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Breast cancer immunotherapy: mechanisms of immune evasion, biomarkers, and emerging therapeutic strategies

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Abstract

Breast cancer remains the most prevalent malignancy worldwide and a major cause of cancer-related mortality, representing a heterogeneous and therapeutically challenging disease. Although immunotherapy has revolutionized the treatment of several malignancies, its efficacy in breast cancer is constrained by tumor heterogeneity, low immunogenicity, particularly in hormone receptor (HR)-positive subtypes, and diverse immune evasion mechanisms. This review provides a comprehensive overview of current advances in understanding key mechanisms of breast tumor immune evasion and their overcoming by modern immunotherapy approaches, including immune checkpoint inhibitors (ICIs), cancer vaccines, and adoptive cell therapies, emphasizing biomarker-guided patient selection. We examine the roles of tumor-infiltrating lymphocytes (TILs), tumor mutational burden (TMB), antigen presentation, and programmed death-ligand 1 (PD-L1) expression in the tumor immune evasion and predicting response to immunotherapy. Our main focus is also on emerging strategies, including neoantigen- and DNA/RNA-based vaccines, chimeric and engineered antigen receptors, bispecific T-cell engagers, oncolytic viruses, and targeted immunotherapeutic approaches, which are promising tools for overcoming immune resistance. Furthermore, we evaluate rational combinations of immunotherapy with chemotherapy, radiotherapy, and targeted agents, added by immunosorption as an essential detoxification approach. Finally, we explore future directions emphasizing personalized, multimodal immunotherapy guided by multiomics and spatial profiling, integrated with artificial intelligence. Finally, we synthesize a framework for advancing immunotherapy in breast cancer and identify key areas requiring further translational and clinical investigation.

Keywords Breast cancer, Tumor microenvironment, Immune evasion, Immune biomarkers, Immune checkpoint inhibitors, Adoptive immunotherapy, Cancer vaccines, Combination immunotherapy

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1 Introduction

Breast cancer (BC) is the most frequently diagnosed malignancy and the leading cause of cancer-related mortality among women worldwide. Between 1990 and 2021, the global incidence of BC new cases rose from 0.87 million to 2.08 million, and BC-associated deaths increased from 350,577 to 660,925. At this, China (88,107), India (78,879), and the United States (52,869) accounted for approximately 33% of global breast cancer deaths in 2021 [1].

Despite substantial progress in early detection and advances in surgery, radiotherapy, endocrine manipulation, and targeted therapies, mortality associated with advanced or metastatic BC remains significant, primarily due to therapeutic resistance and high tumor heterogeneity [2, 3, 4].

Unlike chemotherapy or radiotherapy, which directly target tumor cells, immunotherapy offers a transformative paradigm shift from conventional cytotoxic approaches to harnessing the host immune system to recognize and eliminate malignant cells. Immunotherapeutic approaches aimed at enhancing immune-mediated recognition and cytotoxicity potentially achieve durable tumor control through the activation and persistence of memory T cells. Recent developments, including immune checkpoint inhibitors (ICIs), cancer vaccines, and adoptive cell therapies (ACTs), have yielded encouraging results in different subsets of BC patients [5–7]. However, the efficacy of immunotherapy depends on the intrinsic immunogenicity of the tumor and the patient's immune competence, which highlights the need for personalized immunotherapeutic strategies that account for both tumor-specific factors and host-related immune parameters [2, 8, 9]. While immunotherapy has already yielded remarkable success in melanoma, lung cancer, and hematological cancers, its benefits in breast cancer remain modest due to the relatively immune-resistant nature of most breast tumors and their molecular diversity [10].

Molecular profiling identifies at least three major intrinsic BC subtypes, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-positive, and triple-negative breast cancer (TNBC), each characterized by distinct oncogenic drivers, immune landscapes, and therapeutic vulnerability [7, 11, 12] (Fig. 1).

HR-positive subtypes, including estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive tumors, typically exhibit low immunogenicity characterized by limited invasion by tumor-infiltrating lymphocytes (TILs) [13–15], a reduced tumor mutation burden (TMB), impaired antigen presentation, and an

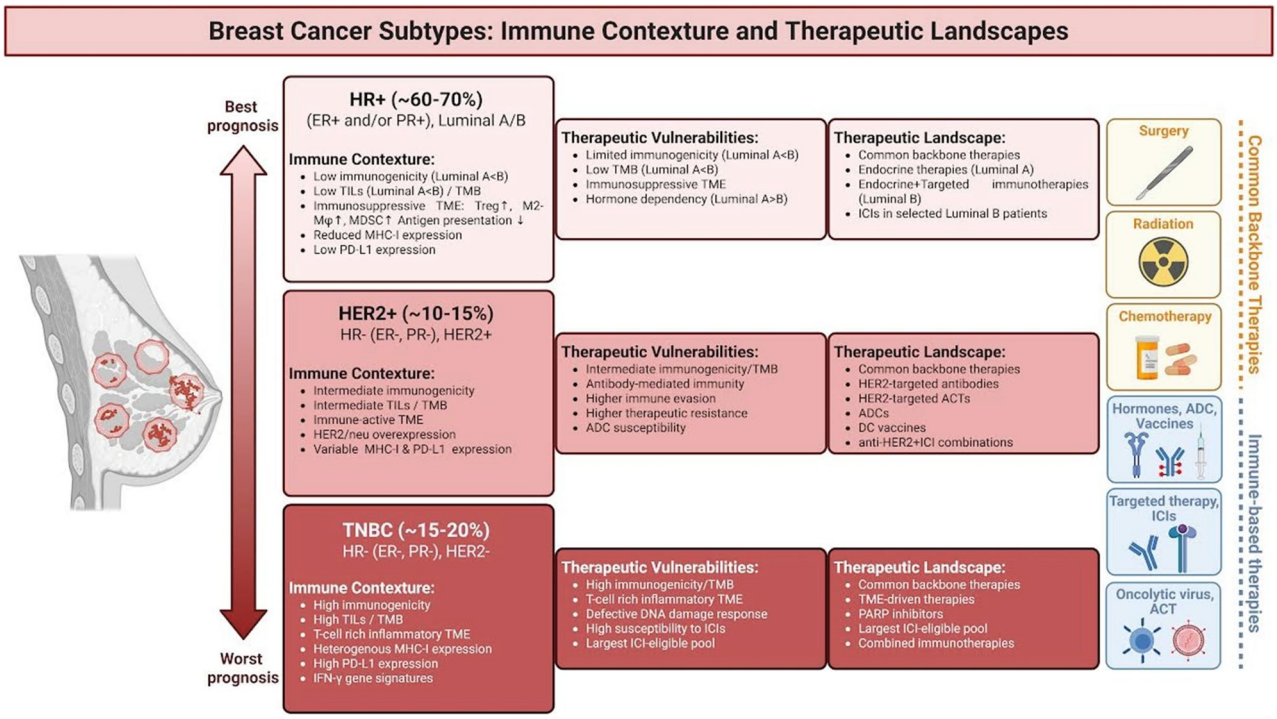

Fig. 1 Breast cancer subtypes: immune contexture and therapeutic landscapes. Up arrow - increase; down arrow - decrease. *ACT, adoptive cell therapy; ADC, antibody-drug conjugate; DC, dendritic cell; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICIs, immune checkpoint inhibitors; IFN-γ, interferon γ; Mø, macrophage; MDSC, myeloid-derived suppressor cell; MHC-I, major histocompatibility complex class I molecules; PARP, poly(ADP-ribose) polymerase; PD-L1, programmed death ligand-1; PR, progesterone receptor; TILs, tumor-infiltrating lymphocytes; TMB, tumor mutation burden; TME, tumor microenvironment; TNBC, triple-negative breast cancer; Treg, regulatory T cell.* Created in BioRender. https://BioRender.com/9wzmzw2

immunosuppressive tumor microenvironment (TME) [16–18]. Decreased major histocompatibility complex (MHC) molecule class I expression and dysfunctional antigen processing [19–21], as well as increased presence of regulatory T cells (Tregs) [22], myeloid-derived suppressor cells (MDSCs) [23–25] and immunosuppressive cytokines [14, 15] in the TME, contribute to immune escape of breast tumors. Therefore, novel immunomodulatory approaches targeting these mechanisms have been developed and investigated to enhance immune responsiveness in low-immunogenicity BC tumors, particularly HR-positive subtypes [7]. In contrast, TNBC, defined by the absence of ER, PR, and HER2 expression, demonstrates a comparatively higher immunogenic profile. TNBC is frequently associated with increased TILs and elevated programmed cell death ligand 1 (PD-L1) expression, which may enhance susceptibility to immune checkpoint blockade [12, 24, 26]. Despite this immunogenicity, TNBC remains clinically challenging due to its aggressive behavior, rapid progression, limited availability of targeted therapies, and high relapse rates despite intensive chemotherapy [3, 27].

HER2-positive tumors constitute another immunologically distinct BC subtype, characterized by HER2/neu overexpression and variable PD-L1 expression. Elevated PD-L1 levels in this subtype have been associated with immune evasion and therapeutic resistance [17, 28, 29]. Combination strategies incorporating anti-HER2 agents, such as trastuzumab, with ICIs, including pembrolizumab, have demonstrated synergistic potential by enhancing antitumor immune responses [18]. However, responses to immunotherapy among HER2-positive patients remain heterogeneous and appear to depend on PD-L1 expression levels and the composition of immune cell infiltration within the TME [18].

Overall, although significant progress has been achieved, the efficacy of immunotherapy across BC subtypes remains variable. Further optimization of clinical outcomes will require a comprehensive understanding of immune escape mechanisms and TME the identification of reliable predictive biomarkers, and the implementation of rational combination strategies.

This review provides a comprehensive analysis of immunotherapeutic strategies in BC, with particular emphasis on ICIs, ACTs, and cancer vaccines, as well as the development of personalized immunotherapeutic approaches guided by tumor and host immune profiling. We examine the key determinants of immunotherapy efficacy in BC, with special focus on the epitope-based vaccines and cell-based therapies employing chimeric antigen receptors (CARs) and genetically engineered T-cell receptors (TCRs). These advanced modalities represent innovative strategies for targeting tumor-associated antigens (TAAs) with enhanced specificity and precision. Furthermore, this review explores how personalized immunotherapy approaches, particularly when integrated into rational combination strategies, may improve therapeutic responsiveness and enable more tailored treatment paradigms for patients with BC. In addition, we provide an overview of immune escape mechanisms in BC, critically evaluate current immunotherapeutic modalities, and outline future directions aimed at enhancing clinical efficacy and expanding the therapeutic scope of immunotherapy in BC.

2 Immune evasion mechanisms in breast cancer

2.1 Cancer immunoediting

Cancer immunoediting is a dynamic interaction between the immune system and tumor cells, encompassing three sequential phases: Elimination, Equilibrium, and Escape, through which immune pressure both restrains and shapes tumor evolution. During Elimination phase, transformed cells are recognized and destroyed. In Equilibrium phase, immune-mediated dormancy of tumor cells selects for less immunogenic variants. Finally, in Escape phase, edited tumor clones resume progressive growth, establish clinical disease, and generate an immunosuppressive [30] (Fig. 2).

BC is a highly heterogeneous malignancy that exploits multiple immune evasion strategies to facilitate progression, largely orchestrated by the TME. The TME comprises immune and stromal cell populations embedded within a network of soluble mediators that collectively modulate tumor growth and therapeutic responsiveness. Immune escape mediated by TME-dependent mechanisms includes activation of the PD-1/PD-L1 axis, secretion of immunosuppressive cytokines, and expansion of Tregs and myeloid-derived MDSCs [31]. Tumor-associated immunosuppressive cells, particularly Tregs derived from both tumor tissue and peripheral blood, facilitate tumor initiation and progression in a BC subtype-specific manner [31].

Within the TME, immune populations exert bidirectional effects: effector cells attempt to constrain tumor growth, whereas immunoregulatory subsets promote progression and metastasis. This duality is consistent with the immunoediting paradigm, in which immune escape enables tumor outgrowth and dissemination. Reduced tumor immunogenicity, characterized by diminished production of danger signals, further limits immune recognition and facilitates immune evasion [32].

The Escape phase represents a critical transition from immune-mediated control to sustained tumor expansion within an immunosuppressive TME. In BC, this stage is increasingly understood not as passive immune failure but as an active, tumor-driven reprogramming of the microenvironment into an immunosuppressive niche [33, 34]. Within this framework, next-generation immune

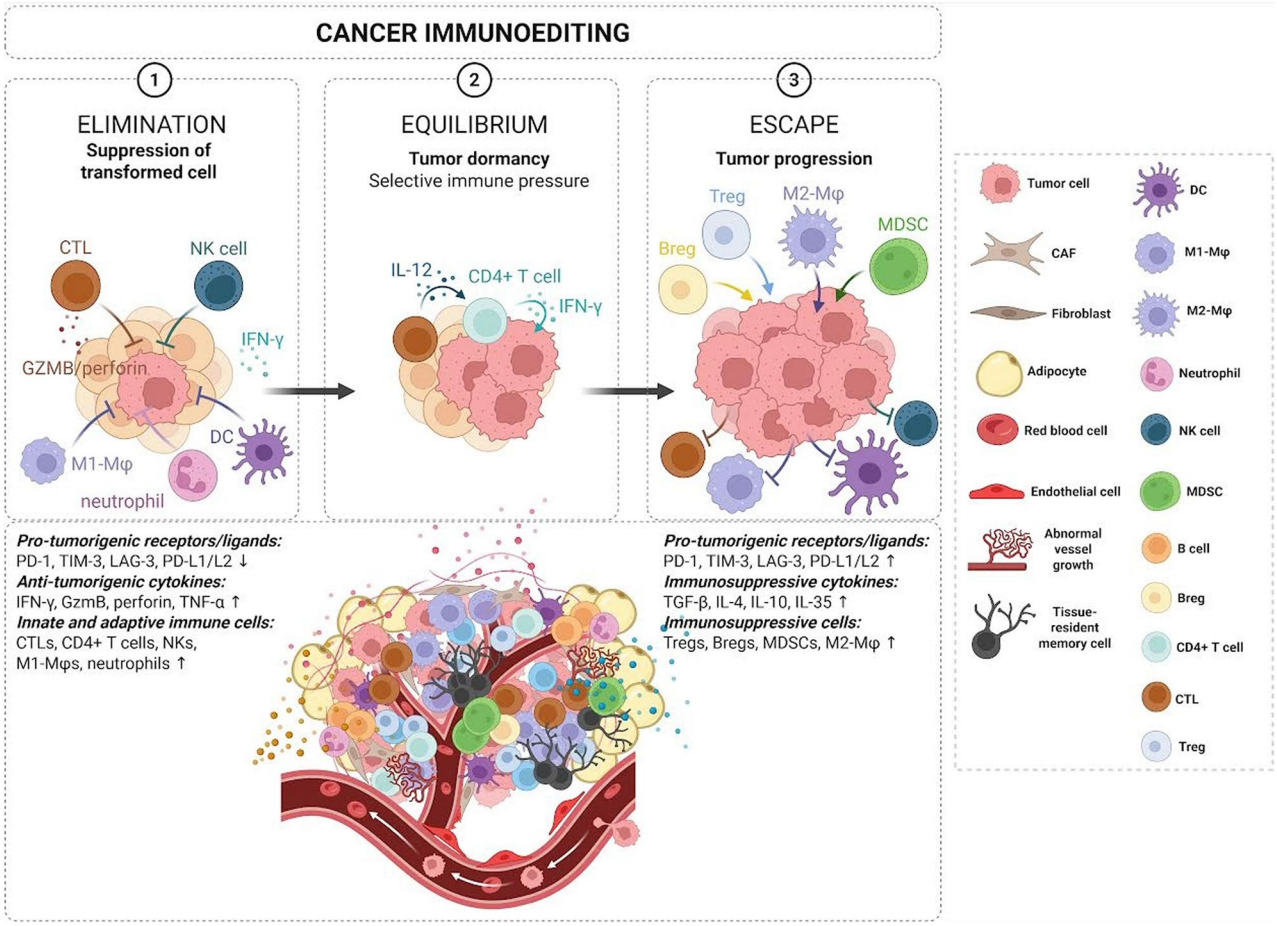

Fig. 2 Dynamic phases of cancer immunoediting within the TME. Cancer immunoediting progresses through three "*Es*" *(Elimination*, *Equilibrium*, *Escape)*, shaped by shifting immune pressure and dynamic changes in the TME. The *Elimination phase* is characterized by the removal of transformed malignant cells through strong cytotoxic activity supported by effector cytokines and immune-stimulatory signals, with minimal pro-tumorigenic influence. During *Equilibrium phase*, persistent immune pressure restrains the expansion of neoplastic cells while selecting for less immunogenic variants. In the *Escape phase*, tumor cells acquire immune-evasive features driven by suppressive receptor–ligand interactions, inhibitory cytokine networks, and the expansion of immunosuppressive cell populations, collectively facilitating tumor progression and outgrowth. *Breg*, *regulatory B cell; CAF*, *cancer-associated fibroblast; CTL*, *cytotoxic T lymphocyte; DC*, *dendritic cell; GZMB*, *granzyme B; IFN-γ*, *interferon γ; IL*, *interleukin; LAG-3*, *lymphocyte activation gene-3 protein; Mø*, *macrophage; MDSC*, *myeloid-derived suppressor cell; NK*, *natural killer cell; PD-1*, *programmed cell death protein-1; PD-L1/L2*, *programmed death ligand-1/-2; TGF-β*, *transforming growth factor β; TIM-3*, *T-cell immunoglobulin and mucin domain-3; TNF-α*, *tumor necrosis factor α; Treg*, *regulatory T cell.* Created in BioRender. https://BioRender.com/9wzmzw2

checkpoint receptors such as LAG-3 and TIM-3 contribute substantially to immune escape, acting synergistically with broader TME-driven mechanisms to consolidate tumor progression.

