requires longer follow-up. Biomarkers based on tumor stromal characteristics, such as collagen deposition, warrant further exploration to optimize patient stratification strategies.

The exploration of immunotherapy in HR+/HER2- type breast cancer lags behind that in TNBC. The combination of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors with ICIs represents a strategy of considerable interest. CDK4/6 inhibitors can theoretically enhance ICI efficacy through mechanisms, including enhanced tumor antigen presentation, promotion of T-cell infiltration, and modulation of the tumor microenvironment. Multiple clinical studies involving CDK4/6 inhibitors combined with ICIs are ongoing, including the NEWFLAME (palbociclib + nivolumab) and PACE studies (palbociclib + avelumab)[19]. A meta-analysis demonstrated acceptable safety of CDK4/6 inhibitors combined with ICIs in HR+ breast cancer, although the efficacy data require further validation[20]. Notably, the combination of anti-estrogen therapy with ICIs is under exploration. Estrogen signaling can indirectly suppress antitumor immune responses by modulating immune cell function and influencing the tumor ECM. Exploratory analyses from the KEYNOTE-028 and KEYNOTE-086 studies suggested that ER-positive breast cancer patients have a limited response to ICI monotherapy but combination with endocrine therapy may improve efficacy[21]. Currently, multiple combination regimens, including fulvestrant plus pembrolizumab and abemaciclib plus atezolizumab, are under clinical investigation.

HER2+ breast cancer: exploring immune synergistic effects

HER2+ breast cancer accounts for 15%–20% of all breast cancers. The success of anti-HER2 targeted therapy has transformed this subtype from having the poorest prognosis to becoming the subtype with the most abundant treatment options. Interestingly, HER2+ breast cancer exhibits increased TIL infiltration and a relatively high TMB, suggesting potential sensitivity to immunotherapy. More importantly, anti-HER2 monoclonal antibodies can mediate immune cell-mediated tumor killing through antibody-dependent cell-mediated cytotoxicity (ADCC), providing a theoretical rationale for combination with ICIs.

The PANACEA study was the first phase II trial to evaluate pembrolizumab combined with trastuzumab in trastuzumab-resistant HER2+ metastatic breast cancer[22]. The ORR was 15% and the disease control rate (DCR) was 25% in PD-L1-positive tumors, while nearly no responses were observed in PD-L1-negative tumors, suggesting that PD-L1 expression is an important predictor of efficacy. Unfortunately, this study was terminated early at the time of the interim analysis because the addition of atezolizumab failed to improve PFS. Similarly, the IMpassion050 study evaluated atezolizumab combined with neoadjuvant chemotherapy plus dual anti-HER2 therapy in HER2+ early breast cancer and also failed to meet the primary endpoint[23]. These negative results suggested that simply adding ICIs to existing anti-HER2 regimens may be insufficient to provide additional benefit. Indeed, HER2+ breast cancer is highly sensitive to anti-HER2 therapy with limited room for further improvement and other suppressive factors are present in the tumor microenvironment.

ADCs combined with ICIs represent an emerging direction in HER2+ breast cancer immunotherapy.

Trastuzumab deruxtecan (T-DXd) induces ICD through the release of the cytotoxic payload deruxtecan, which promotes tumor antigen release and DC maturation, and theoretically enhancing tumor immunogenicity. In addition, the "bystander effect" of T-DXd can kill heterogeneous tumor cells with low HER2 expression, further releasing neoantigens. The DESTINY-Breast08 study explored T-DXd combined with various treatment regimens (including ICIs) in HER2-low breast cancer[24]. T-DXd combined with endocrine therapy demonstrated favorable efficacy and safety in the HR+/HER2− subgroup. The T-DXd plus ICI cohort is ongoing.

Core strategies for precision immunotherapy

The success of precision immunotherapy hinges on robust biomarkers that accurately predict therapeutic response. Classic biomarkers, such as PD-L1, TMB, and TILs, have provided a foundational framework for patient selection, particularly in TNBC[25]. Microsatellite instability-high (MSI-H) remains a potent predictor across cancer types but is rare in breast cancer[26]. Nevertheless, the predictive power is imperfect, revealing the complexity of the tumor immune microenvironment. Emerging biomarkers are refining our understanding of therapeutic responsiveness in patients with TNBC. Multi-omic classifications, such as the Fudan classification, which integrates genomic and immunologic features, offer a more holistic view of tumor biology[27]. Furthermore, the intratumoral and gut microbiome is emerging as a novel predictive and prognostic factor, influencing both systemic immunity and local therapeutic responses[28]. Based on the interplay between the extracellular matrix and TILs, we propose a novel immuno-collagenic classification for predicting responses to immunotherapy across various solid tumors, including TNBC[29]. The future lies in composite biomarker models that synthesize these diverse data streams.

