Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(6): 45995
https://doi.org/10.31083/FBL45995

Review

Molecular Mechanisms and Therapeutic Strategies for Immune Checkpoint Inhibitors in Breast Cancer: From Pathogenesis to Precision Medicine

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Academic Editor: Sukmook Lee
Submitted: 23 August 2025 Revised: 18 November 2025 Accepted: 21 November 2025 Published: 17 June 2026

Abstract

The advent of immunotherapy, and particularly the development of immune checkpoint inhibitors (ICIs), has revolutionized the landscape of breast cancer treatment, especially for triple-negative breast cancer. However, some patients still do not benefit from immunotherapy. Breast cancer is inherently an immunotherapy "cold" tumor, which results in suboptimal clinical outcomes when ICIs are used as monotherapy. Identifying additional immunotherapeutic targets and drugs, along with developing novel strategies for combination therapy, is crucial for addressing the challenges posed by immunotherapy resistance and tumor immune escape driven by multiple mechanisms. For instance, the combination of the programmed cell death protein 1 inhibitor, pembrolizumab, with chemotherapy has demonstrated remarkable clinical efficacy and is now the preferred first-line treatment for neoadjuvant, adjuvant, and metastatic breast cancer. This review discusses recently developed ICIs and focuses on strategies combining ICIs with chemotherapy, targeted therapy, nanotherapy, and other approaches in breast cancer. This review aims to summarize recent advances in immune checkpoint inhibitor-based combination strategies in breast cancer and to provide insights into improving therapeutic efficacy, overcoming treatment resistance, and ultimately enhancing patient outcomes.

Keywords: immune checkpoint inhibitors; breast cancer; chemotherapy; targeted therapy; radiotherapy; phototherapy; microwave ablation; traditional Chinese medicine

1. Introduction

Recent advancements have positioned immunotherapy as a pivotal frontier in oncology, with immune checkpoint inhibitors (ICIs) at the forefront of tumor immunotherapy. Tumor cells can evade immune detection by mimicking immune checkpoint ligands, a mechanism that ICIs counteract by reactivating T lymphocyte responses against tumor cells [1]. The clinical efficacy and safety of ICIs, especially humanized monoclonal antibodies (mAbs), have been substantiated in breast cancer (BC) management. Crucially, Phase III clinical trials, including IMpassion130, KEYNOTE-355, and KEYNOTE-522, have led to regulatory approvals of ICIs in specific settings of triple-negative breast cancer (TNBC). In particular, atezolizumab (initially approved by the U.S. FDA in 2019 for PD-L1-positive metastatic TNBC and withdrawn in 2021) and pembrolizumab (approved for PD-L1-positive metastatic and high-risk early-stage TNBC in 2021) exemplify the evolving landscape of immunotherapy in breast cancer [2]. This review synthesizes preclinical and clinical advances in the use of ICIs in BC, thus underpinning evidence-based clinical decisions and guiding future research.

2. Recent Advances in ICIs

Immune checkpoints are crucial regulatory molecules on immune cells that maintain T-cell activation at optimal levels. The most prominent ICIs include mAbs targeting programmed cell death protein one and its ligand (PD-1/PD-L1), and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) [3], as illustrated in Fig. 1. Recently, emerging ICIs targeting novel checkpoints, such as lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin domain and mucin domain-3 (TIM-3), cluster of differentiation 47 (CD47), T-cell immunoglobulin and ITIM domain (TIGIT), and V-set immunoglobulin domain suppressor of T-cell activation (VISTA), have been intensively investigated in preclinical studies and clinical trials, however, the effectiveness of these agents varies across different clinical contexts.

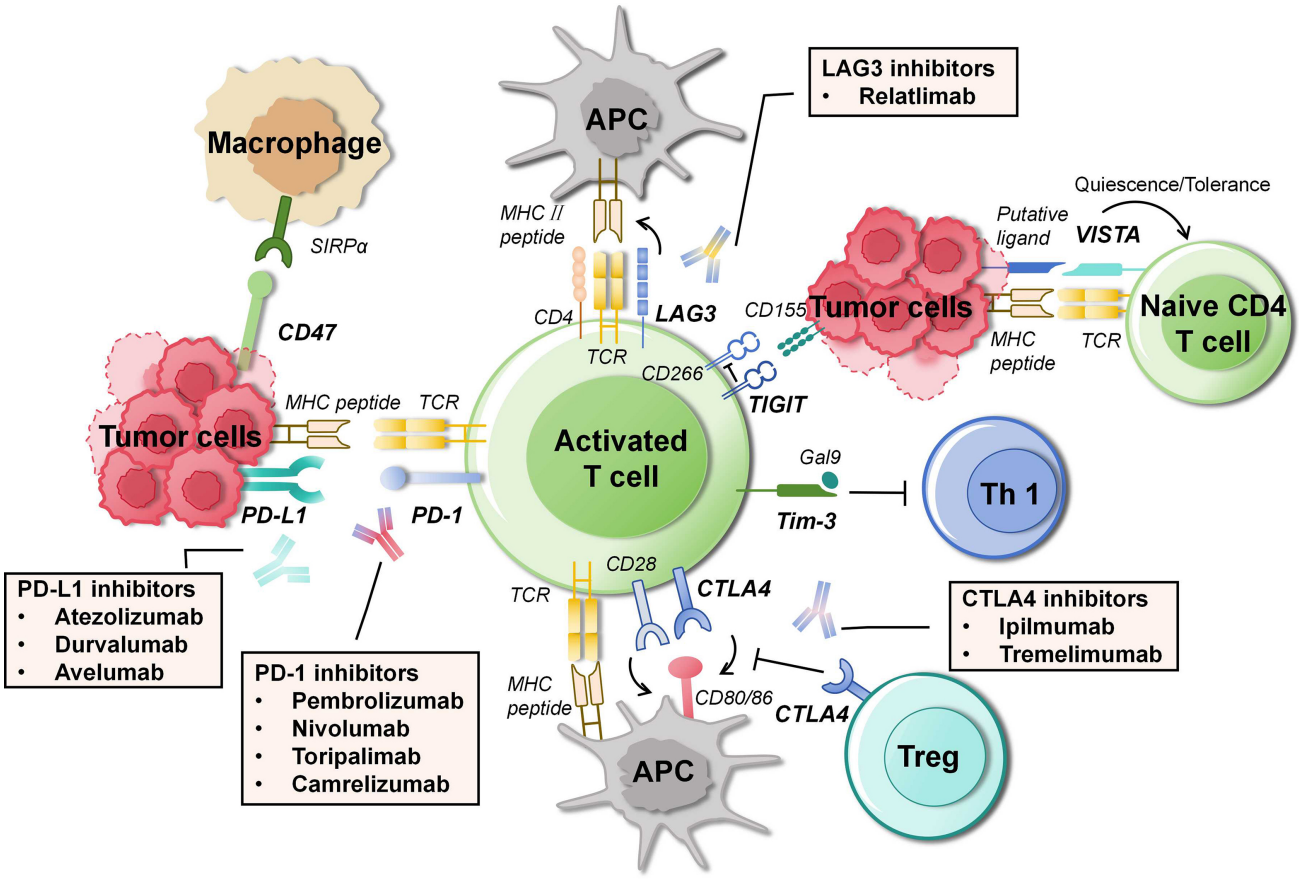

Fig. 1. Mechanisms of action of ICIs. Immune checkpoint inhibitors enhance the body's ability to attack cancer cells by blocking key pathways in the immune system. These drugs primarily target critical immune checkpoint molecules, including PD-1, PD-L1, CTLA-4, and LAG-3, thereby effectively activating the patient's immune response and combating cancer. Arrows indicate activation or binding; blunt-ended lines (T-bars) represent inhibition. Abbreviations: APC, antigen-presenting cell; Treg, regulatory T cell; MHC, major histocompatibility complex; TCR, T-cell receptor; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; LAG-3, lymphocyte activation gene-3; Tim-3, T-cell immunoglobulin domain and mucin domain-3; CD47, cluster of differentiation 47; TIGIT, T-cell immunoglobulin and ITIM domain; VISTA, V-set immunoglobulin domain suppressor of T-cell activation; SIRPα, signal regulatory protein alpha. This figure was created using Microsoft PowerPoint.

2.1 PD-1 and PD-L1 Inhibitors

PD-1, a target of ICIs, is present on immune cells, including activated T cells, and it binds to PD-L1 and PD-L2, which are often overexpressed in tumors. This interaction helps tumors evade the immune system. PD-1/PD-L1 inhibitors disrupt this pathway by enhancing the immune response against tumor cells [4]. These inhibitors differ in their molecular interactions and potential clinical outcomes. Several approved monoclonal antibodies (mAbs) targeting PD-1 and PD-L1 are available, including pembrolizumab and atezolizumab. Unlike PD-1 inhibitors, PD-L1 inhibitors can bind to PD-L1 on both tumor and antigen-presenting cells, thus promoting stronger antitumor immunity. Pembrolizumab is especially effective in BC immunotherapy and is often used with chemotherapy. A meta-analysis revealed greater severe adverse event rates in patients treated with PD-1 inhibitors than in those treated with PD-L1 inhibitors (odds ratio [OR] = 1.58, confidence interval [95% CI]: 1.00–2.54) [5]. Common immune-related adverse effects include hepatitis and colitis. PD-1 inhibitors are typically engineered on an IgG4 backbone, whereas most PD-L1 inhibitors utilize an IgG1 backbone. Although Fc-region differences have been proposed as one contributing factor to toxicity variation, the mechanism remains inconclusive [6].

Recent meta-analyses further comparing the two classes in breast cancer indicate that PD-1 and PD-L1 inhibitors yield similar overall survival outcomes in advanced BC. In contrast, PD-1 inhibitors may offer higher pathological complete response rates in early-stage neoadjuvant settings. Notably, PD-1 inhibitors are associated with more immune-related adverse events, whereas PD-L1 inhibitors tend to show lower toxicity, despite comparable grade $\geq$2 adverse events. These findings provide a more comprehensive understanding of the relative efficacy and safety profiles of the two ICI classes [7].

2.2 CTLA-4 Inhibitors

CTLA-4, an immunosuppressive molecule on activated T cells, binds to CD80/CD86 on dendritic cells (DCs), disrupting T-cell signaling and enhancing immunosuppression via regulatory T cells. CTLA-4 and PD-1 blockades activate T cells at different stages of the immune response, and CTLA-4 inhibitors, such as ipilimumab and tremelimumab, significantly enhance the immune response in the early phases [8]. Ipilimumab, a humanized mAb, is FDA-approved for treating melanoma and shows promise in BC [9]. However, due to broad T-cell activation, ipilimumab can cause distinct immune-related adverse events (irAEs), including anemia, hypothyroidism, diarrhea, fatigue, limb pain, and dyspnea, which may significantly limit its clinical utility [10].

2.3 LAG-3 Inhibitors

LAG-3, an inhibitory receptor on activated T cells, B cells, natural killer (NK) cells, and plasmacytoid DCs, is essential for controlling the antitumor immune response. LAG-3 regulates immunity by engaging with MHC class II molecules to suppress CD4+ T-cell activation [11]. However, soluble LAG-3 variants can enhance the immune response, thus increasing the complexity of their role [12]. Recent discoveries have identified fibrinogen-like protein 1 (FGL1) as a significant ligand for LAG-3, which is highly expressed in cancers [13]. These findings underscore the potential of targeting the FGL1/LAG-3 interaction for the development of new ICI therapies.