These receptors promote immune evasion through several non-redundant mechanisms:

1. Suppressive receptor–ligand interactions: LAG-3 engagement with MHC class II molecules and TIM-3 binding to ligands such as galectin-9 transmit potent inhibitory signals that attenuate T-cell receptor (TCR) signaling and diminish cytotoxic granzyme B release by effector T cells [35].
2. Metabolic competition and reprogramming: The Escape phase is characterized by profound metabolic stress and nutrient competition. Tumor-derived factors, including lactate accumulation, activation of hypoxia-inducible factor 1α (HIF-1α), and indoleamine 2,3-dioxygenase (IDO) activity, generate a metabolically hostile milieu that preferentially sustains Treg survival and suppresses cytotoxic T-lymphocyte (CTL) function [36].
3. Expansion of immunosuppressive myeloid populations: TIM-3 signaling is associated with the recruitment and expansion of MDSCs and M2-polarized macrophages, thereby amplifying local immunosuppression and limiting effective antitumor responses [37].
4. Inhibitory cytokine networks: The Escape-phase TME is enriched in immunosuppressive cytokines,

including IL-10 and TGF-β, and, in specific contexts, IL-35 and IL-4. These mediators promote the conversion of conventional T cells into induced Tregs and support M2 macrophage polarization, effectively shielding tumor cells from cytotoxic attack [38, 39].

Immunological phenotypes of BC further influence escape dynamics. "Cold" tumors exhibit limited T-cell infiltration, permitting unchecked tumor growth, whereas "hot" tumors may evade immune destruction through reduced MHC class I expression, transcriptional or epigenetic reprogramming, and upregulation of immune checkpoints, culminating in T-cell exhaustion [40, 41]. The clinical aggressiveness of BC reflects the coexistence of diverse and context-dependent immune evasion strategies, which may partly account for heterogeneous therapeutic outcomes. Collectively, these insights provide a strong rationale for therapeutic strategies aimed at TME reprogramming, including immune checkpoint blockade and approaches targeting immunosuppressive cellular compartments (Fig. 3).

2.2 T-cell exhaustion and dysfunction

The progression of T-cell exhaustion is dictated by the "immunological heat" of the BC subtype. In "cold" tumors (typical of HR-positive/HER2-negative), the primary barrier is a lack of T-cell infiltration. However, in "hot" tumors (often TNBC or HER2-positive), terminal exhaustion occurs despite high infiltration. This state is driven by reduced MHC-I expression, which prevents effective antigen presentation and the simultaneous upregulation of multiple immune checkpoints. This synergy ensures that TILs remain in a permanent state of metabolic and functional paralysis [42, 43]. The key inhibitory receptors implicated in this dysfunctional state are summarized in Table 1.

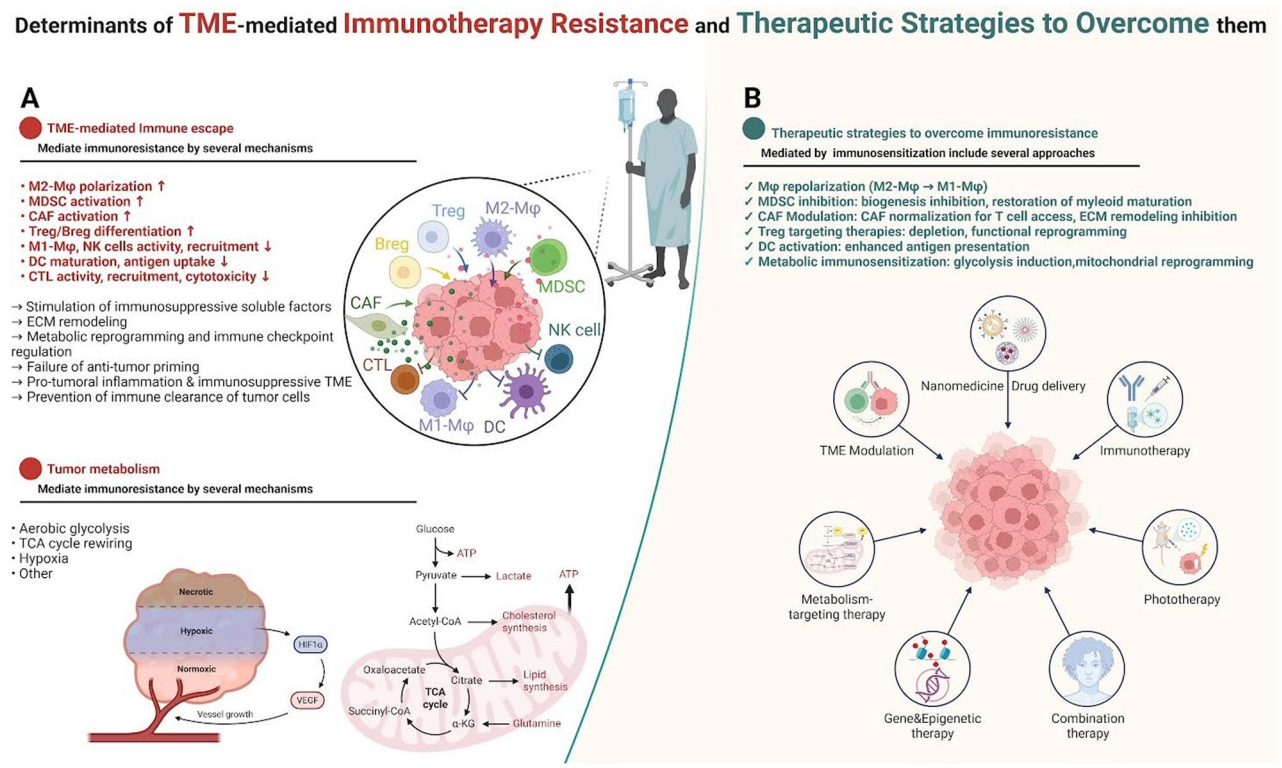

Fig. 3 TME-mediated immune tolerance in breast cancer: biomolecular mechanisms and therapeutic targeting. **A** Biomolecular mechanisms of TME–mediated immunotherapy resistance. Immune escape–mediated immunotherapy resistance is orchestrated within the TME through coordinated biomolecular mechanisms involving suppressive cellular networks, metabolic reprogramming, immune checkpoint signaling, and dynamic TME remodeling. In breast cancer, tumor cells, Tregs, MDSCs, tumor-associated Møs along with innate and stromal components, collectively shape an immunosuppressive niche, characterized by ECM remodeling, hypoxia and metabolic constraints. **B** Therapeutic strategies to overcome TME–mediated immunotherapy resistance. Therapeutic strategies to counteract TME-driven immunotherapy resistance include several monotherapeutic or combined approaches encompassing ICIs and other targeted therapies, ACT, vaccines, tumor metabolism–targeting therapies, gene and epigenetic editing, phototherapy-based interventions, and nanomedicine-driven drug delivery systems. *ACT, adoptive cell therapy; Breg, regulatory B cell; CAF, cancer-associated fibroblast; CTL, cytotoxic T lymphocyte; DC, dendritic cell; ECM, extracellular matrix; HIF-1α, hypoxia-inducible factor-1α; ICIs, immune checkpoint inhibitors; Mø, macrophage; MDSC, myeloid-derived suppressor cell; NK, natural killer cell; TCA, tricarboxylic acid; TME, tumor microenvironment; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.* Created in BioRender. https://BioRender.com/9wzmzw2

Table 1 Key inhibitory receptors

Checkpoint molecule	Key ligand	Primary target cells	Mechanism of immune evasion
LAG-3	MHC Class II	CTLs, Tregs	High-affinity binding to MHC-II outcompetes CD4, dampens TCR signaling, and enhances Treg suppressive function.
TIGIT	CD155 (PVR), CD112	T-cells, NK cells	Directly inhibits NK cell cytotoxicity and competes with CD226 to prevent T-cell costimulation.
TIM-3	Galectin-9, CEACAM1, HMGB1, phosphatidylserine	T-cells, DCs	Modulates DC function to impair cross-presentation; induces terminal T-cell exhaustion.

CEACAM1 Carcinoembryonic antigen-related cell adhesion molecule 1, *CTLs* Cytotoxic T lymphocytes, *DCs* Dendritic cells, *HMGB1* High-mobility group protein B1, *LAG3* Lymphocyte-activation gene 3, *MHC* Major complex histocompatibility, *NK* Natural killer, *TI* T-cell immunoglobulin and mucin domain 3, *TIGIT* T-cell immunoreceptor with Ig and ITIM domains, *Treg* Regulatory T cells

2.3 Treg-mediated suppression of CTL activation

Tregs are the primary architects of immune tolerance within the BC TME. Rather than merely being present, Tregs in BC are hyper-functional, upregulating LAG-3 and TIM-3 to maintain a dominant suppressive phenotype. The functional consequence of this upregulation involves several key pathways:

Restriction of CTL activation: Tregs utilize LAG-3 to bind MHC-II on antigen-presenting cells, delivering inhibitory signals that prevent the "licensing" of DCs required for CTL activation [44].

The GARP-TGF-β1 complex: Tregs express GARP (LRRC32), which captures and activates latent TGF-β1 on the cell surface. This localized release of active TGF-β directly suppresses nearby effector T cells and promotes stroma remodeling [45, 46].

CCR8-mediated recruitment: The CCR8 receptor acts as a specific gateway for Treg recruitment into the TME. Blockade of this axis is a strategic priority to deplete TME-resident Tregs while sparing systemic immune homeostasis [47].

FoxP3 stability: Inhibitory checkpoints receptors such as CTLA-4, PD-1, and LAG-3 are highly expressed on FoxP3$^+$ Tregs and contribute to their suppressive function, collectively reinforcing collectively reinforcing an immunosuppressive environment [48].

2.4 PD-1/PD-L1 pathway activation

The PD-1/PD-L1 axis is a major checkpoint that regulates T-cell activity. In BC, tumor PD-L1 binds PD-1 on T cells, inducing T-cell exhaustion and immune evasion in cancer cells [49, 50]. In addition, the overexpression of JAK2 in BC activates STAT1/STAT3, which promotes PD-L1 transcription, increasing cytotoxic T lymphocyte (CTL) exhaustion and tumor immune evasion. Inhibition of these factors may reduce PD-L1 expression and increase immune system anticancer activity [51, 52]. Epigenetic regulators such as BRD4 and microRNAs (miRNAs), including miRNA-200, also modulate PD-L1 levels, impacting the anticancer efficacy of the immune system [53, 54] (Fig. 4).

Therefore, PD-1/PD-L1 blockade can restore antitumor immunity, enhancing T-cell function and clinical outcomes in BC patients, although response rates vary by BC subtype [49, 50, 55].

2.5 Immunosuppressive cytokines

Immunosuppressive cytokines play a central role in TME-associated immune evasion, interacting with MDSCs and M2 tumor-associated macrophages (M2-TAMs) to suppress effector T cells and promote tumor infiltration by Tregs [56, 57] (Fig. 2).

Among immunosuppressive cytokines, TGF-β has dual roles: it is tumor suppressive in early BC but protumorigenic in advanced stages [58]. It inhibits CTL activity, dampens Th1 responses, modulates function dendritic cells (DCs), promotes M2 polarization, and recruits Tregs and MDSCs [59]. Increased TGF-β levels also influence TME metabolism, which is correlated with therapy resistance [60–62]. Collectively, these data highlight TGF-β as a central driver of therapeutic resistance and a compelling target for combinatory interventions in BC.

IL-10 is another key immunosuppressive cytokine secreted by Th2 cells, B cells, Tregs, Bregs, ligand-expressing tolerogenic DCs. It promotes tumor survival via the JAK/STAT1/3 and IL-6/JAK/STAT3 pathways [63, 64], enriches the TME with hyperactivated Tregs [65] and M2-TAMs [66], and is a poor prognostic marker in late-stage BC [65]. In contrast to end-stage cancers, IL-10 can exhibit antitumoral activity at the early stage of TNBC, ER-positive, and PR-positive BCs [67, 68]. Overall, IL-10 is one of the key mediators of tumor growth and metastasis; it regulates the immune response against cancer cells and impacts the TME habitat, which is beneficial for tumor growth, making it both a challenge and an opportunity for therapeutic targeting.

IL-4 promotes tumor metabolism via the JAK/STAT6 and mTOR pathways, upregulates antiapoptotic gene expression and IL-4 receptor expression in tumor cells, as well as recruits M2- TAMs, and thus promotes significant tumor growth [69, 70]. In advanced stages of the disease, IL-4 may also promote the recruitment of CTLs

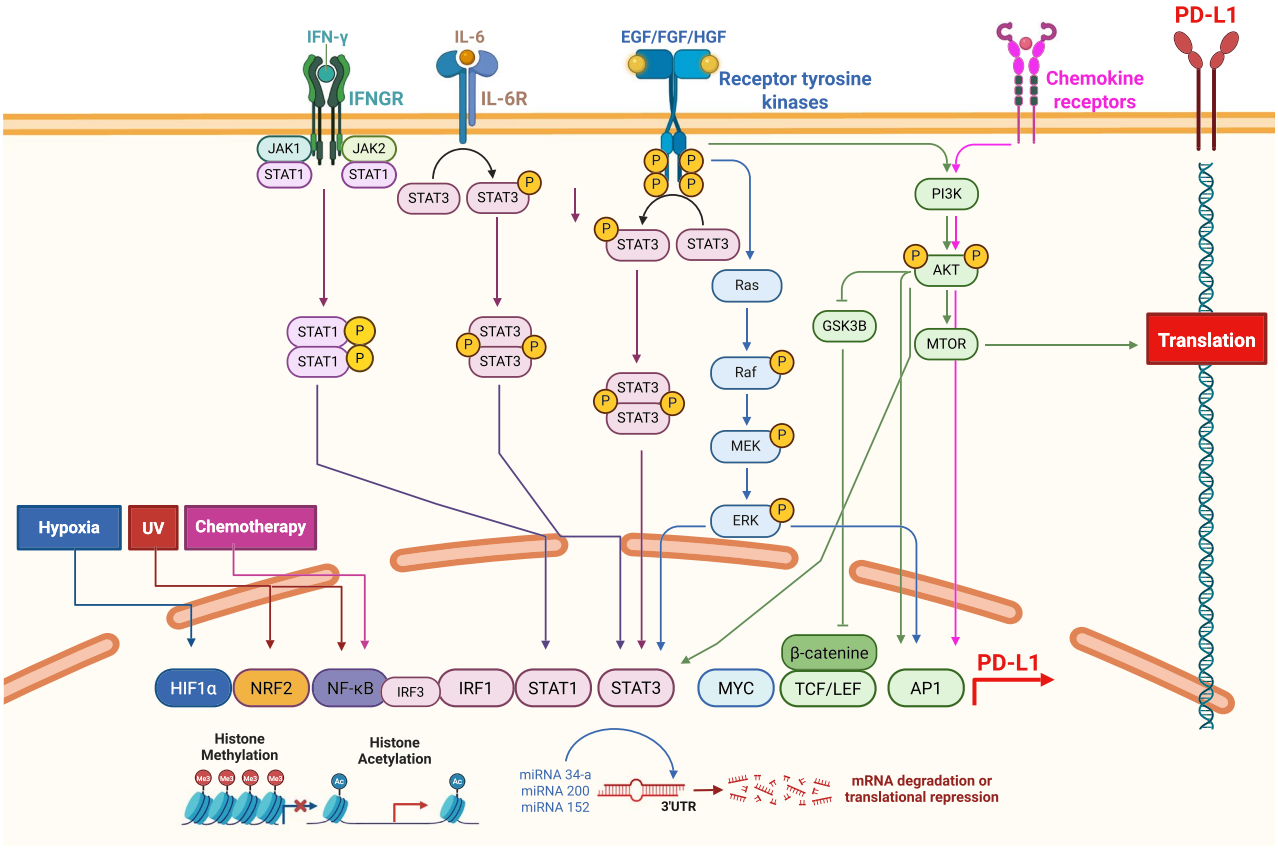

Fig. 4 The regulatory mechanism of PD-L1 expression. PD-L1 expression is regulated by diverse signaling pathways mediated through cytokine and chemokine receptors, oncogenic growth factor signaling, and epigenetic, transcriptional, and post-transcriptional regulatory mechanisms. *AKT, protein kinase b; AP-1, activator protein 1; EGF, epidermal growth factor; ERK, extracellular signal–regulated kinase; FGF, fibroblast growth factor; GSK3β, glycogen synthase kinase 3β; HGF, hepatocyte growth factor; HIF1α, hypoxia-inducible factor-1α; IFN-γ, interferon-γ; IFNGR, interferon-γ receptor; IL-6, Interleukin-6; IL-6R, interleukin 6 receptor; IRF1/3, interferon regulatory factor 1/3; JAK1/2, Janus Kinase 1/2; LEF, lymphoid enhancer-binding factor; MEK, mitogen-activated protein kinase kinase; miRNA, microRNAs; mTOR, mechanistic target of rapamycin; MYC, myc proto-oncogene; NF-κB, nuclear factor κB; NRF2, nuclear factor erythroid 2–related factor 2; PD-L1, programmed death ligand-1; PI3K, phosphatidylinositide 3-kinase; Raf, rapidly accelerated fibrosarcoma kinase; Ras, rat sarcoma small gtpase; STAT1/3, signal transducer and activator of transcription 1/3; TCF, T cell-specific transcription factor; 3'UTR, 3' untranslated region.* Created in BioRender. https://BioRender.com/9wzmzw2

[71]. Nevertheless, given its dual and context-dependent immunomodulatory roles, IL-4 continues to represent a potential therapeutic target in BC [72].

IL-35 is secreted by Tregs and Bregs, promoting tumor growth and metastasis via STAT1/STAT3 signaling and the conversion of conventional T cells into Tregs [73–76]. IL-35 also exerts systemic effects on additional mechanisms of immune evasion, including the release of small, tumor-derived extracellular vesicles that actively promote tumor angiogenesis [76]. Accordingly, therapeutic targeting of IL-35 signaling may represent a promising immunomodulatory strategy to enhance the efficacy of BC therapies.