A central challenge in breast cancer, particularly the HR+/HER2− subtype, is the presence of a profoundly immunosuppressive tumor microenvironment. Effective immunotherapy in this setting therefore requires strategies capable of converting immunologically "cold" tumors into inflamed tumors through rational combinations that enhance antigen presentation, T-cell priming and trafficking, and relieve stromal immune barriers. In this regard, growing evidence underscores the importance of the ECM, especially collagen deposition, as a critical determinant of immune exclusion[30]. Transforming growth factor-beta (TGF-β) signaling and cancer-associated fibroblasts (CAFs) emerge as key orchestrators of this process, shaping a stromal architecture that limits cytotoxic T-cell infiltration. Consistent with this concept, therapeutic interference with TGF-β signaling has been shown to alleviate stromal immune exclusion and enhance the efficacy of immune checkpoint blockade[31].

In addition to a structural role, CAFs display marked phenotypic heterogeneity with distinct immunoregulatory functions. Specific CAF subsets are preferentially enriched in HR+/HER2− tumors and contribute to immune suppression by fostering regulatory T-cell-dominated niches[32]. Single-cell and spatial profiling studies further support the notion that TGF-β-associated fibroblast programs spatially coordinate T-cell exclusion and dysfunction, thereby reinforcing resistance to immunotherapy[33,34]. Importantly, recent data suggest a novel therapeutic axis in HR+/HER2− breast cancer, whereby anti-progestin therapy modulates CAF activity and remodels the ECM, providing a potential molecular rationale for combining endocrine therapy with immunotherapy[35]. Collectively, these findings highlight stromal reprogramming, particularly disruption of the collagen barrier, as a promising strategy to overcome immune exclusion in this disease.

Translational and clinical challenges

The path to precision immunotherapy remains challenging because primary and acquired resistance limit durable clinical benefit and reflect a complex interplay between tumor-intrinsic programs and host-related systemic factors[36]. In parallel, immune-related adverse events (irAEs) constitute a major barrier to broader clinical application, contributing substantially to treatment morbidity, and in rare cases, mortality. irAEs span a wide clinical spectrum, affecting multiple organ systems and often necessitating treatment interruption or immunosuppressive intervention, thereby complicating long-term disease control[37]. Although corticosteroids and selective immunosuppressive agents remain the cornerstone of irAE management, emerging evidence suggests that targeted cytokine modulation, particularly IL-6 receptor blockade, may mitigate toxicity without necessarily compromising, and potentially even enhancing, antitumor immunity[38].

Accordingly, the identification of reliable biomarkers to predict irAE risk has become a key translational priority. Genetic susceptibility, including specific human leukocyte antigen (HLA) genotypes, has been linked to organ-specific irAEs, while pre-existing autoantibodies and dynamic cytokine profiles further reflect an underlying predisposition to immune toxicity[39]. In addition to host-intrinsic factors, the gut microbiome has emerged as an important modulator of ICI-associated inflammation, with distinct microbial signatures correlating with immune-related colitis[40]. Integrating these genetic, serologic, immunologic, and microbial parameters into a unified framework may enable personalized risk stratification and proactive toxicity management, ultimately improving the therapeutic index of immunotherapy in breast cancer.

Despite these challenges, the horizon of immunotherapy in breast cancer is expanding. Novel agents, such as bispecific

antibodies and cellular therapies, are entering clinical investigation, offering new mechanisms of action[41]. Artificial intelligence (AI) and multi-omics technologies are poised to revolutionize precision medicine. A multi-omics machine learning model has been developed that integrates clinical data, digital pathology, and genomic and transcriptomic features to predict pCR to neoadjuvant chemotherapy for breast cancer. Notably, the model identified pre-existing immune infiltration features as key predictors of treatment response[42]. Dynamic monitoring is becoming a prevailing trend. Liquid biopsy based on circulating tumor DNA (ctDNA) enables tracking of clonal evolution and early signs of resistance, while serial imaging combined with radiomics may non-invasively assess changes in the tumor microenvironment[43,44]. These tools support a goal-directed therapeutic strategy, allowing therapeutic adjustments before clinical progression becomes evident.

Conclusions

Precision immunotherapy for breast cancer has evolved into an indispensable component of clinical management. This journey began with landmark success in TNBC and is now progressively expanding to challenge other subtypes. The critical developmental pathway has been delineated. Specifically, the pathway fundamentally relies on the guiding role of biomarkers, the driving effect of combination therapies, and the conceptual framework provided by a deep understanding of the tumor microenvironment. For example, promising strategies targeting the ECM in HR+/HER2− breast cancer exemplify the innovative thinking required to overcome biological barriers. Looking ahead to the next 3–5 years, progress will likely hinge on moving beyond conventional checkpoint blockade toward immune-redirecting and biomarker-steered strategies. Bispecific antibodies and ADC–ICI combinations may broaden benefit by actively recruiting/activating effectors and priming tumors for checkpoint blockade, while spatial multi-omics/AI biomarker and microbiome information strategies should be able to optimize patient selection and enhance treatment efficacy.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Yongmei Yin and Xiang Huang.
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