LAG-3-targeted therapies are currently divided into two main categories: soluble dimeric LAG-3, which stimulates the immune response, and anti-LAG-3 monoclonal antibodies (mAbs), which block its inhibitory pathway. The soluble LAG-3 fusion protein IMP321 has shown potential as an immune enhancer in early clinical trials, specifically activating CD8+ T cells and offering a novel route for cancer immunotherapy [14]. The expression of LAG-3 on tumor-infiltrating lymphocytes (TILs) has been linked to poor prognosis, but its co-expression with PD-L1 is a promising therapeutic target, especially in BC [15]. It has been reported that in mice receiving anti-PD-1 therapy, LAG-3 expression within TILs increases. This observation suggests that blocking both LAG-3 and PD-1 may work synergistically to improve clinical outcomes. Relatlimab, the first LAG-3-blocking antibody in clinical development, has demonstrated safety in trials, albeit with limited efficacy as a monotherapy. However, the combination of relatlimab and nivolumab, an anti-PD-1 antibody, demonstrated significant antitumor efficacy in the I-SPY2 trial, especially in patients with early-stage human epidermal growth factor 2-negative (HER2–) BC, paving the way for new combination therapies in the field of immunotherapy [16]. Overall, the focus on LAG-3 in BC immunotherapy, especially the combination of relatlimab and nivolumab for HER2– BC, shows promise for improving treatment outcomes.

2.4 TIM-3 Inhibitors

TIM-3 acts as a negative immune regulator and has emerged as a critical target in the landscape of cancer immunotherapy, given its broad expression across various cell types. Its primary ligand, galectin-9, engages with TIM-3 to mediate T-cell exhaustion, thereby impairing immune function [17]. Preclinical models have illuminated the pivotal role of TIM-3 inhibition in amplifying antitumor responses. In particular, combining anti-TIM-3 antibodies with paclitaxel chemotherapy reduces the tumor size in BC mouse models, underscoring the influence of TIM-3 on CD103+ DC functionality and responsiveness to chemotherapy [18].

Several mAbs targeting TIM-3, such as Sym023, LY3321367, and INCAGN2390, are undergoing early clinical trials to explore their efficacy in cancer treatment [19]. Emerging evidence also links TIM-3 upregulation with the development of resistance to PD-1/PD-L1 inhibitors, positioning anti-TIM-3 and PD-1 inhibitor combinations as a research focus to overcome this challenge. However, this ubiquity raises concerns about systemic side effects and toxicities. The pursuit of more precise therapeutic strategies targeting TIM-3 within TILs is pivotal to harness its antitumor potential while minimizing adverse effects, thus paving the way for safer and more effective cancer treatments.

2.5 CD47 Inhibitors

The expression of CD47 on various solid and hematological tumors serves as a “do not eat me” signal by interacting with signal regulatory protein alpha (SIRPα) on macrophages, thereby inhibiting phagocytosis [20]. Targeting the CD47-SIRPα axis is a novel therapeutic approach, with several strategies, including anti-CD47 antibodies, targeted SIRPα antibodies, and CD47-SIRPα fusion proteins, showing promising outcomes in early clinical trials. In addition, the upregulation of CD47 and HER2 is observed during BC radiotherapy (RT), suggesting a new therapeutic approach involving a dual blockade to eliminate RT-resistant BC cells [21]. Despite the promise of CD47-targeted therapies for treating hematological malignancies and BC, common adverse events such as anemia and thrombocytopenia pose challenges due to the presence of CD47 on erythrocytes and platelets, thus underscoring the need for refined strategies to minimize side effects.

2.6 TIGIT Inhibitors

By engaging with three known ligands (CD155, CD112, and CD113), TIGIT can modulate T-cell and NK cell activity, attenuate T-cell activation, and compromise the immune response [22]. TIGIT expression is elevated across a broad spectrum of malignancies, including colorectal cancer, ovarian cancer, BC, and melanoma, and

its expression level is negatively correlated with patient prognosis [23]. Specifically, immunohistochemical analyses of BC samples with bone metastases have indicated the significant roles of TIGIT and interleukin (IL)-1β in promoting metastatic progression [24]. Concurrent inhibition of these targets is a potentially innovative approach for the management of BC bone metastases. The therapeutic potential of targeting TIGIT with monoclonal antibodies (mAbs) is a focal point of both preclinical and clinical cancer immunotherapy research. Notably, the synergistic application of anti-TIGIT and anti-PD-1/PD-L1 antibodies has yielded promising results, indicating enhanced therapeutic outcomes [25]. However, to date, no TIGIT inhibitors have progressed to phase III clinical trials for BC, thus highlighting an urgent need for research and development in this area.

2.7 VISTA Inhibitors

VISTA has structural similarity to the PD-1 ligands PD-L1 and PD-L2, and it is predominantly expressed in myeloid-derived suppressor cells. It is implicated in the immune evasion of various cancers, including lung, kidney, and colorectal cancers. Importantly, studies using mouse models of colorectal cancer have demonstrated that the combined blockade of VISTA and PD-L1 yields significant therapeutic benefits, underscoring the potential of anti-VISTA antibodies in cancer treatment [26]. The promising results from preclinical investigations warrant further research in clinical trials to ascertain the efficacy and safety profile of anti-VISTA therapies in patients with cancer.

3. ICIs Combined With Chemotherapy

The efficacy of ICIs alone in treating BC is modest, but their combination with chemotherapy has shown promise, especially for metastatic TNBC (mTNBC) (Table 1). While the IMpassion130 trial highlighted an increase in median overall survival (OS) with atezolizumab plus nab-paclitaxel (nab-P) in PD-L1-positive patients, the follow-up IMpassion131, which used paclitaxel instead of nab-paclitaxel, did not show a significant OS benefit, revealing regimen-dependent responses [27,28]. The KEYNOTE-355 and TORCHLIGHT trials further demonstrated the potential of combining ICIs with nab-P, which significantly improved outcomes of patients with mTNBC [29,30]. Four randomized controlled trials (RCTs), namely, KEYNOTE-522 [31], IMpassion031 [32], I-SPY2 [33], and GeparNuevo [34], have shown the efficacy of combining ICIs with neoadjuvant chemotherapy, demonstrating higher pathologic complete response (pCR) rates in combination with ICIs plus chemotherapy. This enhanced efficacy trend is further supported by recent phase III trials in high-risk, early-stage ER+/HER2– breast cancer. The CheckMate 7FL and KEYNOTE-756 studies demonstrated improved pathologic complete response (pCR) rates with ICIs combined with anthracycline-based chemotherapy (pCR: 24.5% vs 13.8% and 24.3% vs 15.6%, respectively) [35,36]. However, the IMpassion050 study in HER2+ early breast cancer did not improve pCR rates, confirming that trastuzumab-pertuzumab plus chemotherapy remains the standard of care. Recently, the NeoTRIPaPDL1 trial evaluated neoadjuvant atezolizumab in combination with platinum-based chemotherapy in TNBC, showing encouraging pCR rates, particularly in PD-L1-positive tumors. Although disease-free survival (DFS) data are not yet mature, the study supports further investigation of ICI plus platinum-based regimens as a potential neoadjuvant strategy [37]. The first international metronomic chemotherapy-based ICI strategy adopted a Bayesian adaptive umbrella trial design, evaluating in a phase II trial with 103 enrolled patients. The results suggested not only the promising clinical efficacy of the combination of metronomic VEX chemotherapy (cyclophosphamide, capecitabine, and vinorelbine) and PD-1 blockade (toripalimab) but also a considerable synergistic effect, with promising efficacy signals indicating an OS benefit. Therefore, the combination of ICIs in the treatment of "immuno-cold" tumors, especially BC, is crucial. Different dose regimens or combination strategies may achieve different efficacies even with the same chemotherapeutic agents [38]. These findings suggest that the integration of ICIs with chemotherapy holds promise across various BC types, although the optimal chemotherapeutic agents and patient groups remain to be explored.

4. ICIs Combined With Targeted Therapies

Currently, numerous existing studies have confirmed the synergistic effect of ICIs combined with targeted therapy (Table 2).

4.1 Monoclonal Antibodies

Recent clinical studies indicate heterogeneous results when combining HER2-targeted antibodies with immune checkpoint inhibitors [39]. For advanced HER2-positive disease, the single-arm PANACEA trial reported a 15% response rate in PD-L1-positive patients treated with trastuzumab plus pembrolizumab. In contrast, PD-L1-negative patients derived little benefit, highlighting a potential role for PD-L1 status in patient selection [40]. In early-stage settings, some neoadjuvant regimens that incorporated ICIs (for example, Neo-PATH with atezolizumab) yielded relatively high pCR rates, particularly among patients with PD-L1-positive tumors. In contrast, other trials, such as IMpasion050 and APTneo, did not demonstrate consistent benefit [41–43]. These negative results suggest that the efficacy ceiling of chemotherapy combined with dual HER2-targeted therapy may already be near maximal. That immunotherapy does not necessarily further enhance treatment response in unselected patients. Importantly, the Phase II WSG-KEYRICHED-1 (N = 48) and DTP (N = 39) trials provide early randomized evidence supporting chemotherapy-free neoadjuvant immunotherapy strategies

in HER2-enriched breast cancer. Both studies reported manageable safety profiles without new safety signals, although larger confirmatory trials are needed [44,45]. Collectively, these findings underscore the complexity of integrating ICIs with HER2-targeted therapies in BC treatment, and indicate variable responses based on patients' PD-L1 status and disease stage. Additional research is necessary to identify predictive biomarkers and optimize therapeutic strategies in this setting.

4.2 Small-Molecule Inhibitors

Research has focused on the combination of ICIs and targeted therapies such as poly (adenosine diphosphate (ADP)-ribose) polymerase (PARP) inhibitors [39], cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors [39], phosphoinositide 3-kinase (PI3K) inhibitors [46], and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors [47]. Among these agents, PARP inhibitors have emerged as up-and-coming therapeutic options for treating TNBC. The Phase II MEDIOLA and TOPACIO trials reported the efficacy of combining ICIs (pembrolizumab and durvalumab) with PARP inhibitors (olaparib and niraparib) in advanced TNBC (aTNBC), demonstrating significant clinical benefits [48,49]. The KEYLYNK-009 trial showed that maintenance therapy combining pembrolizumab with olaparib provided superior outcomes for TNBC patients with breast cancer susceptibility gene (BRCA) mutations, prolonging the median progression-free survival (mPFS) to 12.4 months, compared with 8.4 months for patients treated with pembrolizumab plus chemotherapy [50]. The Phase II DORA trial evaluated olaparib with or without the PD-L1 inhibitor durvalumab as a chemotherapy-free maintenance therapy in aTNBC patients with prior platinum-based therapy. The positive results in both groups demonstrated the value of PARP inhibition in maintenance therapy for aTNBC [51]. Positive outcomes of PARP inhibitor combination therapies have also been observed in patients with early-stage and locally advanced TNBC [52]. However, these studies are limited by sample size and trial phase, and their findings remain preliminary pending confirmation in Phase III trials. Additionally, the MARIO-3 study evaluated the combination of eganelisib (a PI3K inhibitor), atezolizumab, and nab-P as a first-line treatment for mTNBC, which showed promising antitumor activity with an objective response rate (ORR) of 55.3% and a disease control rate (DCR) of 84.2% [53]. Similarly, the combination therapy of the ICI camrelizumab with apatinib (an antiangiogenic agent) achieved a significantly greater ORR than either therapy alone, confirming the potential clinical benefit of combining ICIs with antiangiogenic agents [54]. Overall, recent studies have not only suggested that PARP inhibitors, as well as agents such as apatinib and famitinib, may effectively treat TNBC, but have also highlighted the need for personalized medicine due to varied patient responses and potential side effects.