2.6 Regulatory T cells

Tregs are a specialized subset of $CD4^+$ T cells that play crucial roles in maintaining immune homeostasis. In both humans and mice, Tregs account for approximately 5–10% of circulating $CD4^+$ T cells. They are broadly classified into two main types: thymus-derived Tregs (tTregs) and peripherally induced Tregs (pTregs). Under physiological conditions, Tregs suppress excessive immune activation through the secretion of inhibitory cytokines, the suppression of cytolytic activity, and the induction of metabolic disruption, thereby preserving immune tolerance and preventing autoimmunity [77].

However, in the context of cancer, these same immunosuppressive mechanisms can be hijacked to support tumor growth. Tregs suppress effector T-cell function, facilitate tumor progression, and maintain an immunosuppressive TME. The expansion of these cells within tumors is promoted by cytokines, such as IL-10, TGF-β, and IL-35, which contribute to therapeutic resistance across various breast BC subtypes [31, 65] (Fig. 2).

Compared with Tregs found in normal tissues, tumor-infiltrating Tregs exhibit greater viability, increased proliferative potential, and enhanced suppressive activity [78]. By attenuating antitumor immune responses, these

cells play pivotal roles in tumor progression and immune evasion [22]. Therefore, effective modulation or depletion of Tregs has become a key objective in improving the efficacy of antitumor immunotherapies [79, 80].

One promising approach involves selectively targeting Tregs within the TME to restore effector T-cell activity [81]. In particular, Tregs upregulate multiple immune checkpoint molecules that inhibit cytotoxic T-cell responses. The introduction of ICIs has revolutionized cancer treatment by blocking these inhibitory pathways, thereby reactivating immune cells to recognize and destroy tumor cells [82]. Over the past decade, ICIs have demonstrated remarkable clinical success in several malignancies, including melanoma, hepatocellular carcinoma, and lung, gastric, and colorectal cancers, resulting in significant improvements in both overall and progression-free survival [83].

2.7 Myeloid-derived suppressor cells

MDSCs represent a heterogeneous population of immature myeloid cells with potent immunosuppressive properties. MDSCs are classified into two major subpopulations: granulocytic or polymorphonuclear MDSCs (PMN-MDSCs), which resemble neutrophils morphologically and phenotypically, and monocytic MDSCs (M-MDSCs), which share similarities with [25, 84–87] (Fig. 2).

In humans, MDSCs typically express CD33 and CD11b but display low levels of HLA-DR [23]. The granulocytic subset shows a $CD11b^{+}Ly6G^{+}Ly6C^{low}$ phenotype, whereas the monocytic subset exhibits a $CD11b^{+}Ly6G^{-}Ly6C^{high}$ phenotype [84]. Although both subsets suppress T-cell activity, they employ distinct inhibitory mechanisms.

PMN-MDSCs constitute more than 70% of the total MDSC population, whereas M-MDSCs account for less than 30% of the total population. In addition, several minor subgroups have been identified. Early MDSCs (e-MDSCs) appear in tumors and strongly suppress T cells both in vivo and in vitro, thereby promoting tumor growth and metastasis. Another peripheral blood subset, fibrocytic MDSCs (F-MDSCs), has also been described. Moreover, MDSC-like cells (MDSC-LCs), which share MDSC surface markers but lack immunosuppressive functions, are detectable in the early stages of tumor development. Proteome analyses have confirmed that MDSCs represent a unique myeloid subset with specialized functional properties [25, 87].

A hallmark of MDSCs is their scarcity in the peripheral blood of healthy individuals and marked expansion under pathological conditions such as chronic inflammation, infection, or cancer. The proliferation of these cells is driven by multiple factors, including prostaglandins, stem cell factor (SCF), macrophage colony-stimulating factor (M-CSF), granulocyte/macrophage colony-stimulating factor (GM-CSF), IL-6, and vascular endothelial growth factor (VEGF). The activation of MDSCs is further promoted by IFN-γ, Toll-like receptor ligands, IL-4, IL-13, and TGFβ [25, 85, 87].

Within the TME and peripheral blood, MDSCs generate high levels of reactive oxygen species, reactive nitrogen species, and peroxynitrite and display elevated arginase-1 activity. These factors collectively suppress T-cell responses, induce T-cell dysfunction, and facilitate tumor immune escape by impairing the function of key molecules such as the T-cell receptor, STAT1, and indoleamine 2,3-dioxygenase [23, 84, 85] (Fig. 3).

In BC, MDSCs play a pivotal role in suppressing antitumor immunity. Strategies aimed at reducing their accumulation or inhibiting their immunosuppressive activity have been shown to enhance therapeutic efficacy [23, 87].

2.8 Downregulation of MHC class I molecules

MHC-I molecules are key mediators of antigen presentation to cytotoxic $CD8^{+}$ T lymphocytes, enabling immune recognition and elimination of malignant cells. In BC, downregulation of MHC-I constitutes a central immune evasion mechanism within the immunoediting process, allowing tumors to escape from T-cell-mediated cytotoxicity while potentially increasing susceptibility to NK cell killing. This suppression is driven by genetic alterations, transcriptional and epigenetic modulation, and impaired antigen presentation, often involving PR-dependent signaling and HER2 expression. Reduced MHC-I levels are correlated with aggressive BC, metastasis, and diminished responses to immune checkpoint blockade [19, 88].

In TNBC, high expression of myelin and lymphocyte protein 2 (MAL2), a transmembrane protein that regulates MHC-I surface levels, is correlated with reduced $CD8^{+}$ T-cell cytotoxicity, indicating that MAL2 suppresses MHC-I–dependent immunosurveillance [89]. Loss or downregulation of MHC-I molecules occurs in more than 70% of BC patients [90]. Thus, MHC-I expression may serve as a predictive biomarker, whereas its loss represents a major obstacle to PD-1- and PD-L1–targeted immune checkpoint blockade.

At the transcriptional level, MHC-I expression is regulated primarily by NLRC5, a master activator of MHC-I genes that also induces B2M, TAP1, and PSMB9 [91, 92]. Through the formation of the CITA enhanceosome complex with RFX5 and RFXAP, NLRC5 promotes the transcriptional activation of MHC-I [91]. Interferons (IFN-α, -β, and -γ) further increase MHC-I expression via JAK/STAT signaling, engaging NF-κB and IRFs, whereas NLRC5 in turn modulates IFN responses, forming a feedback loop regulating MHC-I transcription [93].

Epigenetic regulation further constrains MHC-I expression. Inhibitors of DNA or histone methyltransferases can restore MHC-I levels [94, 95], whereas

noncoding RNAs (ncRNAs), particularly miRNAs, modulate MHC-I transcription and antigen presentation, influencing immune escape [20].

Other mechanisms contributing to MHC-I loss include loss of heterozygosity, promoter hypermethylation, and point mutations within HLA or antigen presentation pathway genes [19]. A newly identified SUSD6/TMEM127/WWP2 inhibitory axis mediates MHC-I ubiquitination and lysosomal degradation, leading to reduced surface expression and impaired antitumor immunity [96]. Targeting this pathway could represent a novel strategy to restore $CD8^+$ T-cell function.

Downregulation of MHC-I molecules underlies both intrinsic and acquired resistance to immunotherapy. An MHC-I-low phenotype, which is observed in 40–90% of human malignancies, including BC, is correlated with poor prognosis [97, 98]. This reduced expression arises through multiple mechanisms, including gene deletion or mutation, epigenetic silencing, mRNA instability, and enhanced lysosomal degradation mediated by MAL2 and PCSK9 [21].

Together, these findings highlight that impairment of antigen presentation is a central mechanism of immune escape. Therefore, restoration of MHC-I expression or reactivation of the antigen presentation machinery represents a promising strategy to enhance tumor immunogenicity and improve the efficacy of immunotherapy in BC.

2.9 Cancer-associated fibroblasts and immune modulation

Cancer cells recruit endogenous stromal cells in its neighborhood and these tumor-associated stromal cells arise from distinct cellular origins such as fibroblasts, pericytes, bone marrow-derived mesenchymal stem cells (MSCs), adipocytes, endothelial cells that underwent EMT. The transition of some of these cells into cancer-associated fibroblasts (CAFs) occurs by soluble factors within the tumor microenvironment [99, 100].

CAFs interact extensively with cancer cells and infiltrating immune cells directly or indirectly via secreting cytokines and remodeling of ECM [101]. CAFs induce "desmoplastic" reaction by producing extracellular matrix proteins such as laminin, collagen types I, III, IV, V and hyaluronic acid as well as by degrading the ECM via proteases like MMPs, urokinase-type plasminogen activator. This process remodels the TME, promoting stromal fibrosis, and creating a scaffold that hinders immune cell and drug penetration, leading to immune evasion and drug resistance [102, 103]. CAFs interfere infiltration and activation of immune cells not only by remodeling the ECM constructing immune barriers but also by secreting immunosuppressive cytokines such as TGF-beta [104].

The physical barriers and ECM created by CAFs also hinder T cell infiltration and migration towards the tumor site, exacerbating T cell dysfunction [105]. It was shown that expression of Adipocyte Enhancer-Binding Protein 1 (AEBP1), which is mainly produced by CAFs, positively correlates with T cell dysfunction and indicative of unfavorable patient outcomes in TNBC patients. Furthermore, deletion of fibroblast AEBP1 enhanced T cell cytotoxicity and suppressed tumor growth in mice [106].

Biglycan, a prognostic biomarker for predicting immunotherapy response was found to be highly upregulated in CAFs derived from TNBC patient's specimens who did not respond to immunotherapy. CAF-derived biglycan may facilitate the interaction of CAFs with immune cells, inhibiting NK cells and $CD8^+$ T cells [107].

CAFs include heterogeneous and plastic populations, which might be due to the multiple origins of the precursor cells. The main subsets of CAFs include αSMA high IL-6 low myofibroblasts (myCAFs) and αSMA low IL-6 high inflammatory CAFs (iCAFs) [108]. iCAFs are generally considered to promote cancer growth and metastasis via secretion of inflammatory cytokines and growth factors [109]. myCAFs exhibit dual tumor-restraining and tumor promoting roles, depending on the stage of the tumor and the complex context of the surrounding TME [109]. A novel subpopulation characterized by the expression of major histocompatibility complex class II molecules was identified and termed antigen-presenting CAFs (apCAFs) suggesting their immunodulatory function [110], as well as an immunosuppressive role in BC since they induce Treg cell formation [111]. Furthermore, new spatially and functionally distinct CAF subpopulations such as vascular CAFs (vCAFs), cycling CAFs (cCAFs), and developmental CAFs (dCAFs) have been characterized in BC using single cell RNA sequencing [111].

Recent studies have shown that CAFs cooperate with specific $SPP1^+$ subsets of macrophages to create an immunosuppressive tumor microenvironment. A conserved interaction between CAFs and $SPP1^+$ macrophages may promote angiogenesis, extracellular matrix remodeling and immune exclusion, contributing to resistance to ICI therapy [112]. High infiltration of tumors by $CA9^+$CAFs/$SPP1^+$TAMs is related to reduced infiltration of effector immune cells, poor prognosis, and decreased response to immunotherapy [113]. The CAF-induced TAMs exhibit an elevated expression of immune checkpoints such as PD1 and cause immunosuppression by reducing T-cell activation and proliferation. In BC, the recruitment of monocytes to the tumor is triggered by the CAF-driven CXCL12/CXCR4 axis, which also supports the acquisition of an immunosuppressive lipid-associated macrophage (LAM) phenotype [114].

2.10 Neuronal activity

The TME encompasses not only immune and stromal components but also nerve fibers and associated Schwann cells, which contribute to cancer progression and the therapeutic response. Increasing evidence highlights dynamic bidirectional crosstalk between the nervous system and tumors as well as between stromal and immune cells, influencing both carcinogenesis and the efficacy of anticancer therapies [115] (Fig. 5).

Neuronal activity within BC tissue has been detected in murine models [116]. The type of neural signaling determines whether this interaction promotes or inhibits tumor growth. Tumor innervation arises from the sensory, parasympathetic, and sympathetic nervous systems. Notably, parasympathetic fibers generally exert protective or tumor-suppressive effects, whereas sympathetic activation is typically protumorigenic [117].

Sympathetic nerve activity can potentiate the immunosuppressive function of MDSCs through β_2-adrenergic receptor signaling, thereby facilitating tumor progression [118]. In BC, nearly 85% of tumors contain nerve fibers, which are predominantly of sympathetic origin, and their presence is correlated with poor prognosis [119]. Since normal breast tissue is innervated by multiple neuronal subtypes, including sensory fibers, tumorigenesis is thought to remodel the neural microenvironment by inducing neoneurogenesis and axonogenesis [120].

A distinct subset of unmyelinated sensory neurons expressing the transient receptor potential vanilloid 1 (TRPV1) channel plays a pivotal role in modulating immune responses in various diseases, including cancer [121]. The activation of these neurons triggers the release of vasoactive neuropeptides, such as vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP), which regulate local blood flow and immune cell

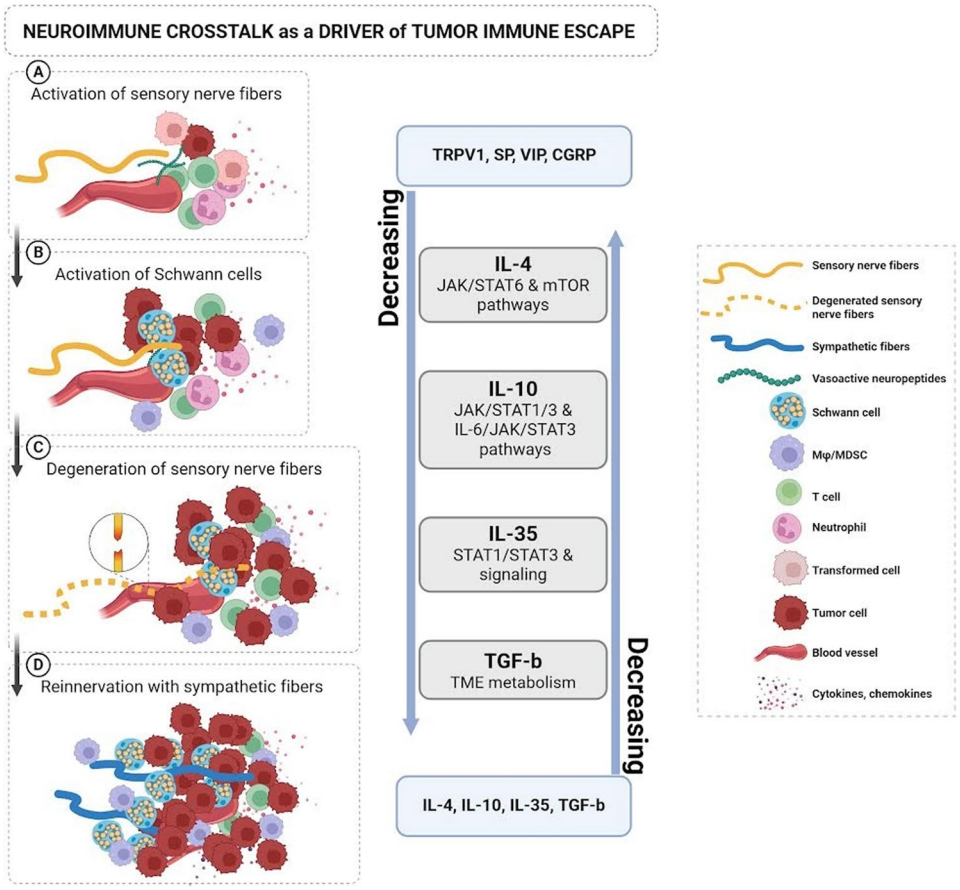

Fig. 5 The impact of neuronal activity on cancer cell escapes from the immune system targeting and development of resistance to immunotherapy. **A** Activation of sensory nerve fibers by factors released from transformed cells, as well as TRPV1 agonists, triggers the eradication of acute inflammation. **B** Activation of Schwann cells decreases the release of vasoactive neuropeptides by macrophages, leading to the dormancy of subacute inflammation. **C** Degeneration of sensory nerve fibers leads to chronic inflammation, increased tumorigenesis, metastatic potential, and resistance to immunotherapy. **D** Reinnervation with sympathetic fibers leads to increased angiogenesis, metastasis, enhanced chronic inflammation, and resistance to immunotherapy. *CGRP, calcitonin gene-related peptide; JAK, janus kinase; IL, interleukin; Mφ, macrophage; MDSC, myeloid-derived suppressor cell; mTOR, mechanistic target of rapamycin; SP, substance P; STAT1/3, signal transducer and activator of transcription 1/3; TGF-β, transforming growth factor β; TME, tumor microenvironment; TRPV1, transient receptor potential vanilloid 1; VIP, vasoactive intestinal peptide.* Created in BioRender. https://BioRender.com/9wzmzw2

activity [122]. Experimental inactivation of sensory fibers via high-dose capsaicin enhances the metastatic spread of TNBC and induces marked gene expression changes in murine models [123].

Sensory neurons rapidly respond to a variety of stimuli, including pathogens, danger-associated molecular patterns (DAMPs), and inflammatory mediators. Their response kinetics are considerably faster than those of immune cells, allowing the nervous system to act as an early responder in coordinating host defense mechanisms, including anticancer immunity [120]. Consequently, disruption of neural-immune communication or aberrant neurogenesis may contribute to resistance to chemoimmunotherapy, underscoring the importance of understanding sensory nerve plasticity and dysfunction in the development of more effective therapeutic strategies.

3 Key predictive and prognostic biomarkers in breast cancer immunotherapy

BC displays a wide spectrum of immunogenicity, shaped by molecular, cellular, and microenvironmental factors that critically influence tumor progression and therapeutic responsiveness. Overall, BC is considered a poorly immunogenic malignancy that is typically characterized by a low TMB, scarce TILs, defective antigen presentation, and a highly immunosuppressive TME [13–18]. Therefore, the identification of robust and reproducible biomarkers remains essential for selecting BC patients most likely to benefit from immunotherapy. Currently, the most promising biomarkers include PD-L1 expression, TMB level, neoantigen load, TIL density, and cannabinoid receptor expression [10, 124–126] (Fig. 6).

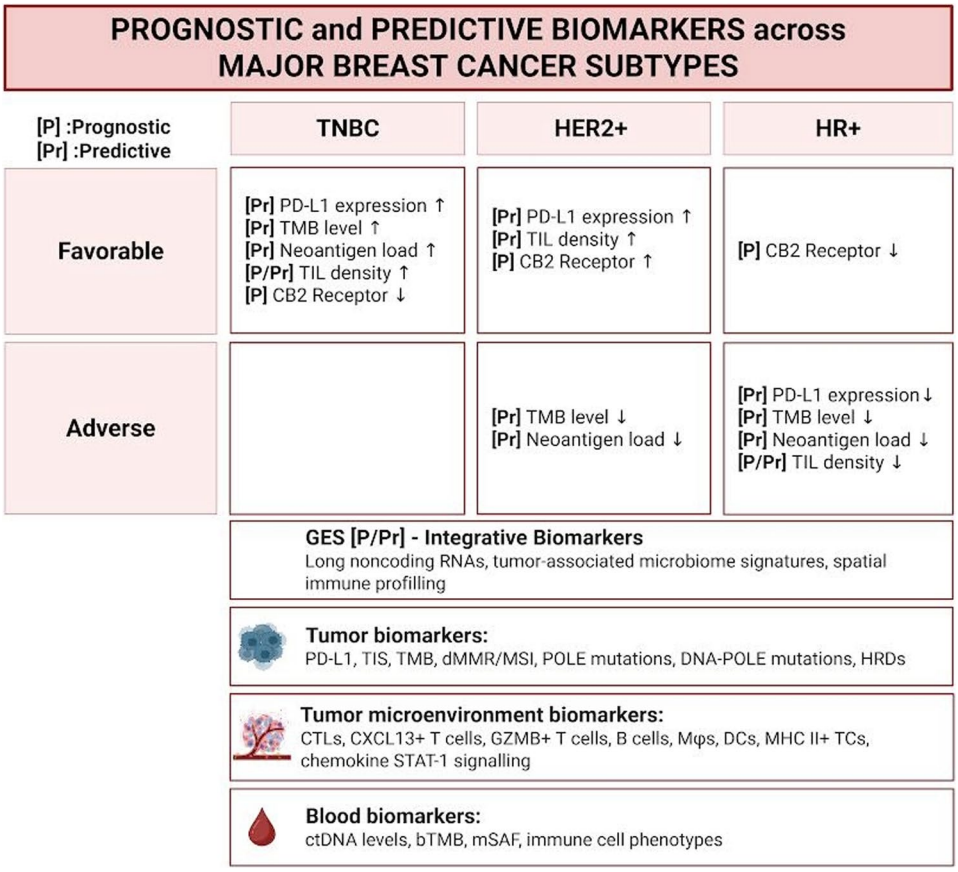

Fig. 6 Prognostic and predictive biomarkers across major breast cancer subtypes. The figure summarizes representative biomarkers associated with prognosis and/or prediction of therapeutic response across major breast cancer subtypes. Annotations reflect the predominant clinical and biological context and may vary depending on disease subtype and treatment setting. Up arrow - increase; down arrow - decrease. *bTMB, blood-based tumor mutational burden; CB2, cannabinoid receptor 2; ctDNA, circulating tumor DNA; CTL, cytotoxic T lymphocyte; CXCL13, C–X–C motif chemokine ligand 13; DC, dendritic cell; dMMR/MSI, deficient mismatch repair/ microsatellite instability; GES, gene expression signature; GZMB, granzyme B; HER2*$^{+}$*, human epidermal growth factor receptor 2-positive; HR*$^{+}$*, hormone receptor-positive; HRDs, homologous recombination defects; ICIs, immune checkpoint inhibitors; Mø, macrophage;; MHC II, major histocompatibility complex class II molecules; mSAF, maximum somatic allele frequency; PD-L1, programmed cell death ligand-1; POLE, polymerase epsilon; STAT1, signal transducer and activator of transcription 1; TCs, tumor cells; TILs, tumor-infiltrating lymphocytes; TIS, tumor inflammation signature; TMB, tumor mutational burden; TME, tumor microenvironment; TNBC, triple-negative breast cancer.* Created in BioRender. https://BioRender.com/9wzmzw2

3.1 Programmed death ligand 1 expression

PD-L1 expression is routinely assessed by immunohistochemistry and serves as a key predictive biomarker for response to ICIs targeting the PD-1/PD-L1 axis. However, the lack of assay harmonization, including differences in antibodies, scoring systems, and positivity thresholds, complicates cross-study comparisons and clinical interpretation [127, 128]. The combined positive score (CPS), which quantifies PD-L1 expression on both tumor and immune cells, is currently the most accepted scoring system for guiding immunotherapy use in BC (Fig. 6).

High PD-L1 expression is generally associated with improved responses to anti-PD-1/PD-L1 therapies, particularly in TNBC and HER2-positive BC subtypes [12, 129, 130]. In TNBC, PD-L1 positivity is correlated with increased TIL density, increased immune gene signatures, and increased sensitivity to atezolizumab and pembrolizumab. Notably, the KEYNOTE-355 and IMpassion130 trials demonstrated significant survival benefits from PD-1/PD-L1 blockade in PD-L1-positive TNBC patients [10, 128, 131–133].

PD-L1 expression, however, exhibits substantial heterogeneity across BC subtypes and even within individual tumors. HR-positive and HER2-low tumors often display low or no PD-L1 expression, limiting their responsiveness to checkpoint inhibition [134]. Moreover, temporal and spatial variability, influenced by prior treatments, hypoxia, and cytokine exposure (e.g., IFN-γ), can dynamically modulate PD-L1 expression, emphasizing the need for serial assessment and context-dependent interpretation [56, 135].

In addition to its role as a predictive biomarker, PD-L1 expression also has prognostic value. In TNBC, PD-L1 positivity generally correlates with favorable prognosis, reflecting a more inflamed TME. Conversely, in HR-positive tumors, PD-L1 upregulation may signal adaptive immune resistance and predict poorer clinical outcomes [12, 130, 136, 137].

Emerging research highlights the importance of PD-L1 expression on immune cells, particularly macrophages and DCs, which may predict immunotherapy response more accurately than tumor-cell PD-L1 alone [138]. Additionally, epigenetic and posttranslational regulation of PD-L1, including miRNA-mediated silencing, glycosylation, and ubiquitination, are under investigation as novel therapeutic targets to increase ICI therapy efficacy [139].

Overall, while PD-L1 remains the most clinically validated biomarker in BC immunotherapy, its predictive precision can be enhanced by integration with other indicators, such as TMB, TIL density, and immune gene expression profiles, supporting a multifactorial biomarker approach for patient stratification and personalized treatment.

3.2 Tumor mutational burden and neoantigen load

TMB quantifies the number of somatic mutations per megabase of the tumor genome, whereas neoantigen load represents the number of mutated peptides that can be recognized by T cells. These interrelated biomarkers have shown predictive value in multiple cancers, but their clinical relevance in BC is still under investigation. Early evidence suggests they may be particularly informative in BC subtypes with high mutational rates, such as TNBC [12, 140, 141]. Standardizing TMB assessment and defining clinically meaningful thresholds are essential for its broader use in BC immunotherapy (Fig. 6).

TMB serves as a surrogate marker for neoantigen load, which can stimulate strong antitumor immune responses. Tumors with high TMB often show increased infiltration by CTLs and other immune effector cells [142], as the greater diversity of neoantigens enhances MHC-mediated immune recognition [143, 144]. As a result, high-TMB tumors are generally more responsive to PD-1/PD-L1 immune checkpoint blockade [2]. Across solid tumors, BC has an intermediate TMB of approximately 2.6 mutations per megabase (mut/Mb) compared with melanoma (13.5 mut/Mb) and lung cancer (7.2 mut/Mb) [145, 146]. Only approximately 5% of BCs are classified as TMB-high [3]. These tumors tend to present elevated TIL densities, enriched immune gene signatures, and improved outcomes following PD-1/PD-L1 inhibition [144].

TMB also varies among BC molecular subtypes. TNBC, particularly basal-like tumors, typically has a higher TMB than do ER-positive or HER2-positive cancers [143, 144]. PD-L1-positive TNBCs are frequently associated with abundant TILs and enhanced responses to ICI [3, 147]. Furthermore, metastatic BCs constitute a greater proportion of TMB-high cases than primary tumors (8–11% vs. 2–5%, respectively), possibly reflecting cumulative genomic instability during tumor evolution [3]. However, current data do not establish a direct relationship between TMB and metastatic potential [146]. Ongoing studies aim to validate TMB as a predictive biomarker for early-stage BC and refine its role in patient stratification for ICI therapies.

3.3 Tumor-infiltrating lymphocyte density

TILs are immune cells that reside within the TME and serve as key indicators of antitumor immune activity. High TIL density is correlated with improved prognosis and enhanced responses to chemotherapy and immunotherapy, particularly in TNBC and HER2-positive BC [13, 26]. Histopathological assessment of TILs provides

valuable prognostic information and supports patient selection for immunotherapy [148].

TILs comprise diverse immune subsets, including $CD8^+$ CTLs, $CD4^+$ helper T cells (Th), $FOXP3^+$ Tregs, B cells, and natural killer (NK) cells [13]. Their density, localization, and phenotype reflect immune surveillance within the TME. High $CD8^+$ CTL infiltration predicts favorable outcomes and better responses to chemotherapy and ICIs, whereas low TIL levels indicate weak immune recognition and poor prognosis [148] (Fig. 6).

The clinical relevance of TILs varies by molecular subtype. In TNBC, elevated TIL levels strongly predict a favorable prognosis and increased sensitivity to chemotherapy and immunotherapy [26, 147], while in HER2-positive BC, TIL abundance reflects an anti-HER2 therapy response. In luminal (HR-positive/HER2-negative) tumors usually exhibit low TIL infiltration and limited prognostic relevance [13, 149].

TILs are classified by their degree of localization: stromal TILs (sTILs) occupy the tumor stroma, and intratumoral TILs (iTILs) reside within tumor nests [150]. High sTIL density in early-stage TNBC is associated with excellent survival following adjuvant chemotherapy [26]. Increased $CD8^+$ and iTIL infiltration after neoadjuvant therapy predict a greater pathological complete response, whereas enrichment with $FOXP3^+$ Tregs indicates shorter survival [151, 152].

TIL composition is shaped by tumor genomic and therapeutic factors. In ER-positive BC with PIK3CA mutations, increased $CD8^+$ infiltration may predict recurrence [153]. PD-L1 expression suppresses TIL cytotoxicity [154], whereas neoadjuvant therapy can reduce the number of immunosuppressive subsets [151, 155]. In highly infiltrated tumors, TILs often form tertiary lymphoid structures (TLSs), which are associated with an enhanced chemotherapy response and longer survival [156].

Although TILs are present in both primary and metastatic lesions, immune infiltration generally decreases with progression, and their prognostic significance in advanced BC remains uncertain [13, 149]. TIL density varies even in preinvasive lesions such as ductal carcinoma in situ, with unclear prognostic implications. The HER2-positive and TNBC subtypes exhibit greater immunogenicity and stronger TIL infiltration, explaining their superior responsiveness to immunotherapy [14, 147, 157].

Standardized and automated TIL assessment [13, 15, 149], including artificial intelligence (AI) based approaches, may improve reproducibility and refine patient selection [158, 159]. Integrating standardized TIL evaluations into clinical trials will reinforce their predictive value and support the development of personalized immunotherapy strategies in BC.

3.4 Antigen presentation

Effective antigen presentation is fundamental to antitumor immunity, enabling the recognition of tumor-derived peptides by T cells. DCs and other antigen-presenting cells (APCs) process and present tumor antigens via MHC molecules to initiate T-cell activation [19, 160]. Impairments in this process, such as MHC I downregulation or defective antigen-processing machinery, promote immune escape [19] (Fig. 6). Therapeutic approaches that restore or enhance antigen presentation, such as DC-based vaccines or agents that modulate MHC expression, hold promise for reactivating antitumor immunity [10, 161].

Defective antigen presentation has been implicated in metastasis. In BC with liver metastasis, macrophages and DCs exhibit markedly reduced MHC expression compared with that in primary tumors, which is correlated with a worse prognosis [160]. The re-expression of MHC, particularly MHC-I, thus represents a key therapeutic target for advanced BC.

Recent evidence has identified a novel subset of antigen-presenting mast cells capable of cross-presenting tumor antigens in TNBC [162]. In preclinical and pilot clinical studies, high levels of these cells were linked to improved anti-PD-1 efficacy. Pharmacologic activation of mast cell antigen presentation, for example, with cromolyn, a clinically approved antiallergic drug, enhances T-cell activation and sensitizes tumors to PD-1 blockade [163]. These findings highlight an unexpected role for mast cells in antigen presentation and suggest a new avenue to improve immunotherapy efficacy in patients with BC, particularly TNBC.

3.5 Cannabinoid receptor expression

Cannabinoid receptors, particularly type 2 cannabinoid receptor (CB2), have emerged as potential biomarkers and therapeutic targets in BC because of their dual role in tumor progression and immune regulation. Unlike CB1, which is expressed primarily in the central nervous system, CB2 is predominantly expressed on immune cells and various tumor types, where it modulates tumor–immune interactions and affects oncogenic signaling [142, 164, 165].

CB2 expression typically exceeds that of CB1 in BC and is enriched in HR-negative and HER2-positive tumors. Approximately 75% of breast adenocarcinomas express CB2, with strong association with HER2 positivity and aggressive disease [166] including worse prognosis, increased local recurrence, and enhanced tumor aggressiveness, suggesting context-dependent oncogenic function [166] (Fig. 6).

In addition to affecting tumor cells, CB2 contributes to the immunosuppressive landscape of the TME. It is expressed on TAMs and Tregs, where its activation

promotes immune tolerance inhibiting CTL function, inducing M2 macrophage polarization, and suppressing proinflammatory cytokine release [167–169]. As a result, CB2 signaling may impair antitumor immunity and reduce the effectiveness of ICIs [165].

Conversely, CB2 blockade or modulation has demonstrated immunostimulatory effects in preclinical models by enhancing $CD8^+$ T-cell infiltration, cytokine production, and myeloid cell reprogramming [169, 170], and shows synergy with PD-1/PD-L1 blockade [165, 169].

Integrating CB2 expression profiling with established biomarkers such as PD-L1, TMB, and TIL density could improve the predictive accuracy of immunotherapy outcomes [165], particularly in immunologically "cold" BC subtypes, such as luminal and HER2-low tumors, where immune infiltration and checkpoint activity are limited [166, 170, 171]. Further clinical validation is required to define CB2's prognostic and predictive value and to support its incorporation into personalized immunotherapy strategies.

3.6 Other essential biomarkers

In addition to established markers such as PD-L1, TMB, TILs, and CB2, a range of immune-related gene expression signatures are being explored as tools for predicting the immunotherapy response in BC patients. These panels assess immune cell infiltration, cytokine and chemokine expression, and antigen presentation pathways, providing a comprehensive view of the tumor immune landscape. Platforms such as Oncotype DX, MammaPrint, and the Tumor Inflammation Signature (TIS) have demonstrated the potential to stratify patients according to their immune activation status and likelihood of benefiting from immune checkpoint blockade [130, 172, 173]. The integration of such gene expression signatures with traditional biomarkers, along with free TNF receptor and isoforms of IL-8 in blood and urine [174], may significantly increase predictive precision and benefit personalized immunotherapy strategies [175, 176].

Within TNBC, a subtype characterized by greater immune infiltration and genomic instability, emerging biomarkers include immune checkpoint-related long noncoding RNAs (lncRNAs), tumor-associated microbiome signatures, and spatial immune profiling. These parameters provide additional insight into tumor-immune cell interactions, local immunometabolic gradients, and therapy-induced immune remodeling, all of which may determine the response or resistance to immunotherapy [177] (Fig. 6).

The integration of multiomic biomarkers, encompassing genomic, transcriptomic, epigenetic, and microbiome data, represents a major step toward precision immuno-oncology in BC. Combining such multidimensional datasets with AI-driven analytic frameworks could enable the identification of robust composite predictors and guide individualized treatment algorithms [172, 173, 175, 176].

However, the standardization and validation of these emerging biomarkers remain critical challenges, in fact large-scale, prospective studies are needed to confirm their prognostic and predictive value, harmonize assay methodologies, and define clinically relevant thresholds.

4 Immunotherapeutic approaches in breast cancer

Immunotherapy has revolutionized the management of multiple cancers by harnessing the patient's immune system to recognize and eliminate tumor cells. More recently, it has emerged as a promising strategy in BC. Current approaches focus primarily on ICIs, with ongoing development of cancer vaccines, ACT, and oncolytic viruses [5–7, 178–181] (Fig. 7).

4.1 Immune checkpoint inhibitors

4.1.1 Established immune checkpoint targets: PD-1/PD-L1 and CTLA-4 pathways

ICIs, monoclonal antibodies (mAbs) targeting the PD-1/PD-L1 axis, have become central to cancer immunotherapy for multiple malignancies, including BC [6, 182]. By blocking inhibitory signals that dampen T-cell responses, these mAbs restore effector T-cell activity and promote antitumor immunity (Fig. 7).

PD-1 inhibitors (e.g., pembrolizumab and nivolumab) prevent PD-1 interaction with PD-L1/PD-L2, thereby reversing T-cell exhaustion [129, 183]. PD-L1 inhibitors, including atezolizumab and durvalumab, block PD-L1 interactions with PD-1 and CD80, reactivating antitumor immunity [184, 185].

Clinical trials demonstrate subtype-specific efficacy of ICIs in BC. In TNBC, the IMpassion130 trial showed improved progression-free survival with atezolizumab plus nab-paclitaxel in PD-L1-positive disease, marking the first FDA approval of ICIs in BC in March 2019. However, it was later voluntarily withdrawn in August 2021 due to failure of a subsequent trial (IMpassion131) to confirm benefits and lack of strong overall survival (OS) data [132]. KEYNOTE-355 [128, 131, 133, 186], KEYNOTE-522 [187], and I-SPY2 [188] studies evaluated pembrolizumab combined with chemotherapy in TNBC patients and HR-positive/HER2-negative BC patients and reported enhanced overall survival and higher pathological complete response rates than did chemotherapy alone. The KEYNOTE-756 randomized phase III trial of pembrolizumab with cytotoxic chemotherapy in the neoadjuvant setting revealed superior rates of pathological complete response than did chemotherapy alone in patients with HR-positive/HER-negative BC (24.3% vs. 15.6%, respectively) [189].