4.3 Antibody-Drug Conjugates

Antibody-drug conjugate (ADC) combinations with ICIs have synergistic effects that promote the activation of immune cells [55]. In the phase II KATE2 trial, researchers evaluated the efficacy of combining atezolizumab with trastuzumab emtansine (T-DM1) in patients with locally advanced or metastatic HER2+ BC. This combination did not significantly enhance PFS in the overall population, but was actively restricted to the PD-L1-positive subgroup [56]. The phase III ASTEFANIA study (T-DM1 $\pm$ atezolizumab in patients with postoperative residual disease) has not yet reported results, and the KATE3 trial was terminated early due to slow enrollment [57,58]. These findings suggest that, despite a strong biological rationale, the combination of ICIs with ADC in HER2-positive breast cancer remains an unmet clinical need. In contrast, HER2-low and TNBC have shown substantially greater sensitivity to ADC-ICI combinations. In the Phase II BEGONIA trial, Cohorts 6 and 7 evaluating trastuzumab deruxtecan (T-DXd) and datopotamab deruxtecan (Dato-DXd) in combination with durvalumab across varying levels of PD-L1 expression, demonstrated moderate but preliminary efficacy. Notably, the combination of T-DXd with ICIs achieved a 56.9% ORR in TNBC patients with low HER2 expression, while first-line Dato-Dxd and ICIs in mTNBC achieved an ORR of 79% and an mPFS of 13.8 months [59]. This combination of ICIs with Dato-Dxd is currently being evaluated in both early and advanced TNBC patients in phase III randomized trials (NCT06112379 and NCT06103864). The ASCENT-04/KEYNOTE-D19 trial further demonstrated that sacituzumab govitecan (SG) combined with pembrolizumab significantly prolonged PFS in PD-L1-positive mTNBC [60]. These data collectively highlight that TNBC is emerging as the leading setting for combining ICI with ADC strategies, signaling a potential shift toward chemo-free, biomarker-guided first-line therapy in this subtype. In hormone receptor-positive breast cancer, clinical evidence for ADC-ICI combination remains limited. The SACI-IO study reported no subtype-specific efficacy improvements and results remain exploratory between SG combined with pembrolizumab, thus reflecting the continued exploration of immunotherapeutic strategies for this challenging disease landscape [61].

5. ICI Two-Drug Combination Therapy

Despite the promise of immunotherapy in oncology, its application as a monotherapy for BC remains limited by suboptimal outcomes. This underscores the need to explore combinational treatments, particularly the integration of ICIs with other therapeutic modalities (Table 3). The Nimbus trial demonstrated that patients with high tumor mutational burden HER2-negative mBC can benefit from the combination of nivolumab and ipilimumab, with a confirmed ORR of 20% [62]. The BELLINI trial, a pioneering

Table 1. Pivotal clinical trials of the combination of ICIs and chemotherapies.

Trial	Phase	N	Setting	Treatment arms vs Control arms	PD-L1 cutoffs	Primary endpoint	Key results	Median follow-up
Neoadjuvant therapy								
KEYNOTE-522 (NCT03036488)	III	1174	eTNBC	(PTXCb-AC/EC) + Pembro vs Placebo → Pembro vs Placebo	22C3 pharmDx; CPS ≥1	pCR, EFS	pCR 64.8 vs 51.2% (95% CI: 5.4–21.8, $p < 0.001$) 5-year EFS 81 vs 72%; 5-year OS 87 vs 82%	75.1 months
IMpassion031 (NCT03197935)	III	333	eTNBC	(nab-P-EC) + Atezo vs Placebo → Atezo vs Placebo	VENTANA; SP142; IC ≥1%	pCR	pCR 57.6 vs 41.1% (95% CI: 6–27, $p < 0.001$) 2-year EFS 85 vs 80%; 2-year OS 95 vs 90%	20.0 months
NSABPB-59/GBG-96-GeparDouze (NCT03281954)	III	1550	eTNBC	(wPTXCb-AC/EC) + Atezo vs Placebo → Atezo vs Placebo	VENTANA; SP142; IC ≥1%	EFS	4-year EFS 85.2 vs 81.9% (HR = 0.80, 95% CI: 0.62–1.03, p = 0.08)	46.9 months
CamRelief (NCT04613674)	III	441	eTNBC	(nab-PCb-EC) + Camre vs Placebo → Camre vs Soc	E1L3N; CPS ≥1	pCR	pCR 56.8 vs 44.7% (95% CI: 3.3–21.2, p = 0.004)	14.4 months
NeoTRIP (NCT02620280)	III	280	eTNBC	(nab-PCb) + Atezo vs nab-PCb	VENTANA; SP142; IC ≥1%	EFS	pCR 48.6 vs 44.4% (OR 1.18, 95% CI: 0.74–1.89, p = 0.48) 5-year EFS 71 vs 75%	54 months
NeoPACT (NCT03639948)	II	115	eTNBC	PTXCb + Pembro	22C3 pharmDx; CPS ≥10	pCR	pCR 58% (95% CI: 48%–67%)	27.4 months
GeparNuevo (NCT02685059)	II	174	eTNBC	Durva vs Placebo – (wnab-P-EC) + Durva vs Placebo	VENTANA SP263; IC/TC ≥1%	pCR	pCR 53 vs 44% (OR 1.45, 95% CI: 0.80–2.63, p = 0.182) 7-year iDFS 73.7 vs 60.7% 7-year OS 91.6 vs 74.7%	86.4 months
TREND (ChiCTR2000035262)	II	44	eTNBC	(nab-P-EC) + Tisleizumab	22C3 pharmDx; CPS ≥20	pCR	pCR 68.18% (30/44)	18.1 months
KEYNOTE-756 (NCT03725059)	III	1278	ER+/HER2–	[(wPTX-AC/EC) → ET] + Pembro vs Placebo	22C3 pharmDx; CPS ≥1	pCR, EFS	pCR 24.3% vs 15.6% (95% CI: 4.2–12.8, p = 0.00005)	33.2 months
CheckMate 7FL (NCT04109066)	III	510	ER+/HER2–	(wPTX-EC) + Nivo vs Placebo → ET + Nivo vs Placebo	VENTANA SP142; IC ≥1%	pCR	pCR 24.5% vs 13.8% (OR = 2.05, 95% CI: 1.29–3.27, p = 0.0021)	1 year (post-surgery)
Adjuvant therapy								
A-BRAVE (NCT02926196)	III	466	eTNBC	Avelumab vs Observation	73-10 RUO; PD-L1-positive ≥21%	DFS (ITT, Stratum B)	3-year DFS ITT: 68.3 vs 63.2% (HR = 0.81, 95% CI: 0.61–1.09, p = 0.172) Stratum B: 66.9 vs 60.7% (HR = 0.66, 95% CI: 0.45–0.97, p = 0.035)	52.1 months

Table 1. Continued.

Trial	Phase	N	Setting	Treatment arms vs Control arms	PD-L1 cutoffs	Primary endpoint	Key results	Median follow-up
IMpassion030 (NCT03498716)	III	2300	eTNBC	(wPTX×12-ddAC/EC×4) + Atezo vs Observation	VENTANA SP142; IC ≥1%	iDFS	iDFS 11.5% vs 10.2% (HR = 1.12, 95% CI: 0.87–1.45, $p = 0.37$)	25 months
Advanced therapy								
IMpassion130 (NCT02425891)	III	902	aTNBC	Nab-P + Atezo vs Placebo	VENTANA SP142; IC ≥1%	PFS, OS (ITT, PD-L1+)	PD-L1+ population: mPFS 7.5 vs 5.0 months (HR = 0.62, 95% CI: 0.49–0.78, $p < 0.0001$) mOS 25.4 vs 17.9 months (HR = 0.67, 95% CI: 0.53–0.86)	18.8 months
IMpassion131 (NCT03125902)	III	651	aTNBC	PTX + Atezo vs Placebo	VENTANA SP142; IC ≥1%	PFS (PD-L1+)	mPFS 6.0 vs 5.7 months (HR = 0.82, 95% CI: 0.60–1.12, $p = 0.20$)	8.8 vs 8.5 months
IMpassion132 (NCT03371017)	III	595	aTNBC	CT + Atezo vs Placebo	VENTANA SP142; IC ≥1%	OS	mOS 12.1 vs 11.2 months (HR = 0.93, 95% CI: 0.73–1.20, $p = 0.59$)	9.8 months
KEYNOTE-355 (NCT02819518)	III	847	aTNBC	CT + Pembro vs Placebo	22C3 pharmDx; CPS ≥1	PFS, OS	CPS ≥10 population: mPFS 9.7 vs 5.6 months (HR = 0.65, 95% CI: 0.49–0.86, $p = 0.001$) mOS 23.0 vs 16.1 months (HR = 0.73, 95% CI: 0.55–0.95, $p = 0.0185$)	44.1 months
TORCHLIGHT (NCT04085276)	III	531	aTNBC	Nab-P + Toripalimab vs Placebo	22C3 pharmDx; CPS ≥1	PFS (ITT, PD-L1+)	PD-L1+ population: mPFS 8.4 vs 5.6 months (HR = 0.65, 95% CI: 0.47–0.91, $p = 0.0102$) mPFS 8.4 vs 6.9 months (HR = 0.77, 95% CI: 0.60–0.99, $p = 0.0445$)	14 months

Abbreviation: eTNBC, early triple negative breast cancer; HER2+, human epidermal growth factor receptor 2-positive; ER+, estrogen receptor-positive; HER2–, human epidermal growth factor receptor 2-negative; aTNBC, advanced triple negative breast cancer; PTXCb-AC/EC, paclitaxel and carboplatin, followed by doxorubicin-cyclophosphamide or epirubicin-cyclophosphamide; Pembro, pembrolizumab; nab-P-EC, nab-paclitaxel followed by doxorubicin and cyclophosphamide; Atezo, atezolizumab; wPTXCb-AC/EC, weekly paclitaxel and every 3 week carboplatin followed by AC/EC; nab-PCb, nab-paclitaxel and carboplatin; Camre, camrelizumab; Durva, durvalumab; ddAC-THP, dose-dense doxorubicin/cyclophosphamide, followed by paclitaxel, and trastuzumab-pertuzumab; ET, endocrine therapy; Nivo, Nivolumab; CT, chemotherapy; CPS, Combined Positive Score; IC, Immune cell; Stratum B, residual invasive carcinoma in the breast and/or axillary lymph nodes; ITT, Intention-to-treat; pCR, pathologic complete response; EFS, event free survival; OS, overall survival; HR, hazard ratio; OR, odds ratio; CI, confidence interval; ORR, objective response rate; iDFS, invasive disease-free survival; DFS, disease-free survival; mPFS, median progression-free survival; mOS, median overall survival. Arrows indicate sequential therapy.

Table 2. Pivotal clinical trials of the combination of ICIs and targeted therapies.