In HER2-positive, trastuzumab-resistant BC, the DIAmOND trial tested durvalumab (anti-PD-L1) in

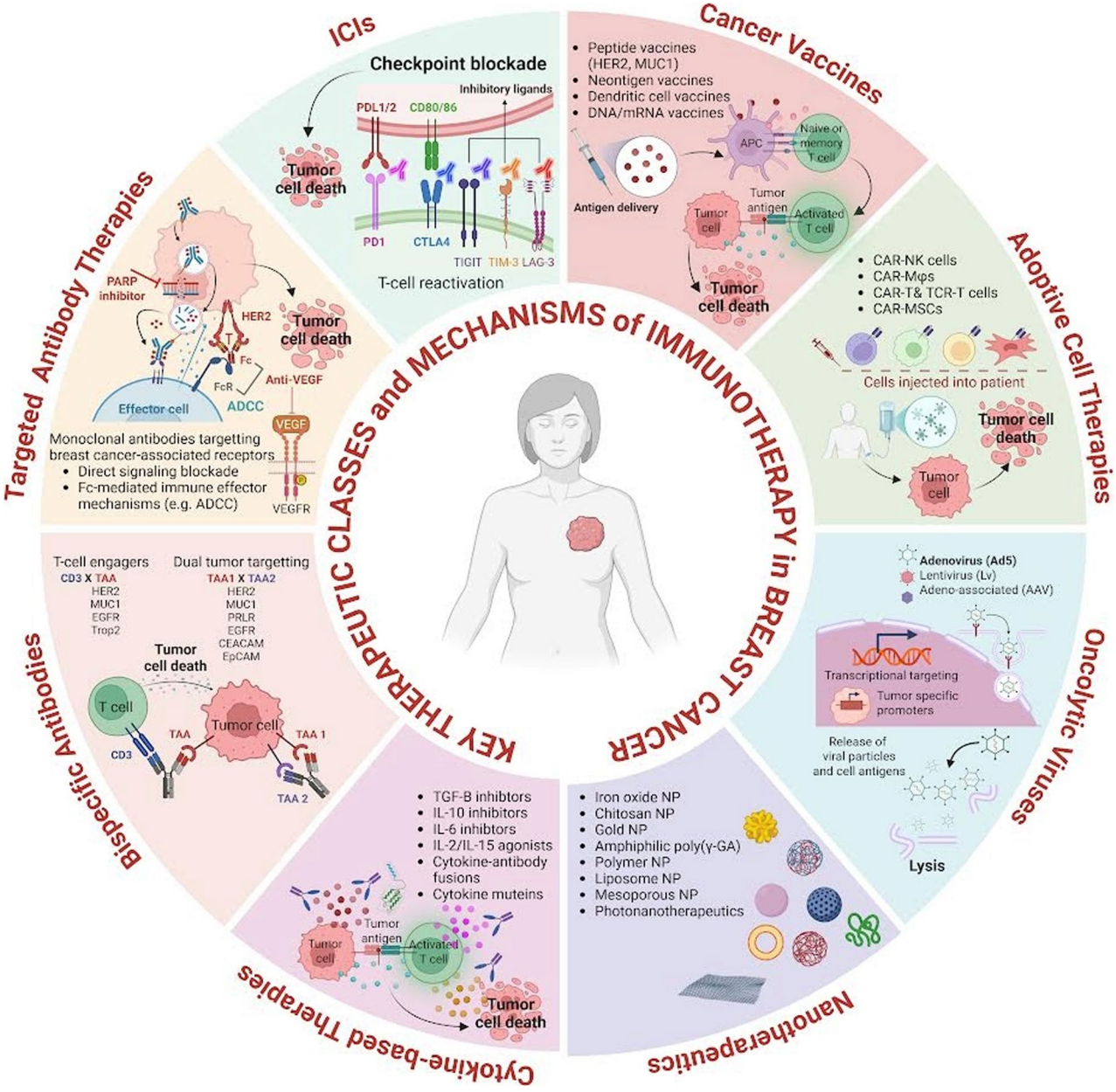

Fig. 7 Key therapeutic strategies and mechanisms of immunotherapy in breast cancer. The figure schematically illustrates major immunotherapeutic strategies in breast cancer, including immune checkpoint blockade, targeted antibody therapies, bispecific antibodies, cytokine-based interventions, nanotherapeutics, oncolytic/viral vector–based approaches, adoptive cell therapies, and cancer vaccines. Each panel highlights representative mechanisms by which these modalities modulate antitumor immunity and contribute to tumor cell eradication. *AAV*, *adeno-associated virus; AD5*, *adenovirus serotype 5; ADCC*, *antibody-dependent cellular cytotoxicity; APC*, *antigen-presenting cell; CAR – chimeric antigen receptor; CEACAM*, *carcinoembryonic antigen–related cell adhesion molecule; CTLA-4*, *cytotoxic T-lymphocyte–associated protein 4; EGFR*, *epidermal growth factor receptor; EpCAM*, *epithelial cell adhesion molecule; FcR*, *Fc receptor; GA*, *glutamic acid; HER2*, *human epidermal growth factor receptor 2; ICIs*, *immune checkpoint inhibitors; IL*, *interleukin; LAG-3*, *lymphocyte activation gene-3; Lv*, *lentiviral vector; Mø*, *macrophage; MSC*, *mesenchymal stromal cells; MUC1*, *mucin 1; NK*, *natural killer cell; NP*, *nanoparticle; PARP*, *poly(ADP-ribose) polymerase; PD-1*, *programmed cell death protein-1; PD-L1/2*, *programmed cell death ligand-1/2; PRLR*, *prolactin receptor; TAA*, *tumor-associated antigen; TGF-β*, *transforming growth factor β; TIGIT*, *T-cell immunoreceptor with Ig and ITIM domains; TIM-3*, *T-cell immunoglobulin and mucin-domain containing protein-3; Trop2*, *trophoblast cell surface antigen 2; VEGF*, *vascular endothelial growth factor; VEGFR; VEGF receptor*. Created in BioRender. https://BioRender.com/9wzmzw2

combination with tremelimumab (anti-CTLA-4) with or without trastuzumab and reported a 27% overall response rate (ORR) and 63% ORR in ER-positive, high-TIL subgroups [190]. Additional combination strategies have also demonstrated promise. Imprime PGG, a dectin-1 agonist, enhances pembrolizumab efficacy in metastatic TNBC, achieving a 14.3% ORR, 2.7-month median progression-free survival (PFS), and 16.4-month median overall survival (OS) [191]. Alpha-lactalbumin vaccines are under early-phase investigation, both as monotherapy and in combination with pembrolizumab, in TNBC and high-risk BC patients [192]. The bispecific antibody BNT327/PM8002, targeting PD-L1 and VEGF, is being evaluated in locally advanced/metastatic TNBC in a phase III trial comparing combination therapy with chemotherapy versus chemotherapy alone [193]. Additionally, durvalumab plus paclitaxel has a 50% ORR in ongoing phase 1/2 trials for metastatic TNBC [194].

Overall, TNBC demonstrates enhanced immunogenicity, reflected by high TIL density and frequent PD-L1 expression, making it particularly responsive to ICIs. Ongoing research focuses on optimizing combination strategies and identifying predictive biomarkers to expand the benefit of ICIs across all BC subtypes. The table summarizes therapeutic targets, specific indications, combination strategies, and current regulatory status or primary endpoints in BC therapy targeting ICIs (Table 2).

4.1.2 Next-generation immune checkpoint targets: LAG-3, TIGIT, TIM-3

While the PD-1/PD-L1 axis has transformed the management of TNBC, most HR-positive/HER2-negative BC patients show only modest responses, consistent with their lower levels of TILs and reduced immunogenicity [195, 196]. This therapeutic ceiling is largely driven by primary and secondary resistance mechanisms that enable the TME to bypass PD-1 blockade. Preclinical and clinical studies demonstrate adaptive upregulation of LAG-3, TIM-3, and TIGIT on T cells following PD-1/PD-L1 inhibition, with co-expression of these receptors associated with resistance and disease progression [197]. Moreover, chronic antigen exposure and PD-1 pathway inhibition promote compensatory expression of these alternative inhibitory receptors, which sustain T-cell exhaustion and limit the efficacy of PD-1 monotherapy [198]. In line with this, several preclinical models and early-phase clinical trials indicate that dual or multi-checkpoint blockade (e.g., PD-1 combined with LAG-3, TIM-3, or TIGIT) enhances antitumor immunity compared with monotherapy and is specifically proposed to overcome acquired resistance [197, 199–201]. Unlike the PD-1/PD-L1 axis, which primarily targets late-stage

Table 2 Overview of key immunotherapy and combination strategies in breast cancer clinical trials

Name/Clinical trial ID	Drug/Target	Breast cancer subtype	Combination therapy	Other characteristics	Ref.
IMpassion130/ NCT02425891	Atezolizumab/ PD-L1	Unresectable or metastatic TNBC	Nab-paclitaxel	FDA approval and later withdrawn in USA	[132]
KEYNOTE-355/NCT02819518; KEYNOTE-522/NCT03036488; I-SPY2/NCT01042379	Pembrolizumab/ PD-1	High-risk early-stage TNBC and metastatic TNBC	Carboplatin, paclitaxel	The most widely used ICI	[128, 133, 186, 188, 190]
DIAmOND/BCT 1703	Durvalumab/ PD-L1 + tremelimumab/ CTLA-4	Advanced HER2+, trastuzumab-resistant	Durvalumab + tremelimumab (+ trastuzumab)	Durable responses in ER+/ high TILs; favorable safety	[190]
Imprime + pembrolizumab/ NCT02981303	Imprime PGG (innate PAMP) + pembrolizumab/PD-1	Metastatic TNBC	Imprime (PAMP) + Pembrolizumab	Safe, immunogenic	[191]
Alpha-lactalbumin vaccine/ NCT04674306	Alpha-lactalbumin protein	TNBC	Alpha-lactalbumin vaccine (+ pembrolizumab)	Phase 1 completed; Phase 2 planned (safe, immunogenic)	[192]
BNT327/PM8002/ NCT06449222	Bispecific antibody (PD-L1 x VEGF-A)	TNBC	BNT327/PM8002 (bispecific ICI)	Phase 3 trial starting in 2025	[193]
BEGONIA/ NCT03742102	Durvalumab/ PD-L1	Stage II-III TNBC	Neoadjuvant Chemo (paclitaxel/carboplatin + AC/EC) + durvalumab	Phase 3 randomized	[194]

CTLA-4 Cytotoxic T-lymphocyte–associated protein 4, *ER* Estrogen receptor, *HER2* Human epidermal growth factor receptor 2, *ICI* Immune checkpoint inhibitor, *PD-L1* Programmed death ligand-1, *TILs* Tumor-infiltrating lymphocytes, *TNBC* Triple negative breast cancer

reactivation of effector T cells, these next-generation molecules modulate broader immunological networks, including innate cell signaling and Treg stability, and act non-redundantly with PD-1 while being frequently co-expressed on exhausted T cells. As tumors evolve under the selective pressure of PD-1 inhibition, they frequently upregulate LAG-3, TIGIT or TIM-3 to maintain an immunosuppressive state [35], providing a clear biological rationale for combination strategies and representing a strategic shift toward multi-nodal checkpoint blockade.

4.1.3 Current therapeutic modalities and future paradigm

The current therapeutic landscape of BC immunotherapy is shifting from reliance on the PD-1/PD-L1 axis toward a broader, multi-checkpoint strategy. The recent regulatory approval of LAG-3 inhibitors, most notably in combination with nivolumab, has validated LAG-3 as a non-redundant target and signaled the beginning of a multi-node checkpoint era. Despite this progress, clinical translation remains complex. The withdrawal of atezolizumab's indication for TNBC following the IMpassion130 trial's failure to meet its overall survival (OS) endpoint highlighted the need for more precise patient stratification. In contrast, the success of KEYNOTE-355 and KEYNOTE-522 has established pembrolizumab as a standard of care in high-risk TNBC, particularly in the neoadjuvant setting where immune priming appears most effective. Adaptive platform trials such as I-SPY2 continue to accelerate evaluation of novel immunotherapeutic combinations by leveraging pathologic complete response (pCR) as an early surrogate endpoint.

Next-generation bispecific constructs, such as BNT327/PM8002 targeting PD-L1 and VEGF, aim to simultaneously counteract immune evasion and pathological angiogenesis - two convergent hallmarks of aggressive TNBC biology. Multiple monoclonal antibodies targeting TIGIT and TIM-3 are in phase I/II development, often combined with anti-HER2 therapy or chemotherapy backbones to evaluate synergistic enhancement of antitumor immunity [199].

Perspective clinical studies are aimed at:

1. Multi-target blockade transitioning to triple-checkpoint inhibition to prevent the compensatory upregulation of alternative receptors.
2. Rational sequencing in utilizing ICIs in the neoadjuvant window (as seen in KEYNOTE-522) to maximize the priming of systemic memory T cells before surgical resection.
3. Metabolic intervention, combining ICIs with agents that target the IDO pathway or with lactic acid transporters to alleviate the metabolic constraints of the escape phase.

Therefore, the future of BC management lies in rational combination strategies designed to convert "cold" tumors into "hot" tumors. This involves the strategic use of chemotherapy or anti-HER2 agents (such as trastuzumab) to induce immunogenic cell death, thereby releasing TAAs and danger signals that sensitize the tumor to next-generation checkpoint blockade. In this focus, multi-omics and spatial profiling are essential to map local immunometabolic gradients and the spatial architecture of the TME. By integrating genomic data with long noncoding RNAs (lncRNAs) and microbiome signatures, clinicians can identify specific immune "neighborhoods" where LAG-3 or TIM-3 are the dominant drivers of exclusion. The integration of these multidimensional datasets with AI-driven frameworks will allow the identification of patients harboring high densities of checkpoint-positive TILs near the tumor-invasive front. This spatial context is vital, since a tumor may be PD-L1-negative but LAG-3-positive, requiring a tailored switch in the immunotherapeutic backbone. Identifying these signatures is the key to evolving from a "one-size-fits-all" approach to a biomarker-guided, personalized oncology model.

4.2 Adoptive cell therapy

ACT involves the infusion of ex vivo expanded or genetically modified tumor-specific cells in patients to enhance antitumor immunity. This strategy encompasses several major modalities, including the use of T cells with chimeric antigen receptor (CAR-T) or genetically modified antigen T-cell receptor (TCR-T) [202, 203] as TILs. Recent advances have expanded ACT through the engineering of CAR constructs in innate immune cells, leading to the development of CAR-NK cells [204], CAR-Ms [205–208], and CAR-MSCs [3, 209] (Fig. 7).

4.2.1 Chimeric antigen receptor T-cell therapy

CAR-T-cell therapy is an advanced immunotherapeutic strategy that exploits genetically engineered T lymphocytes expressing chimeric antigen receptors (CARs) to recognize TAAs, redirecting T-cell specificity and enhancing tumor eradication [209, 210] (Fig. 7). While highly effective in treating hematologic malignancies, CAR-T-cell therapy is promising potential in BC, including the luminal A, HER2-positive, and TNBC subtypes [4].

In luminal A (HER2-negative/ER-positive/PR-positive, low proliferation) and luminal B (HER2-negative/ER-positive/PR-positive, high proliferation) BCs [211], CAR-T cells targeting AXL, B7-H4, EGFR, FcγRI, and HER2 have shown cytotoxicity in luminal A cell lines (MCF7 and SK-BR-3) [212, 213], although evidence in luminal B cancer remain limited [209]. In HER2-positive BC, HER2-CAR-T cells effectively eliminate tumor cells in preclinical models and may synergize with PD-L1

blockade [56], including in trastuzumab-resistant and brain-metastatic settings [209, 214]. To mitigate off-tumor toxicity due to HER2 expression in normal tissues, bispecific CAR targeting HER2 and gp100 or MUC1 have shown improved safety profiles and preclinical efficacy [3, 215].

TNBC, an aggressive subtype lacking ER, PR, and HER2, has shown responsiveness to CAR-T-cell therapy targeting EGFR or antibody-dependent cellular cytotoxicity using CD16/CD32-based chimeric receptors [210, 216]. Advances in CAR engineering from second-generation CARs constructs with costimulatory domains (CD28 and 4-1BB) to third-generation CARs combining multiple costimulatory motifs (e.g., CD27, ICOS, and OX40), and fourth-generation "TRUCKs" include NFAT-inducible IL-12 to recruit innate immune cells. Fifth-generation CARs fuse IL-2Rβ domains with JAK–STAT signaling for enhanced expansion and persistence [209, 217].

Antigen selection remains a major challenge due to "on-target, off-tumor" effects. Emerging strategies, including dual-target CARs, tumor-specific promoters, and suicide switches are being explored [209, 212, 218]. Receptor tyrosine kinases, including AXL, HGFR, and ROR1, are promising targets, particularly in TNBC, where AXL overexpression is associated with poor prognosis and therapy resistance [209, 212, 218].

Although CAR-T-cell therapy for solid tumors remains experimental, advances in CAR design, antigen targeting, and safety engineering provide a strong foundation for its translation into effective treatments for BC.

4.2.2 Chimeric antigen receptor natural killer therapy

Chimeric antigen receptor–engineered natural killer cells (CAR-NK cells) represent a promising immunotherapeutic strategy for BC. Compared with CAR-T cells, CAR-NK cells offer distinct advantages, including a lower risk of graft-versus-host disease and cytokine release syndrome, and off-tumor toxicity [204, 219–225] (Fig. 7).