Trial	Phase	N	Setting	Treatment arms vs control arms	PD-L1 cutoffs	Primary endpoint	Key results	Median follow-up
Monoclonal antibodies								
IMpassion050 (NCT03726879)	III	454	HER2+ EBC	[(ddAC-THP) → HP] + Atezo vs Placebo	VENTANA SP142; IC ≥1%	pCR	ITT: pCR 62.4% vs 62.7% (95% CI: –9.2–8.6, $p = 0.9551$) PD-L1+: pCR 72.5% vs 64.2% (95% CI: –20.6–4.0, $p = 0.1846$)	44.2 vs 43.4 months
APTneo (NCT03595592)	III	661	HER2+ EBC	(AC-TCbHP)/TCbHP + Atezo vs TCbHP → HP + Atezo vs HP	VENTANA SP142; Not reported	EFS	pCR 57.8 vs 52.0% (adjHR 1.33, 95% CI: 0.95–1.86, $p = 0.091$)	Not reported
Neo-PATH (NCT03881878)	II	67	HER2+ EBC	THP + Atezo → HP/TDM-1 + Atezo	VENTANA SP142; IC ≥1%	pCR	pCR 61% (90% CI: 50–71)	Not reported
neoHIP (NCT03747120)	II	138	HER2+ EBC	THP + Pembro vs THP	Not reported	pCR	pCR 67.2% vs 48.3% ($p = 0.03$)	Not reported
ABCSG-52/ATHENE EudraCT no. 2019-002364-27	II	58	HER2+ EBC	HP + Atezo vs HP – HP + Atezo + E	VENTANA SP142; IC ≥1%	pCR	pCR 65.5 vs 55.2% (95% CI: –14.7–35.4)	Not reported
WSG-KEYRICHED-1 (NCT03820141)	II	48	HER2+ EBC	HP + Pembro	CPS ≥1	pCR	pCR 47% (20/43, one-sided 95% CI: lower bound 33%, $p = 0.22$)	8.6 months
DTP (NCT03820141)	II	39	HER2+ EBC	HP + Durva	CPS ≥1	pCR	pCR 67.7% (25/37)	Not reported
NRG-BR004 (NCT03199885)	III	190	HER2+ ABC	PTX/T-HP + Atezo vs Placebo	Not reported	PFS	2-year PFS 54.0% vs 45.6% (HR = 0.73, 95% CI: 0.49–1.09, $p = 0.12$)	31.9 months
PANACEA (NCT02129556)	II	52	HER2+ ABC	Pembro + trastuzumab	Not reported	ORR (PD-L1+)	PD-L1+ group: ORR 15% (90% CI: 7–29)	13.6 months
Small molecule inhibitors								
MEDIOLA (NCT02734004)	I/II	34	HER2– MBC (gBRCAm)	Durva + Olaparib	VENTANA SP142; IC ≥1%	12-week DCR	12-week DCR 80% (90% CI: 64.3–90.9) 12-week ORR 63.3% (95% CI: 48.9–80.1)	6.7 months
TOPACIO/KEYNOTE-162 (NCT02657889)	I/II	54	aTNBC	Pembro + Niraparib	Not reported	ORR, DCR	BRCAm: ORR 47% (90% CI 24–70) vs WT: 11% mPFS 8.3 months (95% CI: 2.1–NR)	Not reported
DORA (NCT03167619)	II	45	aTNBC	Durva + Olaparib; Olaparib alone	22C3 pharmDx; CPS ≥10	PFS	mPFS 6.1 months (95% CI: 3.7–10.1, $p < 0.0001$); 4.0 months (95% CI: 2.6–6.1, $p = 0.0023$)	9.8 months
KEYLYNK-009 (NCT04191135)	II	271	aTNBC	Pembro + Olaparib vs Chemo	22C3 pharmDx; CPS ≥1	PFS, OS	mPFS 5.5 vs 5.6 months (HR = 0.98, $p = 0.4556$) OS 25.1 vs 23.4 months (HR = 0.95)	17.2 months

Table 2. Continued.

Trial	Phase	N	Setting	Treatment arms vs control arms	PD-L1 cutoffs	Primary endpoint	Key results	Median follow-up
DOLAF (NCT04053322)	II	172	ER+/HER2– MBC	Durva + Olaparib + FUL	Not reported	24-week PFSR	24-week PFSR 66.7% (95% CI: 58.6–74.1) mPFS 9.3 months (95% CI: 7.5–12.7)	24.6 months
Antibody-drug conjugates								
KATE2 (NCT02924883)	II	202	HER2+ ABC	T-DM1 + Atezo vs Placebo	VENTANA SP142; IC ≥1%	PFS	mPFS 8.2 vs 6.8 months (HR = 0.82, 95% CI: 0.55–1.23, $p = 0.33$)	8.5 vs 8.4 months
ASTEFANIA (NCT04873362)	III	/	HER2+ EBC	T-DM1 + Atezo vs T-DM1	Not reported	iDFS	Ongoing	/
KATE3 (NCT04740918)	III	96	HER2+ ABC	T-DM1 + Atezo vs Placebo	Not reported	PFS, OS	prematurely terminate (Due to low enrollment)	/
BEGONIA, arm 6 (NCT03742102)	Ib/II	58	aTNBC	T-DXd + Durva	SP263; TAP ≥10%	safety and tolerability	ORR 56.9% (95% CI: 43.2–69.8) mPFS 12.6 months (95% CI: 8.3–NC)	13.4 months
BEGONIA, arm 7 (NCT03742102)	Ib/II	62	aTNBC	Dato-DXd + Durva (any PD-L1 expression)	SP263; TAP ≥10%	safety and tolerability	ORR 79% (95% CI: 66.8–88.3), mPFS 14.0 months (95% CI: 11.0–21.1)	35 months
BEGONIA, arm 8 (NCT03742102)	Ib/II	33	aTNBC	Dato-DXd + Durva (PD-L1 high tumours)	SP263; TAP ≥10%	safety and tolerability	ORR 81.8% (95% CI: 64.5–93.0), mPFS: Not mature	10.7 months
ASCENT-04/KEYNOTE-D19 (NCT05382286)	III	443	aTNBC	SG + Pembro vs CT + Pembro	22C3 pharmDx; CPS ≥10	PFS	PD-L1 CPS ≥10 population mPFS 11.2 vs 7.8 months (HR = 0.65, 95% CI: 0.51–0.84, $p = 0.0009$)	14 months
SACI-IO (NCT04468061)	II	110	HR+/HER2– ABC	SG + Pembro vs SG	22C3 pharmDx; CPS ≥1	PFS	mPFS 8.12 vs 6.22 months (HR = 0.76, 95% CI: 0.47–1.23, $p = 0.26$) mOS 16.9 vs 17.1 months (HR = 0.65, 95% CI: 0.30–1.41, $p = 0.28$)	9.2 months

Abbreviation: HER2+, human epidermal growth factor receptor 2-positive; EBC, early breast cancer; ABC, advanced breast cancer; MBC, metastatic breast cancer; HER2–, human epidermal growth factor receptor 2-negative; aTNBC, advanced triple negative breast cancer; gBRCAm, germline BRCA-mutated; ER+, estrogen receptor-positive; HR+, hormone receptor-positive; ddAC-PTXHP, dose-dense doxorubicin and cyclophosphamide, followed by paclitaxel, trastuzumab and pertuzumab; Atezo, atezolizumab; AC-TCbHP, doxorubicin and cyclophosphamide, followed by carboplatin, trastuzumab and pertuzumab; TCbHP, carboplatin, trastuzumab and pertuzumab; HP, trastuzumab + pertuzumab; THP, docetaxel + trastuzumab + pertuzumab; T-DM1, trastuzumab emtansine; Pembro, pembrolizumab; E, epirubicin; Durva, durvalumab; Chemo, chemotherapy; FUL, fulvestrant; PTX, paclitaxel; T-DXd, trastuzumab deruxtecan; Dato-DXd, datopotamab deruxtecan; SG, sacituzumab govitecan; pCR, pathologic complete response; HR, hazard ratio; CI, confidence interval; RCB, residual cancer burden; PFS, progression-free survival; PD-L1, programmed cell death 1 ligand 1; ORR, objective response rate; DCR, disease control rate; WT, wild type; NR, not reached; OS, overall survival; PFSR, progression-free survival rate; mOS, median overall survival; NC, not calculable; TAP, tumor area positivity. Arrows indicate sequential therapy.

Table 3. Pivotal clinical trials of a combination of two ICIs.

Trial	Phase	NCT identifier	Setting	Intervention	Current status	Estimated study completion	Published results
SYNERGY	II	NCT03616886	aTNBC	Durva/Oleclumab vs Durva	Active, not recruiting	2025-12	CBR 43% vs 44% (p = 0.61) mOS 25.1 vs 20.9 months (HR = 0.97, 95% CI: 0.63–1.50, p = 0.90)
BELLINI	II	NCT03815890	eTNBC	Nivo vs Nivo/Ipi	Recruiting	2033-01-01	Immune activation 53.3 vs 60% pCR 33% (5 of 15)
BreastImmune-03	II	NCT03818685	eTNBC	Nivo/Ipi vs Cape	Active, not recruiting	Terminated	biological myocarditis 11 vs 2%
NIMBUS	II	NCT03789110	HER2– MBC	Nivo/Ipi	Completed	/	confirmed ORR 20% (6/30)

Abbreviation: eTNBC, early triple negative breast cancer; HER2–, human epidermal growth factor receptor 2-negative; aTNBC, advanced triple negative breast cancer; MBC, metastatic breast cancer; Durva, Durvalumab; Nivo, Nivolumab; Ipi, Ipilimumab; CBR, Clinical benefit rate; pCR, pathologic complete response; ORR, objective response rate; mOS, median overall survival; HR, hazard ratio.

Table 4. Pivotal clinical trials of the triplet regimen.

Trial	Phase	N	Setting	Treatment arms vs control arms	Primary endpoint and key results
			Neoadjuvant therapy		
BARBICAN (NCT03800836)	II	140	eTNBC	Atezo + Ipat + CT vs Atezo + CT	pCR 49.3 vs 48.5% (OR = 0.87, $p = 0.729$)
I - SPY2 II - (NCT01042379)	II	372	HER2– EBC	Durva + Olarparib + CT vs CT	pCR 37 vs 20%
			First-line therapy		
CO40151 (NCT03800836)	Ib	114	aTNBC	Atezo + Ipat + PTX/nab-P	ORR 54% (95% CI: 44–63%) mPFS 7.2 months (95% CI: 5.5–7.4)
COLET (NCT02322814)	II	63	aTNBC	Atezo + Cobimetinib + PTX vs nab-P	ORR 34.4 (95% CI: 18.57–53.19) vs 29.0% (14.22–48.04)
MARIO-3 (NCT03961698)	II	69	aTNBC	Atezo + Eganelisib + nab-P	CR 16.7%, ORR 66.7% 1-year PFSR 36.0% (95% CI: 23.7%–49.3%)
ATRACTIB (NCT04408118)	II	100	aTNBC	Atezo + Bevacizumab + PTX	mPFS 11 months (95% CI: 9.0–13.4, $p < 0.001$)
WJOG9917B NEWBEAT (UMIN000031043)	II	57	HER2– MBC	Nivolumab + Bevacizumab + PTX	ORR 69.6% (39/56, 95% CI: 55.9–81.2)
SPARK (NCT04734262)	II	37	aTNBC	Cohrt C: Tisle + Sitravatinib + nab-P	ORR 75.7% (28/37, 95% CI: 58.8–88.2)
BETINA (ChiCTR2200058567)	II	30	aTNBC	Tisle + Bevacizumab + nab-P	ORR 73.3% (22/30)
FUTURE-C-Plus, IM (NCT04129996)	II	48	aTNBC (CHINA)	Camrelizumab + Famitinib + nab-P	ORR 81.3% (95% CI: 70.2–92.3) mPFS 13.6 months (95% CI: 8.4–18.8)
FUTURE-SUPER, IM (NCT04395989)	II	139	aTNBC (CHINA)	Camrelizumab + Famitinib + nab-P	mPFS 15.1 vs 6.5 months (HR 0.37, 95% CI: 0.19–0.73)
IPATunity130 (NCT03337724)	III	255	aTNBC (PD-L1+)	Cohort C: Atezo + Ipat + PTX	ORR 55% (95% CI: 38–71) mPFS 6.2 months (95% CI: 5.4–9.2)
IPATunity170 (NCT04177108)	III	115	aTNBC (PD-L1+)	Atezo + Ipat + PTX vs Atezo + PTX	mPFS 5.6 (95% CI: 5.4–9.2) vs 5.7 (95% CI: 4.0–9.1) months mOS NE (95% CI: 14.1–NE) vs 17.2 (13.4–NE) months
			Late line therapy		
NCT04303741	II	46	aTNBC (CHINA)	Camrelizumab + Apatinib + Eribulin	ORR 37.0% (95% CI: 23.2–52.5)
UTILIZABLE	II	25	aTNBC	Tisle + Bevacizumab + UTD1	ORR 52%, DCR 88%
PACE (NCT03147287)	II	220	HR+/HER2– MBC	FUL vs FUL + Palbociclib vs FUL + Palbociclib + Avelumab	mPFS 4.8 vs 4.6 vs 8.1 months F+P+A vs F (HR = 0.75, $p = 0.23$)
NEWFLAME (UMIN000036970)	II	17	HR+/HER2– MBC	Nivo + Abemaciclib + FUL/Letro	Be terminated in advance due to safety issues
Checkmate 7A8 (NCT04075604)	II	21	ER+/HER2– EBC	Nivo + Palbociclib + Anastrozole	Be terminated in advance due to safety issues
DOLAF (NCT04053322)	II	172	ER+/HER2– MBC	Durva + Olaparib + FUL	24-week PFSR 66%