Structurally, CAR-NK constructs share a modular design with CAR-T-cell, comprising antigen-recognition, transmembrane, and intracellular activation domains [220]. Their flexible antigen-binding domains enable targeting of multiple TAAs, across various BC subtypes. Preclinical studies have demonstrated that CAR-NK cells targeting CD44v6, HER2, tissue factor (TF), B7-H6, EGFR, and PD-L1 effectively eliminate BC cells [225]. In TNBC models, CD44v6-targeted CAR-NK cells exhibit robust cytotoxicity [223]. TF has also emerged as a novel target in TNBC, where L-ICON, an antibody-like immunoconjugate directed against TF, enhanced CAR-NK cytotoxicity in vitro. Furthermore, B7-H6-targeted CAR-NK cells effectively eliminate fulvestrant-resistant tumors [209, 221].

HER2-positive BC is another key target for CAR-NK therapy. HER2-CAR-NK cells, particularly when coexpressing soluble PD-1 (sPD-1), significantly increased their cytotoxic potential against HER2-positive/PD-L1-positive BC cells [225]. HER2-targeted CAR-NK cells also retain potent antitumor activity in the immunosuppressive TME, demonstrating effective killing of solid tumor cells [222]. Moreover, EGFR-directed CAR-NK cells inhibited BC brain metastasis, underscoring their potential in targeting disseminated disease [219].

Advances in CAR-NK cell engineering created new opportunities for BC treatment. With their safety, natural ability to kill tumor cells, and potential to overcome the immunosuppressive TME, CAR-NK therapy is a promising approach for future clinical use in BC.

4.2.3 Chimeric antigen receptor macrophages and mesenchymal stem cell therapy

CAR-Ms and CAR-MSCs represent innovative cellular immunotherapies with emerging potential in BC [7, 205, 206, 208, 226] (Fig. 7).

CAR-Ms leverage the innate phagocytic, antigen-presenting, and proinflammatory capacities of macrophages to recognize and eliminate tumor cells. Unlike CAR-T cells, which rely on cytotoxic lymphocyte, CAR-Ms exploit macrophage plasticity and tumor-homing ability to modulate the immunosuppressive TME [227]. Preclinical data indicate that CAR-Ms enhance antigen presentation, promote a proinflammatory milieu, and disrupt immune evasion pathways in BC [205]. CAR-Ms targeting TAAs such as HER2, VEGFR2, and EpCAM exhibit strong phagocytic and tumoricidal activity while simultaneously recruiting and activating T cells to sustain adaptive antitumor immunity [7, 206].

A major advantage of CAR-M therapy is its ability to overcome tumor resistance to conventional immunotherapies. By reprogramming TAMs from the immunosuppressive M2 phenotype to the proinflammatory M1 phenotype, CAR-Ms amplify both innate and adaptive antitumor responses [170] making them attractive candidates for therapy-resistant and metastatic BC.

Preclinical murine models have demonstrated that VEGFR2- and HER2-targeted CAR-Ms significantly reduce the tumor burden [205, 206] and activation via TLR4 or IFN-γ signaling enhances antitumor efficacy in 4T1 BC-bearing mice [205]. In other malignancies, CAR-Ms targeting HER2, GD2, and CD19 have shown potent antitumor effects in ovarian, neuroblastoma, and hematologic models, supporting their translational relevance across cancer types [227–229].

Despite encouraging outcomes, several challenges impede clinical translation, including limited macrophage persistence, suboptimal in vivo delivery to tumor sites, and the complexity of the TME [230]. To increase

therapeutic efficacy, strategies such as generating CAR-Ms from induced pluripotent stem cell-derived macrophages (iPSC-Ms) and combining CAR-M therapy with ICIs [231], chemotherapy, and radiotherapy [7].

CAR-MSCs, engineered to express CARs, represent an emerging type of cell-based immunotherapy. CAR-MSCs can modulate immune responses, secrete cytokines, and promote tissue repair, potentially enhancing immune cell recruitment and therapeutic delivery within the TME [226]. Although studies remain limited, CAR-MSCs demonstrate considerable promise for BC treatment, offering a complementary and versatile platform for targeted cellular immunotherapy.

4.2.4 Engineered T-cell receptor T-cell therapy

Engineered T-cell receptor (E-TCR) therapy represents the second major category of engineered adoptive T-cell therapies (E-ACTs), alongside CAR-T-cell therapy [202, 232] (Fig. 7).

In this approach, T cells are genetically modified to express tumor-specific TCRs, enabling recognition of peptide–MHC complexes and elimination of malignant cells. Unlike CARs, which bind surface antigens in an MHC-independent manner, E-TCRs allow targeting of both intracellular and surface TAAs, increasing specificity and limiting off-target cytotoxicity [150].

E-TCR constructs use α and β chains from tumor-reactive T cells introduced into patient-derived T cells, which dimerize with CD3 subunits to achieve tumor antigen specificity [233, 234]. Because TCRs recognize peptide-MHC (pMHC) complexes, E-TCR constructs must be matched to the patient's MHC type [235]. Importantly, this strategy allows the targeting of intracellular neoantigens resulting from mutations in PIK3CA, TP53, or ESR1, which are common in BC [202, 232, 234, 236].

Preclinical studies highlight efficacy against antigens including PLAC1 [150], with γδ T cells engineered with tumor-specific receptors showing enhanced cytotoxicity [237] and potential synergy with trastuzumab [238, 239]. However, these cells may also induce immunosuppressive effects on other immune subsets, highlighting the need for further research.

Clinical trials have evaluated E-TCRs targeting NY-ESO-1 and MAGE-A3 [234, 240, 241]. NY-ESO-1-specific TCRs yielded limited responses in BC patients [240], while MAGE-A3 have reported severe off-target effects, including cardiac and pulmonary events, without therapeutic benefit [234, 241]. Conversely, encouraging results were observed in a recent phase II trial, where a chemorefractory BC patient treated with T cells transduced with an HLA-A*02:01-restricted p53 R175H-specific TCR and pembrolizumab exhibited 55% tumor reduction at 14 weeks, with persistence of memory T cells [202].

E-TCR T cells depend efficacy depends on optimal TCR-pMHC binding. Excessive receptor affinity may lead to premature T-cell exhaustion, whereas inadequate affinity reduces tumor recognition. Moreover, modifications of the TCR sequence may cause unexpected cross-reactivity with self-antigens [202, 232]. Recent advances in the use of CRISPR-Cas9 have enabled the precise replacement of endogenous TCRs with transgenic variants, preventing mispairing, enhance stability [242, 243], and enable nonviral multiplex gene editing [244, 245]. Functional in vitro and in vivo assays are essential for validating E-TCR safety, efficacy, and persistence before clinical application [15, 232, 246, 247]. Safety strategies such as logic-gated TCRs and suicide genes are under development to minimize off-target toxicity [248–250].

Combination strategies may also improve therapeutic outcomes. These include coadministration of E-TCR T cells with ICIs [232], PD-1 disruption dominant-negative TGFβR2 expression [251] or interventions to promote stem-cell memory T-cell phenotypes or combining therapy with cytokines, vaccines, or oncolytic viruses, may further augment efficacy [202, 232].

Autologous E-TCRs remain the mainstay, but allogeneic "off-the-shelf" T-cell platforms are under active development, incorporating TRAC locus, which are often combined with HLA class I gene editing to generate universal donor T cells [251].

Ultimately, careful antigen selection and optimization of engineering strategies will be essential to balance efficacy and safety. Integrating E-TCR therapy with modalities such as radiotherapy, checkpoint blockade, or cytokine support may convert immunologically "cold" breast tumors into "hot" tumors, thereby enhancing responsiveness and clinical outcomes.

4.3 Cancer vaccines

Cancer vaccines aim to stimulate antigen-specific immune responses against TAAs, offering a targeted approach to enhance antitumor immunity. These strategies include protein-based and whole-cell vaccines, peptide-based vaccines, DC-based vaccines, DNA- and RNA-based vaccines, and viral vector-based vaccines [7, 252] (Fig. 7), (Table 3).

4.3.1 Protein-based and whole-cell vaccines

Protein-based and whole-cell vaccines are complementary cancer immunotherapy aimed at stimulating both humoral and cellular immune responses. Their shared advantage lies in broad antigenic coverage and the capacity to induce durable antitumor immunity by presenting full-length TAAs in their native conformation, enhancing immune recognition and therapeutic efficacy [7, 261] (Fig. 7).

Table 3 Breast cancer vaccines clinical trials

Vaccine type	Clinical trial ID	BC subtypes	Targeting specificity	Limitations	Ref.
Protein- and whole-cell-based vaccines	NCT04674306 NCT04024800 NCT02427581 NCT01431196	TNBC TNBC TNBC TNBC	Poly-specific	Potential autoreactivity activation	[7, 252, 253]
Peptide-based (Epitope-based) vaccines	NCT00791037 NCT02426892	$HER2^+$	TAAs TSAs MUC1 CEA MAGEA SART3	May have limited efficacy when used individually	[7, 179, 253, 254]
DC-based vaccines	NCT02491697 NCT03450044 NCT03387553 NCT03300843 NCT00923143 NCT00082641 NCT00640861 NCT00003432	$HER2^+$ TNBC	HER2 MUC1	High cost, manufacturing complexity	[7, 161, 180, 255, 256]
DNA-based vaccines	NCT07112053 NCT07078604 NCT03199040	HR^+ $HER2^-$ TNBC	TAAs Neoantigens	Challenges in delivering and immunogenicity	[7, 252, 257]
RNA-based vaccines	VRP-HER2	$HER2^+$	TAAs Neoantigens	Challenges in delivering and immunogenicity	[7, 258]
Viral vector-based vaccines	NCT00706615 AVX701	CEA^+ $MUC1^+$	TAAs genes	Development of anti-vector immunity	[7, 259, 260]

BC Breast cancer, *CEA* Carcinoembryonic antigen, *DC* Dendritic cells, *HER2* Human epidermal growth factor receptor 2, *HR* Hormone receptor, *MUC1* Mucin 1, *TAAs* Tumor-associated antigens, *TNBC* Triple-negative breast cancer, *TSAs* Tumor-specific antigens

HER2 protein-based vaccines have demonstrated favorable safety profiles and the ability to elicit HER2-specific antibody and T-cell responses in preclinical and early clinical studies [262, 263]. Its therapeutic potential is particularly promising for HER2-positive BC, especially when combined with mAbs or chemotherapy [263]. Furthermore, HER2 gene vaccines combined with PD-L1-targeted vaccines have shown synergistic antitumor effects, emphasizing the potential of multitarget vaccine strategies [264].

Whole-cell vaccines employ either autologous (patient-derived) or allogeneic (donor-derived) tumor cells, providing a broad repertoire of tumor antigens that can trigger comprehensive immune responses [261, 265], potentially helping to overcome tumor heterogeneity and immune evasion. Autologous vaccines present patient-specific antigens for highly targeted immunity [263], whereas allogeneic vaccines offer a standardized, scalable alternative when autologous material is unavailable or impractical [265]. Whole-cell vaccines can activate multiple immune components, including DCs, macrophages, and T-cell subsets, engaging both innate and adaptive immunity [266]. The exposure of the immune system to a wide range of antigens may reduce the risk of immune escape and tumor recurrence. Limitations include tissue availability, potential cross-reactivity with self-antigens, and insufficient antigen-presenting cell engagement, which may affect $CD8^+$ T-cell activation and suboptimal cross-presentation [7] (Table 3).

4.3.2 Epitope-based vaccines

Epitope- or peptide-based vaccines represent an advanced strategy in cancer immunotherapy that utilizes short amino acid sequences derived from TAAs to elicit antigen-specific T-cell responses against cancer cells [7, 253] (Fig. 7). By selectively targeting tumor epitopes, these vaccines can activate cytotoxic and helper T-cell responses while minimizing off-target effects on healthy tissues. Commonly used epitopes are derived from TAAs such as HER2, mucin 1 (MUC1), and human telomerase reverse transcriptase (hTERT), all of which have demonstrated the ability to induce potent T-cell responses against tumors expressing these antigens [267, 268] (Table 3).

4.3.2.1 HER2 peptide-based vaccines HER2, a 185 kDa transmembrane glycoprotein belonging to the epidermal growth factor receptor (EGFR) family, regulates cell proliferation and differentiation. Aberrant activation of the HER2 signaling pathway via gene amplification or overexpression occurs in 25–30% of primary BCs and is correlated with aggressive tumor behavior and poor prog-

nosis [269, 270]. Structurally HER2 protein comprises of extracellular (ECD), transmembrane (TMD), intracellular (ICD) domains, and C-terminal tails. Given its oncogenic role, HER2 is a major target for cancer immunotherapy [7].

4.3.2.1.1 HER2 extracellular domain epitopes Multiple epitopes from the HER2 ECD have been evaluated as peptide vaccine development for BC. The P5 and P435 epitopes, which are restricted by MHC class I molecules in BALB/c mice, induce strong CTL responses and effectively inhibit tumor growth [271]. The CH401 epitope (residues 167–175) activates both $CD4^+$ and $CD8^+$ T cells, induce robust HER2-specific antibody responses, and delays tumor progression and improved survival in HER2-positive models [272]. Similarly, the MHC class II–restricted p101 and p373 peptides prevent spontaneous breast tumor development in BALB/c mice by inducing strong antigen-specific T-cell and antibody responses [273].

In clinical settings, combination vaccination with E75 and E90 peptides stabilized disease in 46% of metastatic BC patients, supporting multiepitope vaccine strategies [274]. Overall, HER2 ECD-based peptide vaccine show therapeutic potential in HER2-overexpressing tumors, particularly when combined with trastuzumab or ICI [275]. However, their efficacy as monotherapy in tumors with low HER2 expression remains limited.

4.3.2.1.2 HER2 transmembrane domain epitopes The GP2 peptide, a 9-amino-acid epitope (residues 654–662) derived from the HER2 TMD, is presented by HLA-A2 molecules and specifically activates $CD8^+$ CTLs, which target HER2/neu-positive cells [7]. Preclinical studies using liposomal or bacteriophage-based GP2 formulations demonstrated strong immune responses [276, 277], which was confirmed in clinical trials showing increased numbers of circulating GP2-specific $CD8^+$ T cells and enhanced delayed-type hypersensitivity reactions [278–280].

Trastuzumab treatment sensitizes tumor cells to CTL-mediated killing following GP2 or E75 stimulation, even in tumors with low HER2 expression. Combined GP2 and E75 vaccination elicited additive effects, further enhancing CTL-mediated lysis of HER2-positive targets [281, 282].

4.3.2.1.3 HER2 intracellular domain epitopes The ICD of HER2, encompassing residues 712–1255, includes the oncogenic tyrosine kinase domain, is highly immunogenic. Vaccines encoding HER2 ICD sequences have shown strong immunogenicity and protective antitumor effects in preclinical mammary tumor models. For example, a HER2 ICD vaccine combined with the heat shock protein complex HSP110 elicited potent antitumor immune responses and inhibited spontaneous tumor growth in transgenic mice [283].

A phase I/II trial evaluated a peptide vaccine containing ICD-derived peptides (residues 776–790, 927–941, 1166–1180) in refractory stage IV BC patients. Among vaccinated patients, 82% developed HER2-specific T-cell responses, and 81% exhibited intramolecular epitope spreading, which was correlated with improved overall survival [263]. Interestingly, some HER2-negative tumors express truncated forms of HER2 lacking the ECD but retaining the active ICD, potentially responding to HER2-targeted immunotherapies [284].

The AE37 epitope, a modified version of the native HER2 peptide (aa 776-++790), includes the LRMK modification, which enhances MHC class II presentation and $CD4^+$ T-cell activation [285]. This modification amplifies helper T-cell activity, promoting stronger $CD8^+$ cytotoxic responses and broader HER2 epitope recognition. Thus, AE37-based vaccines hold promise for eliciting coordinated $CD4^+/CD8^+$ immune responses and improving outcomes in HER2-positive BC patients [7, 285].

4.3.2.2 Carbohydrate-based vaccines Carbohydrates are the most abundant biomolecules in nature and are integral components of cell-surface glycoconjugates, such as glycoproteins, glycolipids, and glycosphingolipids, which coat cell surfaces and regulate recognition, signaling, and intercellular communication. Alterations in glycan structures distort these interactions and contribute to tumor initiation and progression [286, 287].

Many tumors exhibit aberrant glycosylation patterns, leading to the expression of tumor-associated carbohydrate antigens (TACAs), which enable immune evasion [288]. Although TACAs are poorly immunogenic, their restricted expression in normal tissues and enrichment in tumor cells make them valuable targets for vaccine design. TACAs are broadly categorized into glycoprotein antigens, which are O-linked to serine or threonine residues, and glycolipid antigens, which are linked to ceramide lipids and anchored in the plasma membrane [289].

Among glycoprotein TACAs, MUC1 is a prominent vaccine target and was ranked by the National Cancer Institute as a top cancer vaccine antigen [290]. Aberrant glycosylation during tumorigenesis produces truncated O-glycans such as Tn (GalNAcα1-O-Ser/Thr) and its sialylated form, STn. These antigens are overexpressed in epithelial cancers, including breast, lung, gastric, and prostate tumors, and are correlated with poor prognosis and immune evasion [291]. Owing to their high tumor specificity and minimal normal tissue expression, Tn and STn are attractive vaccine targets. Because of their low immunogenicity, Tn/STn-based vaccines are usually

conjugated to immunogenic carriers or formulated with adjuvants such as proteins, liposomes, or nanoparticles [292, 293]. Despite promising preclinical and early clinical results, carbohydrate-based vaccines have not yet demonstrated clinical efficacy, exemplified by the failure of the Theratope vaccine in phase III trials, likely due to immune tolerance [294].

To overcome tolerance, researchers have developed nonnatural TACA analogs and mimetics designed to increase immunogenicity and resist glycosidic degradation [295, 296]. Structural modifications have been introduced in the glycosidic linkage, carbohydrate moiety, or both regions, improving antigen stability and antibody recognition [297, 298].

Recently, two synthetic MUC1-inspired constructs have elicited robust Th1-based immune responses and generate antibodies that selectively recognize MUC1-positive cancer cells in vivo [299, 300]. These rationally designed constructs advance the standardization of carbohydrate-based vaccine manufacturing and represent a promising step toward clinical translation.