Abbreviation: eTNBC, early triple negative breast cancer; HER2–, human epidermal growth factor receptor 2-negative; EBC, early breast cancer; aTNBC, advanced triple negative breast cancer; MBC, metastatic breast cancer; PD-L1+, programmed cell death ligand 1-positive; HR+, hormone receptor-positive; ER+, estrogen receptor-positive; Atezo, atezolizumab; Ipat, Ipatasertib; CT, chemotherapy; Durva, durvalumab; PTX, paclitaxel; nab-P, nab-Paclitaxel; Tisle, tislelizumab; UTD1, utidelone; FUL, fulvestrant; pCR, pathologic complete response; OR, odds ratio; ORR, objective response rate; DCR, disease control rate; mPFS, median progression-free survival; HR, hazard ratio; F+P+A vs F, fulvestrant+palbociclib+avelumab vs fulvestrant; PFSR, progression-free survival rate; NE, not estimable.

nonrandomized basket study, sought to evaluate the efficacy of nivolumab and ipilimumab in patients with early-stage TNBC. A significant proportion of TNBC patients, especially those with TILs, exhibited marked immunological enhancement as early as 4 weeks following treatment initiation with this chemotherapy-free regimen, suggesting a promising avenue for further investigation [63].

6. Triplet Regimen (ICI + Chemotherapy + Targeted Therapy)

With further in-depth research on immunotherapy, a three-drug combination regimen incorporating chemotherapy and ICIs has been suggested to improve therapeutic efficacy (Table 4). The ATRACTIB trial evaluating atezolizumab and chemotherapy combined with bevacizumab in the first-line treatment of mTNBC showed an mPFS of 11.0 months [64]. In the FUTURE trial, genomic and transcriptomic analyses of a cohort comprising 465 Chinese patients with TNBC revealed four distinct subtypes: luminal androgen receptor (LAR), immunomodulatory (IM), basal-like immune-suppressed (BLIS), and mesenchymal-like (MES) subtypes. This classification underscores the potential for optimizing treatment based on molecular subtypes in TNBC patients. Notably, the FUTURE-C-PLUS trial demonstrated the longest mPFS (13.6 months) of a triplet regimen combining chemotherapy with camrelizumab and famitinib (a multitargeted tyrosine kinase inhibitor), especially in the advanced IM subtype of TNBC [65,66]. Furthermore, the addition of small molecule inhibitors, including an AKT inhibitor (NCT04177108), a PARP inhibitor, and a MEK inhibitor [67], to standard treatments that combine chemotherapy and ICIs has been explored. Although the current three-drug combination regimen has initially shown considerable efficacy, the sample size is small, and larger RCTs are needed.

7. Emerging Directions in ICI-Based Therapies

7.1 ICIs Combined With Radiotherapy

Preclinical studies have demonstrated that the synergistic application of RT and ICIs can significantly enhance the activation of cytotoxic T lymphocytes and modulate the tumor microenvironment (TME), indicating the potential for improved therapeutic outcomes [68]. Exploratory studies have also described the abscopal effect, in which localized radiation induces systemic immune responses that lead to the regression of distant lesions; however, this phenomenon remains anecdotal and hypothesis-generating. In the TONIC trial, patients with mTNBC underwent a 2-week induction phase consisting of conventional chemotherapies (cyclophosphamide, cisplatin, or doxorubicin) or radiotherapy (three doses of 8 Gy), followed by treatment with nivolumab. The induction phase with doxorubicin resulted in an ORR of 35%, whereas RT induction yielded a lower ORR of 8%, suggesting suboptimal timing for the integration of RT with ICIs [69]. Conversely, a phase II clinical trial investigating the combination of pembrolizumab with RT administered within 3 days of each other in patients with mTNBC reported both safety and promising activity, supporting the hypothesis that a hypofractionated RT regimen concurrently used with ICIs might be well tolerated in heavily pretreated mTNBC patients [70]. Further, the use of stereotactic brain radiation therapy combined with ICIs is anticipated to benefit BC patients with brain metastases [71]. Nevertheless, evidence from randomized controlled trials (RCTs) remains limited, and several critical questions remain unresolved. These include determining the optimal sequencing of RT and ICIs (concurrent vs sequential), defining the fractionation schemes that maximize immunogenicity without excessive toxicity, and addressing overlapping adverse events, particularly pneumonitis and dermatitis. While the use of ICIs in conjunction with RT in neoadjuvant and adjuvant settings remains under investigation, current data from metastatic BC provide an essential rationale for further exploration in prospective randomized studies [72].

7.2 ICIs Combined With Nanotechnology

Emerging oncological treatments have increasingly highlighted the combination of less invasive therapies and immunotherapy. Specifically, the integration of phototherapy—encompassing photodynamic and photothermal therapy—with ICIs represents a promising frontier in BC treatment. Phototherapy significantly enhances the immune system's response to tumor cells by inducing immunogenic cell death [73]. This innovative approach has been exemplified by the development of novel nanomaterials designed for photodynamic applications. Notably, a microwave-triggered nanosystem facilitating targeted ozone release demonstrated a remarkable capacity to increase reactive oxygen species production within tumor sites, thereby augmenting the efficacy of anti-PD-1 antibodies in TNBC mouse models [74]. Furthermore, the application of nanotechnology through the deployment of recombinant nanoparticles and Mucin 1 mRNA nanovaccines has been shown to improve drug delivery and biocompatibility, thus underscoring the potential of combining ICIs with nanotechnological innovations to redefine BC treatment [75].

7.3 ICIs Combined With Microwave Ablation

Recent advances in oncological treatments have shown the potent combination of localized thermal therapies and systemic immunotherapy in combating early-stage BC. Microwave ablation (MWA), a minimally invasive technique, has been highlighted for its capacity to elicit a significant systemic antitumor immune response. This technique, when combined with ICIs, provides a promising therapeutic paradigm, emphasizing less invasive yet highly effective strategies for BC management [76]. A noteworthy

development in this arena is a prospective window WOO clinical trial, which was highlighted at the 2023 San Antonio Breast Cancer Symposium. This trial showcased the combined application of camrelizumab—a PD-1 inhibitor developed in China—with MWA, marking a pioneering effort in the early-stage BC treatment landscape. The findings confirm the feasibility and safety of this combination, revealing a mechanism that enhances therapeutic efficacy [77]. Thus, MWA combined with ICIs may be a promising treatment for early-stage BC patients compared with conventional surgery.

7.4 ICIs Combined With Traditional Chinese Medicine

In oncological research, the integration of traditional Chinese medicine (TCM) with ICIs is emerging as a promising avenue for enhancing cancer treatment efficacy while concurrently addressing the challenge of irAEs [78]. This innovative approach leverages the IM properties of TCM to potentiate the effects of ICIs. This synergistic effect has shown promising results in preclinical and clinical settings across a spectrum of malignancies, including lung, breast, colon carcinoma, melanoma, and ovarian cancer [79]. Among the various TCM compounds under investigation, salvianolic acid B plays a role in facilitating endothelial protection and enhancing CD8+ T-cell infiltration within the TME. This action not only restores vascular function but also improves the efficacy of anti-PD-L1 therapies in BC mouse models. Despite the promising outlook, the dual nature of TCM and ICI interactions, which can both enhance immune function and induce irAEs, necessitates further research to fully harness their therapeutic potential.

8. Predictive Biomarkers

8.1 Established Biomarkers

Identification of reliable biomarkers is essential to optimize patient selection and enhance the clinical efficacy of immunotherapy in BC. Currently, PD-L1 IHC is the only biomarker routinely used in clinical practice; however, its predictive value is limited by assay heterogeneity (e.g., 22C3, SP142, SP263, each with different scoring systems, such as CPS vs TPS), variability in cutoff definitions, and interobserver heterogeneity. Therefore, growing efforts have focused on developing novel and integrative biomarkers that better capture the complexity of the tumor immune microenvironment (TIME) [80].

8.2 Tumor-Intrinsic Features

Emerging evidence suggests that tumor mutational burden (TMB) and neoantigen load correlate with increased tumor immunogenicity and favorable responses to ICIs across cancers, including TNBC [81]. However, intertumor heterogeneity and the lack of standardized cutoffs hinder their routine use. Gene expression profiles (GEPs) and T cell–inflamed signatures provide complementary insights into the pre-existing immune activation within tumors [82]. Tumor-infiltrating lymphocytes (TILs) remain one of the most reproducible markers of antitumor immunity, particularly in early-stage TNBC, where high TIL density predicts improved pathological complete response and survival [4]. Meanwhile, circulating biomarkers, such as circulating tumor DNA (ctDNA) and circulating immune cell subsets, offer a noninvasive means of dynamically monitoring immunotherapy response and resistance [83].

8.3 Tumor Microenvironment and Immune Signatures

Emerging multi-omics exploratory biomarkers have enabled unprecedented spatial and temporal mapping of immune - tumor interactions in breast cancer. Spatial multiplex immunofluorescence and single-cell transcriptomics reveal the prognostic relevance of T cell localization, clonal diversity, and immune cell heterogeneity within the tumor microenvironment, providing insights into potential predictors of ICI response [84]. Genomic features, including MHC genotype diversity and defects in antigen presentation machinery, represent underexplored determinants of ICI sensitivity [85]. Metabolomic profiling and microbiome analyses have also emerged as systemic modulators of immunotherapy efficacy, influencing T-cell priming and immune-related adverse events [86,87]. Integrating these multi-omics datasets from tissue, blood, and microbiome sources offers a promising approach to identify novel biomarkers of response and resistance, ultimately guiding personalized ICI treatment strategies. Despite these advances, significant translational barriers persist, including technical variability and a lack of large-scale validation.

8.4 Emerging Multi-Omics Biomarkers

Germline and somatic alterations in DNA repair genes and other key oncogenic pathways may influence antitumor immunity and response to ICIs. Tumors with homologous recombination deficiency (HRD), resulting from defective double-strand DNA repair, exhibit a distinctive mutational landscape. Germline BRCA1/BRCA2 mutations are the most studied aberration causing HRD, and these tumors usually have a two-fold higher TMB than their wild-type counterpart [88]. Notably, individual genes contributing to HRD may confer differential sensitivity to ICI therapy. Data from the IMpassion130 trial indicate that in metastatic TNBC, somatic BRCA1/BRCA2 mutation status did not significantly affect PD-L1 immune cell positivity or clinical outcomes with atezolizumab plus nab-paclitaxel, compared with the overall population [89]. While HRD and BRCA mutations theoretically increase neoantigen load and TIL infiltration, their predictive value in breast cancer remains uncertain. Other somatic mutations, including those in POLE, TP53, PIK3CA, and PTEN, may modulate the tumor immune microenvironment and influence ICI responsiveness [90]. Prospective studies integrating comprehensive germline and somatic genomic profiling with immune

phenotyping are warranted to clarify their potential as predictive biomarkers.

9. Conclusions

We have meticulously examined the evolving role of ICIs in the treatment of BC, emphasizing their integration with various therapeutic strategies. Among the numerous combination regimens, the triplet combination of ICIs, chemotherapy, and small-molecule targeted therapy appears to have potential, although current evidence is still limited. This regimen may offer benefit for patients who have failed first-line treatment for advanced-stage cancer.