Although carbohydrate-based vaccines are still in early development, they are generally safe and capable of inducing measurable immune responses. Their limited efficacy as monotherapies highlights the need for combination strategies, particularly with ICI or other immunomodulatory agents, to enhance antitumor activity.

4.3.2.3 Triple peptide vaccines In addition to MUC1 and HER2 (ErbB2), carcinoembryonic antigen (CEA) is frequently overexpressed in both breast and ovarian cancers. A triple peptide vaccine comprising HLA-A2-restricted peptides, such as MUC1 (159–167), ErbB2 (368–377), and CEA (605–613), was evaluated in a phase I/II clinical trial involving patients with high-risk, disease-free breast or ovarian cancer [301]. All participants were HLA-A2 positive and had completed standard-of-care therapy. The vaccination began six months after chemotherapy and consisted of six biweekly doses, followed by a booster three months later. The vaccine demonstrated an excellent safety profile and was well tolerated. Eight of the 14 enrolled patients developed antigen-specific $CD8^+$ T-cell responses against at least one of the targeted epitopes. During an eight-year follow-up, all patients remained alive and disease free. Although three individuals experienced recurrence, all responded favorably to subsequent surgery and adjuvant chemotherapy [301]. These results highlight the potential of multivalent peptide formulations to induce durable immune protection in patients at high risk of BC.

4.3.2.4 Multiple peptide vaccines Multipeptide vaccines represent an emerging and versatile approach to BC immunotherapy. An early phase II trial evaluated a 19-peptide vaccine derived from 11 TAAs: SART3, CypB, WHSC2, UBE2V, HNRPL, Lck, MRP3, PSA, PAP, EGFR, and PTHrP [302].

Fourteen patients with advanced metastatic TNBC refractory to chemotherapy received this vaccine emulsified in incomplete Freund's adjuvant. Vaccination elicited a marked increase in peptide-specific IgG responses, which were positively correlated with OS. Patients with high postvaccination IgG titers achieved a median OS of 24 months, substantially longer than typically reported in previous anti-PD-1/PD-L1 trials. While CTL responses exhibited lower sensitivity to immune boosting than humoral responses did, their cooperation suggested synergistic activation of both immune arms. Elevated immune responses to Lck, PAP, CypB, PSA, and UBE2V peptides were associated with improved OS, emphasizing their therapeutic relevance. This mixed 19-peptide vaccine demonstrated robust immunogenicity and promising clinical benefit despite the limited sample size. These findings justify further evaluation in larger, controlled cohorts to validate its clinical utility as a personalized or adjunct immunotherapy for advanced BC [302].

4.3.2.5 MAGEA peptide-based vaccines The melanoma antigen gene A (MAGEA) family encodes a group of cancer-testis antigens typically expressed in germline tissues but aberrantly activated in a wide range of malignancies, including melanoma and pancreatic, breast, and ovarian carcinomas. MAGEA expression is correlated with poor prognosis, increased invasiveness, and increased metastatic potential [7].

In preclinical studies, twelve nanoparticles-based vaccine formulations were developed by conjugating the MAGE-A1 peptide (SQYGEPRKL) to a TLR2 agonist. These self-assembled constructs were efficiently internalized by DCs, induced DC maturation, activated $CD8^+$ T cells, and mediated cytotoxicity against MAGE-A1-positive MCF-7 BC cells in vitro. Among them, conjugate 6 (N-Ac PamCS-M-6) demonstrated the best antitumor efficacy and safety in MCF-7 tumor-bearing BALB/c nude mice [303].

In another preclinical study, several epitopes (MLP1-3, MLP-A4) derived from MAGE-A4 was formulated into a multiepitope peptide vaccine and evaluated in BALB/c mice inoculated with either 4T1-MAGE-$A4^+$ or 4T1-MAGE-$A4^-$ tumor. The vaccine elicited robust, multiepitope-specific CTL responses restricted to the HLA-A1, A2, A3, and A24 superfamilies. When administered alone or in combination with R848, a TLR7/8 agonist, the vaccine elicited significant antitumor activity, confirming its immunogenic and therapeutic potential [304].

Collectively, MAGEA-based peptide vaccines have shown strong preclinical promise because they efficiently activate both innate and adaptive immunity against

MAGEA-expressing tumors. Future studies should explore the clinical translation of these vaccines, particularly in combination with ICI or adjuvants, to overcome tumor-induced tolerance.

4.3.3 Dendritic cell-based vaccines

DC-based vaccines exploit the exceptional antigen-presenting capacity of DCs to elicit robust and tumor-specific immune response. These vaccines are generated by isolating autologous DCs from the patient's peripheral blood, loading them ex vivo with tumor antigens or synthetic peptides, and reinfusing them to activate cytotoxic and helper T lymphocytes. Through this strategy, DCs function as professional APCs capable of bridging innate and adaptive immunity to orchestrate tumor-specific responses [161, 180, 256, 305] (Fig. 7).

The manufacturing process typically involves the differentiation of monocyte-derived DCs followed by pulsing with TAAs or autologous tumor lysates. Once internalized, these antigens are processed and presented via MHC molecules, thereby educating $CD4^+$ Th cells and $CD8^+$ CTLs to recognize and eliminate cancer cells expressing the relevant epitopes. This ex vivo "education" of DCs enables the development of highly personalized vaccines tailored to the unique antigenic profile of an individual's tumor [7].

The first clinical breakthrough in this field was Sipuleucel-T, which was approved by the FDA for the treatment of metastatic prostate cancer, which provided a critical proof of concept and encouraged similar approaches for other malignancies, including BC [180]. DC vaccines targeting HER2 [305] and MUC1 [306] have demonstrated favorable safety profiles and immunogenicity in early-phase clinical trials, supporting their potential role as adjuncts to conventional and immune-based therapies.

Current research focuses on optimizing DC vaccine potency through improved antigen loading techniques, enhanced maturation protocols, and integration with complementary therapeutic modalities. Combination strategies with ICIs, chemotherapy, and targeted therapies are being actively explored to potentiate synergistic antitumor effects [307, 308, 309].

Despite encouraging results, DC-based vaccines face several challenges, including high manufacturing costs, technical complexity, and limited scalability for widespread clinical implementation. Nonetheless, advances in cell culture technologies, antigen identification, and delivery systems are progressively overcoming these barriers. Overall, DC-based vaccines represent an evolving and highly personalized form of cancer immunotherapy with the potential to induce durable and specific immune protection. Continued integration of immunogenomic profiling and next-generation vaccine design is expected to further enhance their clinical efficacy in BC.

4.3.4 DNA-based vaccines

DNA-based vaccines constitute a major advancement in cancer immunotherapy, utilizing the patient's own cells as endogenous bioreactors to produce TAAs that trigger antigen-specific immune responses [7]. These vaccines employ plasmid DNA constructs encoding tumor antigens, which, once internalized by host cells, undergo transcription and translation to generate the encoded antigens. The newly synthesized antigens are subsequently presented via MHC molecules, leading to the activation of both humoral and cellular immune responses directed against tumor cells expressing these antigens [7] (Table 3).

Plasmid-based DNA vaccines offer several advantages, including structural stability, safety, and the ability to incorporate multiple antigenic or immunostimulatory sequences within a single construct. This versatility allows the induction of broad and sustained antitumor immunity, encompassing both CTL and Th responses. However, early clinical trials revealed limitations in immunogenicity due to inefficient DNA uptake and expression in host cells [7, 310].

To address these challenges, advanced delivery strategies, such as electroporation, gene gun delivery, and lipid nanoparticle (LNP)-based systems, are being investigated to increase transfection efficiency and antigen presentation. These strategies have significantly improved antigen expression levels and immune activation in preclinical models [310].

Despite existing challenges, DNA-based vaccines hold strong promise for the development of personalized immunotherapies, particularly for tumors expressing unique neoantigens or patient-specific mutations. Ongoing advances in plasmid design, molecular adjuvant incorporation, and delivery technologies are expected to further enhance their efficacy, positioning DNA vaccines as a key component of next-generation cancer immunotherapy [7].

4.3.5 RNA-based vaccines

RNA-based vaccines, particularly messenger RNA (mRNA) vaccines, have recently gained prominence for their ability to induce potent, rapid, and versatile immune responses. Unlike DNA vaccines, mRNA vaccines deliver the antigen-coding sequence directly in the form of RNA, bypassing the need for cancer cell nuclear entry and transcription. Once translated into the cytoplasm, the encoded antigens are processed and presented by APCs, thereby activating both $CD4^+$ and $CD8^+$ T cells, as well as B-cell–mediated antibody responses [7, 257, 311] (Table 3).

Preclinical and early clinical studies have demonstrated that mRNA vaccines targeting HER2 can elicit strong cellular and humoral immune responses in BC models,

including the activation of DCs and CTLs capable of selectively lysing HER2-expressing tumor cells [312]. Moreover, mRNA vaccines exhibit a favorable safety profile, as they are nonintegrating and noninfectious, eliminating the risks associated with viral vector–based systems [7]. One of the principal advantages of mRNA vaccines lies in their rapid design and manufacturing flexibility, allowing for swift adaptation to tumor heterogeneity, neoantigen emergence, or mutational evolution. This feature makes mRNA vaccines particularly suitable for personalized cancer immunotherapy, where each patient's vaccine can be tailored to their unique tumor antigen repertoire.

Ongoing clinical trials are evaluating mRNA vaccines across multiple tumor types, including BC, both as monotherapies and in combination with ICIs or other immunomodulators [310, 312]. With continued innovation in delivery systems, especially lipid nanoparticle technology, and the integration of bioinformatics-driven neoantigen prediction, nucleic acid-based vaccines are poised to become a transformative platform for targeted, safe, and long-lasting cancer immunotherapy.

4.4 Oncolytic virus-based therapy

Oncolytic viruses (OVs) represent an innovative and rapidly evolving class of cancer immunotherapeutics that selectively infect, replicate within, and lyse tumor cells while sparing normal tissues. In addition to direct oncolysis, these OVs act as potent in situ vaccines, transforming the TME into an immunostimulatory niche by releasing TAAs and proinflammatory cytokines that enhance antitumor immunity [7] (Fig. 7).

There are two mechanisms underlying OV-mediated tumor destruction. First, viral replication within cancer cells induces immunogenic cell death and exposure of previously hidden TAAs. Second, the ensuing inflammation recruits and activates APCs, promoting the priming of tumor-specific CTLs. Consequently, OVs can generate systemic antitumor immunity capable of eliminating both primary and metastatic lesions [181].

Several viral platforms have been engineered for therapeutic use, including adenoviruses, herpes simplex virus (HSV), vaccinia virus, and reoviruses. Among them, Talimogene laherparepvec (T-VEC), a genetically modified HSV-1 expressing GM-CSF, became the first FDA-approved oncolytic virus for melanoma treatment [313]. The success of T-VEC has spurred research into OVs for other malignancies, including BC, where they demonstrate synergistic effects when combined with ICIs, chemotherapy, or radiotherapy [181].

In BC models, oncolytic adenoviruses, HSV-based vectors, and protoparvoviruses have shown selective tropism for tumors and have been genetically modified to express immunostimulatory molecules such as IL-12, GM-CSF, or PD-L1 inhibitors, thereby amplifying immune activation and reversing tumor-induced immune suppression [181]. Next-generation OVs, including oncoviron and Delta-24-RGD adenoviruses, exhibit enhanced tumor selectivity, replication efficiency, and anticancer potency in preclinical BC models, although none are yet approved specifically for BC [314].

Combining OVs with ICIs enhances T-cell activation and mitigates immune escape [315]. OV treatment significantly reduces cell viability in BC-derived organoid cultures [316], and emerging OV-based and phage-display technologies have been highlighted as preventive vaccine strategies for BC [317]. These findings underscore the value of integrating OVs into multimodal immunotherapeutic regimens.

Despite encouraging preclinical and early clinical results, key challenges remain, including antiviral immune responses that limit repeated dosing, systemic toxicity, and barriers to efficient viral delivery. Advances in genetic engineering now allow for the development of targeted OVs that remodel the TME, enhance immune recognition, and synergize with other therapies [181]. Personalized virotherapy approaches aim to optimize viral tropism, replication dynamics, and immunostimulatory capacity according to individual patient and tumor characteristics [314].

Overall, oncolytic virotherapy represents a promising and versatile strategy for BC immunotherapy. Through both direct tumor lysis and immune system reprogramming, OVs can transform immunologically "cold" tumors into "hot" tumors, sensitizing them to checkpoint blockade and other immunomodulatory treatments. Future studies will define their optimal use within personalized and combination immunotherapeutic frameworks.

4.5 Targeted therapies

Compared with traditional chemotherapies, which can harm healthy cells, targeted therapies are designed to attack cancer cells with less damage to normal cells because of their greater specificity. These approaches target specific molecules on the surface or inside cancer cells, such as proteins and genes, and can include mAbs, small chemical compounds, and hormonal drugs [318, 319].

Current targeted therapies for BC primarily focus on inhibitors of the poly (ADP-ribose) polymerase (PARP) enzyme, anti-HER2 agents, and Treg-targeted strategies [320]. PARP inhibitors, such as olaparib, potentiate immunotherapy by enhancing DNA damage response pathways and promoting tumor-specific immune activation [321, 322]. Anti-HER2 therapies, including trastuzumab and pertuzumab, not only eliminate HER2-overexpressing tumor cells but also modulate immune responses within the TME, potentially increasing the

efficacy of immune checkpoint blockade [133, 186, 187, 189] (Table 4).

4.5.1 Treg-targeted therapies

Tregs contribute to immunosuppression in the TME, limiting antitumor immunity and reducing therapeutic efficacy. Therapeutic strategies targeting Tregs aim to restore immune surveillance and enhance the response to treatment [79, 81] (Fig. 8).

Among Treg-associated targets, immune checkpoint molecules have been extensively studied. While CTLA-4 and PD-1 inhibitors have demonstrated limited efficacy in BCr as monotherapy, dual checkpoint blockade appears more effective [323, 324]. In particular, a combination of ipilimumab (anti-CTLA-4 mAb) with nivolumab (anti-PD-L1 mAb), in addition to neoadjuvant chemotherapy, demonstrated 100% survival in stage 3 TNBC in clinical trial ACTRN12617000651381 [323]. Dual inhibition of PI3K using YY20394 and PD-1 blockade with camrelizumab significantly reduced tumor growth and decreased the Treg-to-CD8⁺ T-cell ratio in TNBC [130]. Similarly, the anti-CD25 antibody daclizumab selectively depletes Tregs in metastatic BC [324].

In addition to checkpoint blockade, modulating cytokine and chemokine networks that regulate Treg trafficking offers additional therapeutic potential. ABBV-151, a mAb that targets the GARP-TGFβ1 complex to block TGFβ release by Tregs, is under phase I evaluation alone or with anti-PD-1 therapy [325]. Treg recruitment is largely mediated via CCR4 and CCR8 receptors. In preclinical models, blockade of CCR4 ligands (CCL17/CCL22) or depletion of CCR8⁺ Tregs reduced immunosuppression, promoted T-cell memory formation, and induced tumor regression [339, 340]. The CCR8 antagonist IPG7236 is currently in phase 1/2a trials for advanced solid tumors, including TNBC [326].

Metabolic reprogramming represents another approach to modulate Treg activity. Metformin decreases the Treg frequency in the TME by shifting cellular metabolism toward glycolysis [341], whereas inhibition of the indoleamine 2,3-dioxygenase (IDO) pathway via CN@PHF nanoparticles reduces the number of

Table 4 Breast cancer targeted immunotherapy

Targeted therapy	Impacting drug	BC subtype/model	Target	Effect	Ref.
Treg	Ipilimumab + Nivolumab	TNBC	CTLA-4 PD-L1	Significant	[323] [130]
	Camrelizumab +YY20394	TNBC	PD-1 PI3K	Significant Promising	[324] [325]
	Daclizumab	TNBC	CD-25	Promising	[326]
	ABBV-151	Murine	TGFβ	Promising	[327]
	IPG7236	TNBC	CCR8	Promising	[328, 329]
	CN@PHF nanoparticles	models	IDO inhibition		
	P60		FoxP3 inhibition		
TME	Inhibitors Activators	Murine and human models	TGFβ IDO CSF-1R IDO CB2 STRING	ICI-response↑, Toxic metabolite↓, CTL↑, TAMs↓, MDSCs↓ Synergy Synergy Antigen presentation↑	[55] [330] [331] [169, 332] [333]
TGF-β	Inhibitors, Doxorubicin	Murine and human TNBC models	BMP-1	TGFβ blocking	[334]
Neuroimmunity	β-blockers Olvanil	Human TNBC and murine 4T1 models Murine TNBC	β-adrenergic receptor TRPV1	Oncolytic virotherapy↑ CTL infiltration↑	[335] [336]
Inflammation	NSAIDs, Corticosteroids	"cold" tumors	COX-2/PGE_2/EP2-4 axis blockade	ICI efficacy↑	[337]
	CD200fc PEG-M49 + doxorubicin	Aggressive BC murine models	CD200-CD200R1 pathway modulation	T-cell infiltration↑ CD200 mimicking, CTL infiltration↑ MDSCs↓ CTL activation↑	[338] [334]

BC Breast cancer, *BMP-1* Bone morphogenetic protein 1, *CB2* Cannabinoid receptor, *COX-2* Cyclooxygenase-2, *CSF-1R* Colony stimulating factor-1 receptor, *CTL* Cytotoxic T lymphocyte, *CTLA-4* Cytotoxic T-lymphocyte antigen-4, *GARP* Glycoprotein A repetitions associated protein, *HR* Hormone receptor, *ICIs* Immune checkpoint inhibitors, *IDO* Indoleamine 2,3-dioxygenase, *MDSCs* Myeloid-derived suppressor cells, *NSAIDs* Nonsteroidal anti-inflammatory drugs, *PD-1* Programmed cell death protein-1, *PD-L1* Programmed death ligand-1, *PI3K* Phosphoinositide 3-kinases, *STRING* Stimulator of interferon genes, *TAMs* Tumor-associated macrophages, *TGF-β* Transforming growth factor β, *TME* Tumor microenvironment, *TNBC* Triple-negative breast cancer, *TRPV1* Transient receptor potential vanilloid 1