Comprehensive translational research and the use of biomarkers are crucial to avoid the development of "add-on designs" where a new immune drug is added to a clinically established modality without adequate strategies for each patient. Currently, only PD-L1 IHC expression is used to select TNBC patients for ICI in BC. However, its application in clinical practice remains controversial and is complicated by the availability of various mAbs, diverse scoring systems, and limited inter-observer agreement in PD-L1 assessment. Further efforts are required to standardize PD-L1 assessment across platforms and clinical settings. In addition, emerging blood-based biomarkers and liquid biopsies may offer a non-invasive approach for predicting and monitoring treatment responses; however, these strategies require further validation. Immunotherapy is associated with unique and sometimes severe irAEs, necessitating multidisciplinary collaborative efforts to manage the increasing number of patients treated with ICI and to address emerging toxicities from new immunotherapy and chemotherapy. Evidence-based guidelines recommend proactive monitoring and early intervention, particularly in breast cancer patients receiving combined modalities. For grade 1 toxicities, ICIs can typically be continued with close observation; however, grade 2 or higher events often require temporary treatment interruption and initiation of corticosteroids. Severe manifestations such as pneumonitis, hepatitis, or colitis may warrant high-dose steroids and, if refractory, additional immunosuppressive agents. Since some irAEs can overlap with chemotherapy-related toxicities, routine assessment of thyroid function, liver enzymes, and respiratory symptoms is essential. Real-world evidence is still needed to refine risk stratification and long-term management strategies. To more accurately evaluate the efficacy of ICIs and identify the benefit population, the Immune Response Evaluation Criteria in Solid Tumors (iRECIST) has been developed as an extension of RECIST and is increasingly used in clinical trials as a complementary framework. While RECIST remains the standard in routine clinical practice, iRECIST may provide additional value in research settings and selected clinical scenarios involving immune checkpoint inhibitors.

In summary, the clinical research landscape of immunotherapy in BC continues to evolve with the introduction of novel investigational therapies. However, the long-term clinical benefit, optimal treatment combinations, and appropriate patient selection remain uncertain and warrant further investigation in ongoing trials.

Abbreviations

ADC, antibody-drug conjugate; aTNBC, advanced TNBC; BC, breast cancer; BLIS, basal-like immune-suppressed; BRCA, breast cancer susceptibility gene; CD47, cluster of differentiation 47; CDK4/6, cyclin-dependent kinase 4 and 6 inhibitors; ctDNA, circulating tumor DNA; CTLA-4, cytotoxic T-lymphocyte antigen-4; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DCs, dendritic cells; DFS, disease-free survival; ER+, estrogen receptor-positive; FDA, Food and Drug Administration; FGL1, fibrinogen-like protein 1; HRD, homologous recombination deficiency; HER2, human epidermal growth factor 2; HER2–, HER2-negative; HER2+, HER2-positive; GEPs, Gene expression profiles; ICIs, Immune checkpoint inhibitors; IL-1β, interleukin-1β; IM, immunomodulatory; LAG-3, lymphocyte activation gene-3; LAR, luminal androgen receptor; IrAEs, immunotherapy-related adverse reactions; mAbs, monoclonal antibodies; MEK, mitogen-activated extracellular signal-regulated kinase; MES, mesenchymal-like; mTNBC, metastatic triple-negative breast cancer; MWA, Microwave ablation; nab-P, nab-paclitaxel; NK, natural killer; OS, overall survival; ORR, objective response rate; PARP, poly (adenosine diphosphate (ADP)-ribose) polymerase; pCR, pathologic complete response; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PFS, progression-free survival; RCTs, randomized controlled trials; RT, radiotherapy; SG, Sacituzumab Govitecan; SIRRP α, signal regulatory protein α; TCM, traditional Chinese medicine; TIME, tumor immune microenvironment; T-DM1, Trastuzumab Emtansine; T-DXd, trastuzumab deruxtecan; TMB, tumor mutational burden; Deruxtecan; TIGIT, T cell immunoglobulin and ITIM domain protein; TILs, tumor infiltrating lymphocytes; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; TME, tumor microenvironment; TNBC, triple negative breast cancer; VISTA, V-domain Ig suppressor of T-cell activation.

Author Contributions

XMJ and QPZ performed the literature search. XQW wrote the first draft of the manuscript and prepared the figures. CMX, KNW, and ML contributed to the conceptualization of the study and critically revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was funded by the National Natural Science Foundation of China (grant number 82473449), the Dalian Medical University Interdisciplinary Research Cooperation Project Team Funding (grant number JHCZ2023009) of ML, and the Basic Scientific Research Project of Higher Education Institutions of Liaoning Provincial Department of Education (grant number LJ212410161030), Dalian Medical Science Research Program (grant number 2312017) of KNW.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Ren Y, Song J, Li X, Luo N. Rationale and Clinical Research Progress on PD-1/PD-L1-Based Immunotherapy for Metastatic Triple-Negative Breast Cancer. International Journal of Molecular Sciences. 2022; 23: 8878. https://doi.org/10.3390/ijms23168878.

[2] Tang S, Ning Q, Yang L, Mo Z, Tang S. Mechanisms of immune escape in the cancer immune cycle. International Immunopharmacology. 2020; 86: 106700. https://doi.org/10.1016/j.intimp.2020.106700.

[3] Keenan TE, Tolaney SM. Role of Immunotherapy in Triple-Negative Breast Cancer. Journal of the National Comprehensive Cancer Network. 2020; 18: 479–489. https://doi.org/10.6004/jnccn.2020.7554.

[4] Emens LA. Breast Cancer Immunotherapy: Facts and Hopes. Clinical Cancer Research. 2018; 24: 511–520. https://doi.org/10.1158/1078-0432.CCR-16-3001.

[5] Wang Y, Zhou S, Yang F, Qi X, Wang X, Guan X, *et al*. Treatment-Related Adverse Events of PD-1 and PD-L1 Inhibitors in Clinical Trials: A Systematic Review and Meta-analysis. JAMA Oncology. 2019; 5: 1008–1019. https://doi.org/10.1001/jamaoncol.2019.0393.

[6] Yu J, Song Y, Tian W. How to select IgG subclasses in developing anti-tumor therapeutic antibodies. Journal of Hematology & Oncology. 2020; 13: 45. https://doi.org/10.1186/s13045-020-00876-4.

[7] Xie X, Chen L, Kong X, Huo Y, Huang W, Huang J, *et al*. Comparative efficacy and safety of PD-1 versus PD-L1 inhibitors in breast cancer treatment: A systematic review and meta analysis. International Journal of Cancer. 2025; 156: 1936–1949. https://doi.org/10.1002/ijc.35313.

[8] Zhao Y, Lee CK, Lin CH, Gassen RB, Xu X, Huang Z, *et al*. PD-L1:CD80 Cis-Heterodimer Triggers the Co-stimulatory Receptor CD28 While Repressing the Inhibitory PD-1 and CTLA-4 Pathways. Immunity. 2019; 51: 1059–1073.e9. https://doi.org/10.1016/j.immuni.2019.11.003.

[9] Polk A, Svane IM, Andersson M, Nielsen D. Checkpoint inhibitors in breast cancer-Current status. Cancer Treatment Reviews. 2018; 63: 122–134. https://doi.org/10.1016/j.ctrv.2017.12.008.

[10] Zhang H, Mi J, Xin Q, Cao W, Song C, Zhang N, *et al*. Recent research and clinical progress of CTLA-4-based immunotherapy for breast cancer. Frontiers in Oncology. 2023; 13: 1256360. https://doi.org/10.3389/fonc.2023.1256360.

[11] Maruhashi T, Sugiura D, Okazaki IM, Shimizu K, Maeda TK, Ikubo J, *et al*. Binding of LAG-3 to stable peptide-MHC class II limits T cell function and suppresses autoimmunity and anticancer immunity. Immunity. 2022; 55: 912–924.e8. https://doi.org/10.1016/j.immuni.2022.03.013.

[12] Maruhashi T, Okazaki IM, Sugiura D, Takahashi S, Maeda TK, Shimizu K, *et al*. LAG-3 inhibits the activation of $CD4^+$ T cells that recognize stable pMHCII through its conformation-dependent recognition of pMHCII. Nature Immunology. 2018; 19: 1415–1426. https://doi.org/10.1038/s41590-018-0217-9.

[13] Lecocq Q, Awad RM, De Vlaeminck Y, de Mey W, Ertveldt T, Goyvaerts C, *et al*. Single-Domain Antibody Nuclear Imaging Allows Noninvasive Quantification of LAG-3 Expression by Tumor-Infiltrating Leukocytes and Predicts Response of Immune Checkpoint Blockade. Journal of Nuclear Medicine. 2021; 62: 1638–1644. https://doi.org/10.2967/jnumed.120.258871.

[14] Sauer N, Szlasa W, Jonderko L, Oślizło M, Kunachowicz D, Kulbacka J, *et al*. LAG-3 as a Potent Target for Novel Anticancer Therapies of a Wide Range of Tumors. International Journal of Molecular Sciences. 2022; 23: 9958. https://doi.org/10.3390/ijms23179958.

[15] Wang Y, Dong T, Xuan Q, Zhao H, Qin L, Zhang Q. Lymphocyte-Activation Gene-3 Expression and Prognostic Value in Neoadjuvant-Treated Triple-Negative Breast Cancer. Journal of Breast Cancer. 2018; 21: 124–133. https://doi.org/10.4048/jbc.2018.21.2.124.

[16] Isaacs C, Nanda R, Chien J, Trivedi MS, Stringer-Reasor E, Vaklavas C, *et al*. Abstract GS5-03: Evaluation of anti-PD-1 Cemiplimab plus anti-LAG-3 REGN3767 in early-stage, high-risk HER2-negative breast cancer: Results from the neoadjuvant I-SPY 2 TRIAL. Cancer Research. 2023; 83: GS5-03. https://doi.org/10.1158/1538-7445.SABCS22-GS5-03.

[17] Yang R, Sun L, Li CF, Wang YH, Yao J, Li H, *et al*. Galectin-9 interacts with PD-1 and TIM-3 to regulate T cell death and is a target for cancer immunotherapy. Nature Communications. 2021; 12: 832. https://doi.org/10.1038/s41467-021-21099-2.

[18] de Mingo Pulido Á, Gardner A, Hiebler S, Soliman H, Rugo HS, Krummel MF, *et al*. TIM-3 Regulates $CD103^+$ Dendritic Cell Function and Response to Chemotherapy in Breast Cancer. Cancer Cell. 2018; 33: 60–74.e6. https://doi.org/10.1016/j.ccell.2017.11.019.

[19] Gomes de Morais AL, Cerdá S, de Miguel M. New Checkpoint Inhibitors on the Road: Targeting TIM-3 in Solid Tumors. Current Oncology Reports. 2022; 24: 651–658. https://doi.org/10.1007/s11912-022-01218-y.

[20] Huang CY, Ye ZH, Huang MY, Lu JJ. Regulation of CD47 expression in cancer cells. Translational Oncology. 2020; 13: 100862. https://doi.org/10.1016/j.tranon.2020.100862.

[21] Candas-Green D, Xie B, Huang J, Fan M, Wang A, Menaa C, *et al*. Dual blockade of CD47 and HER2 eliminates radioresistant breast cancer cells. Nature Communications. 2020; 11: 4591. https://doi.org/10.1038/s41467-020-18245-7.

[22] Ziegler AE, Fittje P, Müller LM, Ahrenstorf AE, Hagemann K, Hagen SH, *et al*. The co-inhibitory receptor TIGIT regulates NK cell function and is upregulated in human intrahepatic $CD56^{bright}$ NK cells. Frontiers in Immunology. 2023; 14: 1117320. https://doi.org/10.3389/fimmu.2023.1117320.

[23] Ge Z, Peppelenbosch MP, Sprengers D, Kwekkeboom J. TIGIT, the Next Step Towards Successful Combination Immune Checkpoint Therapy in Cancer. Frontiers in Immunology. 2021; 12: 699895. https://doi.org/10.3389/fimmu.2021.699895.

[24] Monteran L, Ershaid N, Scharff Y, Zoabi Y, Sanalla T, Ding Y, *et al*. Combining TIGIT Blockade with MDSC Inhibition

Hinders Breast Cancer Bone Metastasis by Activating Antitumor Immunity. Cancer Discovery. 2024; 14: 1252–1275. https://doi.org/10.1158/2159-8290.CD-23-0762.

[25] Dixon KO, Schorer M, Nevin J, Etminan Y, Amoozgar Z, Kondo T, *et al*. Functional Anti-TIGIT Antibodies Regulate Development of Autoimmunity and Antitumor Immunity. Journal of Immunology. 2018; 200: 3000–3007. https://doi.org/10.4049/jimmunol.1700407.

[26] Chen L, Bu X, Sun Y, Huang D, Chen Y, Hou T, *et al*. Targeted destruction of VISTA boosts anti-tumor immunotherapy. Cell Research. 2025; 35: 987–1002. https://doi.org/10.1038/s41422-025-01194-5.

[27] Schmid P, Rugo HS, Adams S, Schneeweiss A, Barrios CH, Iwata H, *et al*. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology. 2020; 21: 44–59. https://doi.org/10.1016/S1470-2045(19)30689-8.

[28] Miles D, Gligorov J, André F, Cameron D, Schneeweiss A, Barrios C, *et al*. Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. Annals of Oncology. 2021; 32: 994–1004. https://doi.org/10.1016/j.annonc.2021.05.801.

[29] Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, *et al*. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020; 396: 1817–1828. https://doi.org/10.1016/S0140-6736(20)32531-9.

[30] Jiang Z, Ouyang Q, Sun T, Zhang Q, Teng Y, Cui J, *et al*. Toripalimab plus nab-paclitaxel in metastatic or recurrent triple-negative breast cancer: a randomized phase 3 trial. Nature Medicine. 2024; 30: 249–256. https://doi.org/10.1038/s41591-023-02677-x.

[31] Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, *et al*. Pembrolizumab for Early Triple-Negative Breast Cancer. The New England Journal of Medicine. 2020; 382: 810–821. https://doi.org/10.1056/NEJMoa1910549.

[32] Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, *et al*. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020; 396: 1090–1100. https://doi.org/10.1016/S0140-6736(20)31953-X.

[33] Nanda R, Liu MC, Yau C, Shatsky R, Pusztai L, Wallace A, *et al*. Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer: An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial. JAMA Oncology. 2020; 6: 676–684. https://doi.org/10.1001/jamaoncol.2019.6650.

[34] Loibl S, Untch M, Burchardi N, Huober J, Sinn BV, Blohmer JU, *et al*. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Annals of Oncology. 2019; 30: 1279–1288. https://doi.org/10.1093/annonc/mdz158.

[35] Loi S, Curigliano G, Salgado RF, Diaz RR, Delaloge S, Rojas C, *et al*. LBA20 A randomized, double-blind trial of nivolumab (NIVO) vs placebo (PBO) with neoadjuvant chemotherapy (NACT) followed by adjuvant endocrine therapy (ET) ± NIVO in patients (pts) with high-risk, ER+ HER2- primary breast cancer (BC). Annals of Oncology. 2023; 34: S1259–S1260. https://doi.org/10.1016/j.annonc.2023.10.010.

[36] Cardoso F, McArthur HL, Schmid P, Cortés J, Harbeck N, Telli ML, *et al*. LBA21 KEYNOTE-756: Phase III study of neoadjuvant pembrolizumab (pembro) or placebo (pbo) + chemotherapy (chemo), followed by adjuvant pembro or pbo + endocrine therapy (ET) for early-stage high-risk ER+/HER2- breast cancer. Annals of Oncology. 2023; 34: S1260–S1261. https://doi.org/10.1016/j.annonc.2023.10.011.

[37] Gianni L, Huang CS, Egle D, Bermejo B, Zamagni C, Thill M, *et al*. Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple-negative, early high-risk and locally advanced breast cancer: NeoTRIP Michelangelo randomized study. Annals of Oncology. 2022; 33: 534–543. https://doi.org/10.1016/j.annonc.2022.02.004.

[38] Mo H, Sun X, Zhai J, Han J, Ge H, Wei Y, *et al*. 99P Efficacy and safety of toripalimab plus metronomic chemotherapy in HER2-negative metastatic breast cancer. Immuno-Oncology and Technology. 2023; 20: 100571. https://doi.org/10.1016/j.iotech.2023.100571.

[39] Zhu WY, Jin XY. A narrative review of combination therapy of PD-1/PD-L1 blockade with standard approaches for the treatment of breast cancer: clinical application and immune mechanism. Annals of Palliative Medicine. 2021; 10: 10075–10082. https://doi.org/10.21037/apm-21-2062.

[40] Loi S, Giobbie-Hurder A, Gombos A, Bachelot T, Hui R, Curigliano G, *et al*. Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA): a single-arm, multicentre, phase 1b-2 trial. The Lancet Oncology. 2019; 20: 371–382. https://doi.org/10.1016/S1470-2045(18)30812-X.

[41] Ahn HK, Sim SH, Suh KJ, Kim MH, Jeong JH, Kim JY, *et al*. Response Rate and Safety of a Neoadjuvant Pertuzumab, Atezolizumab, Docetaxel, and Trastuzumab Regimen for Patients With ERBB2-Positive Stage II/III Breast Cancer: The NeoPATH Phase 2 Nonrandomized Clinical Trial. JAMA Oncology. 2022; 8: 1271–1277. https://doi.org/10.1001/jamaoncol.2022.2310.

[42] Huober J, Barrios CH, Niikura N, Jarząb M, Chang YC, Huggins-Puhalla SL, *et al*. Atezolizumab With Neoadjuvant Anti-Human Epidermal Growth Factor Receptor 2 Therapy and Chemotherapy in Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer: Primary Results of the Randomized Phase III IMpassion050 Trial. Journal of Clinical Oncology. 2022; 40: 2946–2956. https://doi.org/10.1200/JCO.21.02772.

[43] Gianni L, Munzone E, Mansutti M, Bianchini G, Izarzuzaga Y, Caremoli ER, *et al*. Abstract LBO1-02: Pathologic complete response (pCR) of neoadjuvant therapy with or without atezolizumab in HER2-positive, early high-risk and locally advanced breast cancer: APTneo Michelangelo randomized trial. Cancer Research. 2024; 84: LBO1-02. https://doi.org/10.1158/1538-7445.SABCS23-LBO1-02.

[44] Kuemmel S, Graeser M, Schmid P, Reinisch M, Feuerhake F, Volk V, *et al*. Chemotherapy-free neoadjuvant pembrolizumab combined with trastuzumab and pertuzumab in HER2-enriched early breast cancer (WSG-KEYRICHED-1): a single-arm, phase 2 trial. The Lancet Oncology. 2025; 26: 629–640. https://doi.org/10.1016/S1470-2045(25)00097-X.

[45] Niravath P, Li M, Guan J, Qian W, Nikolo F, Deng J, *et al*. Abstract RF1-07: Multifactor analysis for pathologic complete response (pCR) in a chemotherapy-free regimen of durvalumab, trastuzumab, and pertuzumab (DTP Trial) in HER2-enriched early breast cancer. Clinical Cancer Research. 2025; 31: RF1-07. https://doi.org/10.1158/1557-3265.SABCS24-RF1-07.

[46] Pascual J, Turner NC. Targeting the PI3-kinase pathway in triple-negative breast cancer. Annals of Oncology. 2019; 30:

1051–1060. https://doi.org/10.1093/annonc/mdz133.
[47] Cheng Y, Tian H. Current Development Status of MEK Inhibitors. Molecules. 2017; 22: 1551. https://doi.org/10.3390/molecules22101551.
[48] Vinayak S, Tolaney SM, Schwartzberg L, Mita M, McCann G, Tan AR, *et al*. Open-label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic Triple-Negative Breast Cancer. JAMA Oncology. 2019; 5: 1132–1140. https://doi.org/10.1001/jamaoncol.2019.1029.
[49] Domchek SM, Postel-Vinay S, Im SA, Park YH, Delord JP, Italiano A, *et al*. Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study. The Lancet Oncology. 2020; 21: 1155–1164. https://doi.org/10.1016/S1470-2045(20)30324-7.
[50] Rugo H, Robson M, Im SA, Dalenc F, Ruiz EY, Im YH, *et al*. Abstract GS01-05: Pembrolizumab + Olaparib vs Pembrolizumab + Chemotherapy After Induction With Pembrolizumab + Chemotherapy for Locally Recurrent Inoperable or Metastatic TNBC: Randomized Open-Label Phase 2 KEYLYNK-009 Study. Cancer Research. 2024; 84: GS01-05. https://doi.org/10.1158/1538-7445.SABCS23-GS01-05.
[51] Tan TJ, Sammons S, Im YH, She L, Mundy K, Bigelow R, *et al*. Phase II DORA Study of Olaparib with or without Durvalumab as a Chemotherapy-Free Maintenance Strategy in Platinum-Pretreated Advanced Triple-Negative Breast Cancer. Clinical Cancer Research. 2024; 30: 1240–1247. https://doi.org/10.1158/1078-0432.CCR-23-2513.
[52] Pusztai L, Yau C, Wolf DM, Han HS, Du L, Wallace AM, *et al*. Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: Results from the adaptively randomized I-SPY2 trial. Cancer Cell. 2021; 39: 989–998.e5. https://doi.org/10.1016/j.ccell.2021.05.009.
[53] Hatem S, Hargis J, Elias A, Lee A, Swart R, Dahkil S, *et al*. Abstract P5-16-02: Updated efficacy, safety and translational data from MARIO-3, a phase II open-label study evaluating a novel triplet combination of eganelisib (IPI-549), atezolizumab (atezo), and nab-paclitaxel (nab-pac) as first-line (1L) therapy for locally advanced or metastatic triple-negative breast cancer (TNBC). Cancer Research. 2022; 82: P5-16-02. https://doi.org/10.1158/1538-7445.SABCS21-P5-16-02.
[54] Liu J, Wang Y, Tian Z, Lin Y, Li H, Zhu Z, *et al*. Multicenter phase II trial of Camrelizumab combined with Apatinib and Eribulin in heavily pretreated patients with advanced triple-negative breast cancer. Nature Communications. 2022; 13: 3011. https://doi.org/10.1038/s41467-022-30569-0.
[55] Torres ETR, Emens LA. Emerging combination immunotherapy strategies for breast cancer: dual immune checkpoint modulation, antibody-drug conjugates and bispecific antibodies. Breast Cancer Research and Treatment. 2022; 191: 291–302. https://doi.org/10.1007/s10549-021-06423-0.
[56] Emens LA, Esteva FJ, Beresford M, Saura C, De Laurentiis M, Kim SB, *et al*. Trastuzumab emtansine plus atezolizumab versus trastuzumab emtansine plus placebo in previously treated, HER2-positive advanced breast cancer (KATE2): a phase 2, multicentre, randomised, double-blind trial. The Lancet Oncology. 2020; 21: 1283–1295. https://doi.org/10.1016/S1470-2045(20)30465-4.
[57] Hurvitz SA, Bachelot T, Bianchini G, Harbeck N, Loi S, Park YH, *et al*. ASTEFANIA: adjuvant ado-trastuzumab emtansine and atezolizumab for high-risk, HER2-positive breast cancer. Future Oncology. 2022; 18: 3563–3572. https://doi.org/10.2217/fon-2022-0485.
[58] Loi S, Schneeweiss A, Song E, Harries M, De Laurentiis M, Li Y, *et al*. 329TiP KATE3: A phase III study of trastuzumab emtansine (T-DM1) in combination with atezolizumab or placebo in patients with previously treated HER2-positive and PD-L1–positive locally advanced or metastatic breast cancer. Annals of Oncology. 2021; 32: S509. https://doi.org/10.1016/j.annonc.2021.08.612.
[59] Schmid P, Wysocki P, Ma C, Park YH, Fernandes R, Lord S, *et al*. Abstract PD11-09: PD11-09 Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): updated results from BEGONIA, a phase 1b/2 study. Cancer Research. 2023; 83: PD11-09. https://doi.org/10.1158/1538-7445.SABCS22-PD11-09.
[60] Tolaney SM, de Azambuja E, Emens LA, Loi S, Pan W, Huang J, *et al*. 276TiP ASCENT-04/KEYNOTE-D19: Phase III study of sacituzumab govitecan (SG) plus pembrolizumab (pembro) vs treatment of physician's choice (TPC) plus pembro in first-line (1L) programmed death-ligand 1-positive (PD-L1+) metastatic triple-negative breast cancer (mTNBC). Annals of Oncology. 2022; 33: S664–S665. https://doi.org/10.1016/j.annonc.2022.07.1860.
[61] Garrido-Castro AC, Kim SE, Desrosiers J, Nanda R, Carey LA, Clark AS, *et al*. SACI-IO HR+: A randomized phase II trial of sacituzumab govitecan with or without pembrolizumab in patients with metastatic hormone receptor-positive/HER2-negative breast cancer. Journal of Clinical Oncology. 2024; 42: LBA1004–LBA1004. https://doi.org/10.1200/JCO.2024.42.17_suppl.LBA1004.
[62] Barroso-Sousa R, Zanudo JGT, Li T, Reddy SM, Emens LA, Kuntz TM, *et al*. Nivolumab plus low-dose ipilimumab in hypermutated HER2-negative metastatic breast cancer: a phase II trial (NIMBUS). Nature Communications. 2025; 16: 4430. https://doi.org/10.1038/s41467-025-59695-1.
[63] Nederlof I, Isaeva OI, Bakker N, De Graaf M, Salgado RF, Klioueva N, *et al*. LBA13 Nivolumab and ipilimumab in early-stage triple negative breast cancer (TNBC) with tumor-infiltrating lymphocytes (TILs): First results from the BELLINI trial. Annals of Oncology. 2022; 33: S1382. https://doi.org/10.1016/j.annonc.2022.08.007.
[64] Cortes M, Salgado AC, Murillo SM, Blancas I, Cortez P, Plaza IC, *et al*. Safety interim analysis (SIA) of atractib: A phase 2 trial of first-line (1L) atezolizumab (A) in combination with paclitaxel (P) and bevacizumab (B) in metastatic triple-negative breast cancer (mTNBC). Journal of Clinical Oncology. 2022; 40: 1084. https://doi.org/10.1200/JCO.2022.40.16_suppl.1084.
[65] Chen L, Zhimin S, Wang Z, Yang W, Jiang Y, Wu S, *et al*. The overall survival analysis of FUTURE-C-PLUS: Combination of famitinib with camrelizumab plus nab-paclitaxel as first-line treatment for advanced, immunomodulatory triple-negative breast cancer—An open-label, single-arm, phase 2 trial. Journal of Clinical Oncology. 2023; 41: 1086. https://doi.org/10.1200/JCO.2023.41.16_suppl.1086.
[66] Fan L, Wang ZH, Ma LX, Wu SY, Wu J, Yu KD, *et al*. Optimising first-line subtyping-based therapy in triple-negative breast cancer (FUTURE-SUPER): a multi-cohort, randomised, phase 2 trial. The Lancet Oncology. 2024; 25: 184–197. https://doi.org/10.1016/S1470-2045(23)00579-X.
[67] Brufsky A, Kim SB, Zvirbule Z, Dirix LY, Eniu AE, Carabantes F, *et al*. Phase II COLET study: Atezolizumab (A) + cobimetinib (C) + paclitaxel (P)/nab-paclitaxel (nP) as first-line (1L) treatment (tx) for patients (pts) with locally advanced or metastatic triple-negative breast cancer (mTNBC). Journal of Clinical Oncology. 2019; 37: 1013. https://doi.org/10.1200/JCO.2019.37.15_suppl.1013.
[68] Pilones KA, Joseph A, Vatner R, Formenti S, Demaria S. Radiation Therapy Sensitizes a Poorly Immunogenic Breast Cancer to PD-1 Blockade. International Journal of Radiation Oncology, Biology, Physics. 2014; 90: S58. https://doi.org/10.1016/j.ijro

bp.2014.05.203.
[69] Voorwerk L, Slagter M, Horlings HM, Sikorska K, van de Vijver KK, de Maaker M, *et al*. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. Nature Medicine. 2019; 25: 920–928. https://doi.org/10.1038/s41591-019-0432-4.
[70] Ho AY, Barker CA, Arnold BB, Powell SN, Hu ZI, Gucalp A, *et al*. A phase 2 clinical trial assessing the efficacy and safety of pembrolizumab and radiotherapy in patients with metastatic triple-negative breast cancer. Cancer. 2020; 126: 850–860. https://doi.org/10.1002/cncr.32599.
[71] Ahmed KA, Kim Y, Arrington JA, Kim S, DeJesus M, Soyano AE, *et al*. Nivolumab and Stereotactic Radiosurgery for Patients With Breast Cancer Brain Metastases: A Nonrandomized, Open-Label Phase 1b Study. Advances in Radiation Oncology. 2021; 6: 100798. https://doi.org/10.1016/j.adro.2021.100798.
[72] Nguyen AT, Shiao SL, McArthur HL. Advances in Combining Radiation and Immunotherapy in Breast Cancer. Clinical Breast Cancer. 2021; 21: 143–152. https://doi.org/10.1016/j.clbc.2021.03.007.
[73] Li Z, Lai X, Fu S, Ren L, Cai H, Zhang H, *et al*. Immunogenic Cell Death Activates the Tumor Immune Microenvironment to Boost the Immunotherapy Efficiency. Advanced Science. 2022; 9: e2201734. https://doi.org/10.1002/advs.202201734.
[74] Li Z, Cai H, Li Z, Ren L, Ma X, Zhu H, *et al*. A tumor cell membrane-coated self-amplified nanosystem as a nanovaccine to boost the therapeutic effect of anti-PD-L1 antibody. Bioactive Materials. 2022; 21: 299–312. https://doi.org/10.1016/j.bioactmat.2022.08.028.
[75] Liu L, Wang Y, Miao L, Liu Q, Musetti S, Li J, *et al*. Combination Immunotherapy of MUC1 mRNA Nano-vaccine and CTLA-4 Blockade Effectively Inhibits Growth of Triple Negative Breast Cancer. Molecular Therapy. 2018; 26: 45–55. https://doi.org/10.1016/j.ymthe.2017.10.020.
[76] Zhu J, Yu M, Chen L, Kong P, Li L, Ma G, *et al*. Enhanced antitumor efficacy through microwave ablation in combination with immune checkpoints blockade in breast cancer: A pre-clinical study in a murine model. Diagnostic and Interventional Imaging. 2018; 99: 135–142. https://doi.org/10.1016/j.diii.2017.12.011.
[77] Zhou W, Yu M, Mao X, Pan H, Tang X, Wang J, *et al*. Landscape of the Peripheral Immune Response Induced by Local Microwave Ablation in Patients with Breast Cancer. Advanced Science. 2022; 9: e2200033. https://doi.org/10.1002/advs.202200033.
[78] Wang Y, Zhang X, Wang Y, Zhao W, Li H, Zhang L, *et al*. Application of immune checkpoint targets in the anti-tumor novel drugs and traditional Chinese medicine development. Acta Pharmaceutica Sinica B. 2021; 11: 2957–2972. https://doi.org/10.1016/j.apsb.2021.03.004.
[79] Yu YX, Wang S, Liu ZN, Zhang X, Hu ZX, Dong HJ, *et al*. Traditional Chinese medicine in the era of immune checkpoint inhibitor: theory, development, and future directions. Chinese Medicine. 2023; 18: 59. https://doi.org/10.1186/s13020-023-00751-7.
[80] Wang X, Jing J. Cancer Immunotherapy in Combination with Radiotherapy and/or Chemotherapy: Mechanisms and Clinical Therapy. MedComm. 2025; 6: e70346. https://doi.org/10.1002/mco2.70346.
[81] Vranic S, Cyprian FS, Gatalica Z, Palazzo J. PD-L1 status in breast cancer: Current view and perspectives. Seminars in Cancer Biology. 2021; 72: 146–154. https://doi.org/10.1016/j.semcancer.2019.12.003.
[82] Wei Y, Ge H, Qi Y, Zeng C, Sun X, Mo H, *et al*. Predictive circulating biomarkers of the response to anti-PD-1 immunotherapy in advanced HER2 negative breast cancer. Clinical and Translational Medicine. 2025; 15: e70255. https://doi.org/10.1002/ctm2.70255.
[83] Qiu P, Yu X, Zheng F, Gu X, Huang Q, Qin K, *et al*. Advancements in liquid biopsy for breast Cancer: Molecular biomarkers and clinical applications. Cancer Treatment Reviews. 2025; 139: 102979. https://doi.org/10.1016/j.ctrv.2025.102979.
[84] Yu X, Song L, Cen L, Cao B, Tao R, Shen Y, *et al*. Pan-cancer γδ TCR analysis uncovers clonotype diversity and prognostic potential. Cell Reports Medicine. 2024; 5: 101764. https://doi.org/10.1016/j.xcrm.2024.101764.
[85] Taylor BC, Sun X, Gonzalez-Ericsson PI, Sanchez V, Sanders ME, Wescott EC, *et al*. NKG2A Is a Therapeutic Vulnerability in Immunotherapy Resistant MHC-I Heterogeneous Triple-Negative Breast Cancer. Cancer Discovery. 2024; 14: 290–307. https://doi.org/10.1158/2159-8290.CD-23-0519.
[86] Zou Y, Zhang H, Liu F, Chen ZS, Tang H. Intratumoral microbiota in orchestrating cancer immunotherapy response. Journal of Translational Internal Medicine. 2025; 12: 540–542. https://doi.org/10.1515/jtim-2024-0038.
[87] Huang L, Li Y, Zhang C, Jiang A, Zhu L, Mou W, *et al*. Microbiome meets immunotherapy: unlocking the hidden predictors of immune checkpoint inhibitors. NPJ Biofilms and Microbiomes. 2025; 11: 180. https://doi.org/10.1038/s41522-025-00819-2.
[88] van Wilpe S, Tolmeijer SH, Koornstra RHT, de Vries IJM, Gerritsen WR, Ligtenberg M, *et al*. Homologous Recombination Repair Deficiency and Implications for Tumor Immunogenicity. Cancers. 2021; 13: 2249. https://doi.org/10.3390/cancers13092249.
[89] Emens LA, Molinero L, Loi S, Rugo HS, Schneeweiss A, Diéras V, *et al*. Atezolizumab and nab-Paclitaxel in Advanced Triple-Negative Breast Cancer: Biomarker Evaluation of the IMpassion130 Study. Journal of the National Cancer Institute. 2021; 113: 1005–1016. https://doi.org/10.1093/jnci/djab004.
[90] Jin M, Fang J, Peng J, Wang X, Xing P, Jia K, *et al*. PD-1/PD-L1 immune checkpoint blockade in breast cancer: research insights and sensitization strategies. Molecular Cancer. 2024; 23: 266. https://doi.org/10.1186/s12943-024-02176-8.