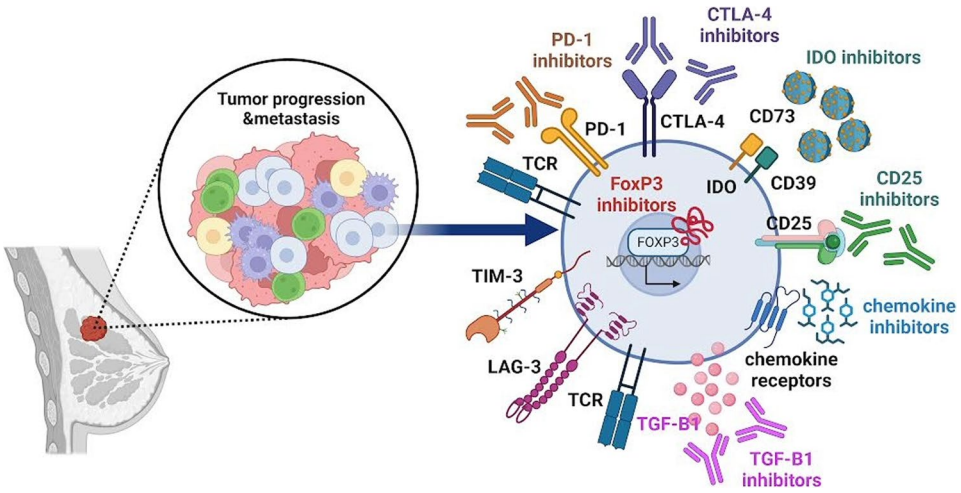

Fig. 8 Targeting Tregs in breast cancer: clinical and biomolecular therapeutic strategies. Within the breast TME, Tregs exploit potent immunosuppressive functions that allow malignant cells to evade immune surveillance of and promote tumor progression and metastasis. Once dominantly recruited into the TME, Tregs exert suppressive activity through key surface molecules and intracellular pathways, including CD25, CTLA-4, PD-1, various cytokine and chemokine receptors, FoxP3, and IDO-mediated metabolic pathways, all of which collectively restrict effector CTL activation and dampen anti-tumor activity. Multiple Treg-targeted therapeutic approaches have been explored to block these pathways - such as mAb therapies or nanoformulations directed against CD25, CTLA-4, the PD-1/PD-L1 axis, TGF-b1, CCR8, or other cytokines and chemokine mediated pathways, IDO inhibitors, synthetic peptides modulating FoxP3 stability. These approaches aim to diminish Treg-mediated suppression and enhance CTL-driven anti-tumor immune responses, and improve therapeutic outcomes in breast cancer. *CCR, C-C chemokine receptor; CTL, cytotoxic T lymphocyte; CTLA-4, cytotoxic T-lymphocyte antigen-4; FoxP3, forkhead box P3; IDO, indoleamine-2,3-dioxygenase; LAG-3, lymphocyte activation gene 3 protein; mAb, monoclonal antibody; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; TCR, T-cell receptor; TGF-β1, transforming growth factor β1; TIM-3, T-cell immunoglobulin and mucin domain-3; TME, tumor microenvironment; Treg, regulatory T cell.* Created in BioRender. Altunbulakli, C. (2026) https://BioRender.com/9wzmzw2

intratumoral Tregs in TNBC models [327]. Additional nanotherapeutic platforms delivering chemotherapeutics or immunomodulators have similarly demonstrated Treg suppression and the restoration of immune balance [331].

Targeting the Treg master transcription factor Forkhead box P3 (FoxP3) also shows preclinical promise. The FoxP3 inhibitor P60 enhances DC vaccine efficacy and reduces Treg-mediated immunosuppression in murine breast tumor models [328, 329]. Recent studies have confirmed that FoxP3 inhibition decreases Treg infiltration, reduces IL-10 secretion, and sensitizes tumors to chemotherapy [340].

In conclusion, a range of Treg-targeted strategies, including checkpoint inhibition, chemokine receptor blockade, metabolic modulation, and FoxP3 inhibition, are being actively investigated to counteract immunosuppression in BC. Although preclinical results are promising, clinical translation remains challenging due to tumor heterogeneity, TME complexity, and safety concerns. Further research are needed to optimize combinations therapies, identify predictive biomarkers, and evaluate long-term efficacy.

4.5.2 Tumor microenvironment modulation

Strategies aimed at reprogramming the TME have emerged as essential components of modern immunotherapy. The principal directions of TME modulation include inhibition of the TGF-β and IDO pathways, blockade of the CSF-1 receptor (CSF-1R), activation of the stimulator of interferon genes (STING) pathway, and targeting of CB2 signaling [2, 167, 332, 335, 336].

TGF-β is a key regulator of immunosuppression within the TME, promoting tumor progression by inhibiting CTL and NK cell functions. Pharmacological inhibition of TGFβ signaling, as exemplified by galunisertib, aims to restore effective antitumor immunity and to enhance responses to immune checkpoint blockade [55]. By blocking tryptophan metabolism, IDO inhibitors prevent the generation of immunosuppressive metabolites such as kynurenine, thereby reducing T-cell exhaustion and immune tolerance. Similarly, inhibition of tryptophan catabolism through IDO blockade prevents the accumulation of immunosuppressive metabolites such as kynurenine, thereby limiting T-cell exhaustion and immune tolerance. IDO inhibition also alters Treg metabolism, strengthen effector T-cell responses and synergize with ICIs in preclinical and clinical settings [332, 337].

Targeting the CSF-1/CSF-1R axis represents another promising approach for TME modulation. CSF-1R blockade selectively reduces TAMs and MDSCs, promoting a shift from an immunosuppressive to an immunostimulatory milieu that supports CTL activation and tumor elimination [338, 339]. Recent studies have also highlighted the immunomodulatory role of CB2 receptor signaling within the TME. CB2 activation can influence Tregs activity and macrophage polarization, suggesting

potential synergy with CSF-1R or IDO inhibitors for the reprogramming of immunosuppressive tumor niches [167, 169].

Furthermore, activation of the STING pathway has gained attention as a strategy to enhance innate and adaptive immunity. STING agonists induce the production of type I interferons and proinflammatory cytokines, thereby increasing antigen presentation and promoting robust antitumor immune responses [340, 335].

Collectively, these complementary approaches to TME modulation represent a multifaceted strategy for overcoming immune evasion and improving the efficacy of current immunotherapies in BC.

4.5.3 Targeting TGF-β-related pathways

TGF-β exerts complex and predominantly protumorigenic effects in BC. Autocrine TGF-β signaling promotes tumor cell invasion and epithelial-mesenchymal transition (EMT), whereas paracrine TGFβ signaling fosters immunosuppression, angiogenesis, and stromal remodeling within the TME [58–61]. Through the induction of Tregs, MDSCs, and cancer-associated fibroblasts, TGF-β establishes an immunosuppressive milieu that facilitates tumor progression.

Recent studies have shown that certain chemotherapeutics capable of inducing immunogenic cell death may paradoxically stimulate TGF-β production by tumor-associated cells, thereby counteracting immune checkpoint blockade. In preclinical models, the coadministration of anti–TGF-β antibodies restored the synergistic antitumor effects of immunogenic chemotherapy and anti-PD-L1 therapy in a $CD8^+$ T-cell-dependent manner [341]. Importantly, the loss of intrinsic TGF-β signaling within tumor cells can further amplify local TGFβ activity, reinforcing immunosuppression [342]. However, owing to the pleiotropic functions of TGF-β in tissue homeostasis, systemic inhibition often causes significant adverse effects [343]. Consequently, strategies that selectively target TGF-β activity within the TME are considered safer and more effective.

TGF-β is primarily stored in a latent form in complex with extracellular matrix proteins, while its active form is correlated with EMT and tumor aggressiveness [344]. Elevated TGF-β levels in breast carcinoma have been associated with increased secretion of bone morphogenetic protein 1 (BMP-1) by TNBC cells [345]. In contrast, nonmetastatic 67NR mammary carcinoma cells display lower BMP-1 expression, suggesting a role for this metalloproteinase in promoting tumor invasiveness and metastatic dissemination.

BMP-1, a member of the BMP-1/toll-like family, regulates multiple physiological processes by proteolytically activating extracellular matrix protein components [346]. Mechanistically, BMP-1 releases active TGF-β from its latent complex, thereby increasing the local bioavailability of TGF-β within the TME. Chemotherapeutic agents such as doxorubicin can also enhance TGF-β signaling and EMT in 4T1 mammary carcinoma models. Pharmacological inhibition of BMP-1 was shown to suppress tumor growth, reduce colony and spheroid formation, and potentiate the antitumor efficacy of doxorubicin in both murine and human TNBC models [334].

Collectively, these findings highlight BMP-1 as a critical activator of TGFβ signaling and a promising therapeutic target for overcoming immunosuppression in BC. Selective BMP-1 inhibitors that block TGF-β activation may enhance the effectiveness of immunotherapy and chemoimmunotherapy while minimizing systemic toxicity.

4.5.4 Neuroimmune modulation

Emerging evidence highlights the bidirectional crosstalk between the nervous and immune systems as a key regulator of tumor progression and therapeutic response. The sympathetic nervous system (SNS), which is responsible for the "fight-or-flight" response, modulates immune activity through α- and β-adrenergic receptors expressed on T cells, macrophages, and DCs [347]. Sustained sympathetic activation supports tumor growth and therapy resistance via catecholamine release [348] (Fig. 5).

Recent studies have revealed that certain immunotherapeutic interventions can also reshape tumor innervation. In both human TNBC xenograft and murine 4T1 models, intratumoral administration of oncolytic HSV promoted sympathetic innervation and increased myeloid cell infiltration [335]. Pharmacological inhibition of sympathetic signaling using β-adrenergic receptor antagonists (β-blockers) enhanced the antitumor efficacy of oncolytic virotherapy and increased T-cell infiltration. Given their established clinical safety, β-blockers represent a feasible and low-risk approach to potentiate immunotherapy outcomes. Interestingly, combined HSV and TGF-β blockade was less effective than HSV with β-blockade, emphasizing the multifaceted role of adrenergic signaling in tumor immunoregulation [335].

Modulation of sensory neuronal pathways has also emerged as an immunoregulatory strategy in BC. Activation of transient receptor potential vanilloid 1 (TRPV1) channels on sensory nerve fibers by olvanil suppressed lung and liver metastases in murine TNBC in a dose-dependent manner [336]. This was associated systemic T-cell expansion, enhanced intratumoral $CD8^+$ T-cell infiltration, increased IFN-γ production, and reduced inflammation.

TRPV1 activation triggers neurogenic inflammation through the release of neuropeptides such as substance P (SP) [121]. SP promotes T-cell proliferation, immunoglobulin synthesis, and lymphokine-activated killer cell cytotoxicity. Through engagement of neurokinin-1

receptors (NK1Rs) on DCs, SP induces IL-12 secretion and DC maturation, thereby increasing the efficacy of DC-based vaccines [349]. In murine TNBC models, prolonged exposure to low SP concentrations synergistically enhances the antitumor effects of radiotherapy [350]. SP also reduces the frequency of tumor-infiltrating MDSCs, attenuates TNF-α signaling, and prevents tumor-induced sensory nerve degeneration while modulating the release of angiogenic factors from tumor-associated fibroblasts (Fig. 5).

Overall, these findings position neuroimmune modulation, particularly through adrenergic blockade, TRPV1 activation, and substance P/NK1R signaling, as a promising, integrative approach to enhance antitumor immunity and boost therapeutic efficacy in BC.

4.5.5 Chronic inflammation modulation

Inflammation plays a dual role in cancer, functioning either as a driver of immune-mediated tumor elimination or as a facilitator of tumor growth, metastasis, and therapeutic resistance, depending on its duration, intensity, and cellular context [351]. Understanding the mechanisms linking chronic inflammation to immune suppression is essential for designing effective combination therapies [352].

The inflammatory response proceeds through three interconnected phases: initiation, amplification, and resolution. During initiation, neuroimmune activation triggers the recruitment of neutrophils, platelets, and macrophages, which release cytokines, chemokines, leukotrienes, and prostaglandins. These mediators sustain the amplification phase, shaping the immune microenvironment and activating adaptive responses [353]. Under physiological conditions, inflammation resolves through the production of anti-inflammatory mediators such as IL-10, TGF-β, and specialized pro-resolving lipid mediators, initiating tissue repair. However, tumor- or TME-derived signals often disrupt this phase, resulting in persistent inflammation that drives tumor progression and impairs immunotherapy efficacy.

Chronic inflammation promotes tumor cell dedifferentiation and immune evasion through mediators such as TNF-α, cyclooxygenase-2 (COX-2, and prostaglandin E_2 (PGE_2). Pharmacological inhibition of the COX-2/PGE_2/EP2-4 axis using nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids enhances immune checkpoint blockade and increases effector T-cell infiltration, converting "cold" tumors into "hot" ones [337]. Retrospective analyses further indicate improved survival in patients receiving NSAIDs together with ICIs [354].

Another important immunoregulatory pathway involved in inflammation-driven tumor progression is the CD200-CD200R1 axis. CD200, a membrane-bound glycoprotein of the immunoglobulin superfamily, delivers inhibitory signals via CD200R on myeloid cells, suppressing the production of proinflammatory cytokines, such as TNF-α, IL-6, and IFNs. In murine models of aggressive BC, CD200 overexpression reduces tumor growth and metastasis, whereas CD200R1 deficiency increases proinflammatory cytokines, neutrophil infiltration, and metastasis [355]. Therapeutic administration of CD200fc, a soluble fusion protein mimicking CD200, enhances $CD8^+$ T-cell infiltration and IFN-γ production, suppressing metastasis [338]. Furthermore, the CD200 mimetic aptamer PEG-M49 synergizes with doxorubicin, to induce complete tumor regression in more than half of treated mice through depletion of MDSCs and activation of $CD8^+$ T cells [334].

Altogether, these findings underscore chronic inflammation as a critical regulator of immune suppression and metastatic progression in BC. Therapeutic strategies targeting chronic inflammation via COX-2 inhibition or modulation of the CD200-CD200R1 pathway represents a promising adjunct to immunotherapy and chemotherapy, enhancing antitumor immunity and reducing metastasis in BC.

4.6 Combination strategies

Combination strategies are central to improving BC immunotherapy by overcoming therapeutic resistance and amplifying antitumor immune responses. Since ICIs alone demonstrate limited efficacy in most BC subtypes, their integration with complementary treatment modalities, such as chemotherapy, radiotherapy, targeted agents, cancer vaccines, cytokine therapy, and microbiome modulation, has become a major focus of translational and clinical research [9, 320]. These synergistic approaches aim to increase tumor immunogenicity, remodel the TME, and broaden the clinical benefit of ICIs [7, 356].

Dual immune checkpoint blockade represents one of the most effective strategies, leveraging the complementary actions of PD-1/PD-L1 and CTLA-4 inhibition. CTLA-4 blockade enhances T-cell priming in lymphoid organs, whereas PD-1/PD-L1 inhibition restores effector T-cell function within the TME [357]. The combined administration of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) significantly improves clinical outcomes in several cancers and has shown promising results in TNBC patients [358, 359].

As previously discussed, cancer vaccines represent another promising strategy to combine with ICIs. By presenting TAAs, vaccines promote CTL activation and durable immune memory. When combined with ICIs, they prevent T-cell exhaustion and amplify antitumor immunity with synergistic effects reported in both preclinical and clinical studies of BC and other solid tumors [360, 361]. Similarly, epigenetic modulators such as histone deacetylases (HDAC) and DNA methyltransferase

inhibitors can potentiate ICIs by enhancing tumor immunogenicity and antigen presentation. For example, the HDAC inhibitor entinostat increased the efficacy of PD-1 blockade in BC models [362].

Cytokine-based immunotherapy also shows promise. IL-2 and IL-15 analogs stimulate T-cell proliferation and persistence, complementing the checkpoint blockade-induced restoration of T-cell activity. Bempegaldesleukin, a pegylated IL-2 variant, has demonstrated synergistic antitumor activity when combined with nivolumab in early-phase clinical trials [363].

Emerging evidence also highlights the gut microbiome is a critical regulator of immunotherapy responsiveness. A balanced and diverse microbiota enhances systemic and intratumoral immune activation, whereas dysbiosis reduces ICI efficacy. Consequently, microbiome-targeted interventions including dietary modulation, probiotics, and fecal microbiota transplantation, are being explored to overcome resistance to checkpoint blockade [364].

Chemotherapy and radiotherapy are indispensable partners of immunotherapy. Both therapies induce immunogenic cell death in cancer cells, releasing TAAs and DAMPs that stimulate T-cell activation. DNA damage enhances neoantigen presentation and PD-L1 upregulation, thereby sensitizing tumor cells to ICIs. Radiotherapy, in particular, augments antigen presentation and T-cell infiltration, often inducing systemic "abscopal" responses. In metastatic TNBC, pembrolizumab combined with radiotherapy is well tolerated and effective even in PD-L1-low tumors [365–367].

However, cytotoxic therapies can also trigger systemic toxicity, immunosuppression, and microbiota disruption, limiting their therapeutic benefits [368–370]. Integration with enterosorption techniques represents a novel supportive strategy to mitigate these adverse effects by removing circulating toxins and immunosuppressive metabolites, restoring gut homeostasis, and supporting immune reactivity. Experimental studies indicate that enterosorbents enhance the efficacy of combined chemo-/radiotherapies and immunotherapies in BC and other malignancies [371–374] (Fig. 9).

Collectively, rational combination strategies that integrate ICIs with conventional, immunomodulatory or supportive modalities, particularly those addressing inflammation, microbiome balance, and systemic toxicity, represent the most promising avenue toward improving immunotherapy outcomes in BC patients.

4.7 Management of immune-related adverse events

4.7.1 Immunotherapy toxicities in breast cancer

The integration of ICIs, ACTs, and cancer vaccines has transformed the management of BC, shifting the

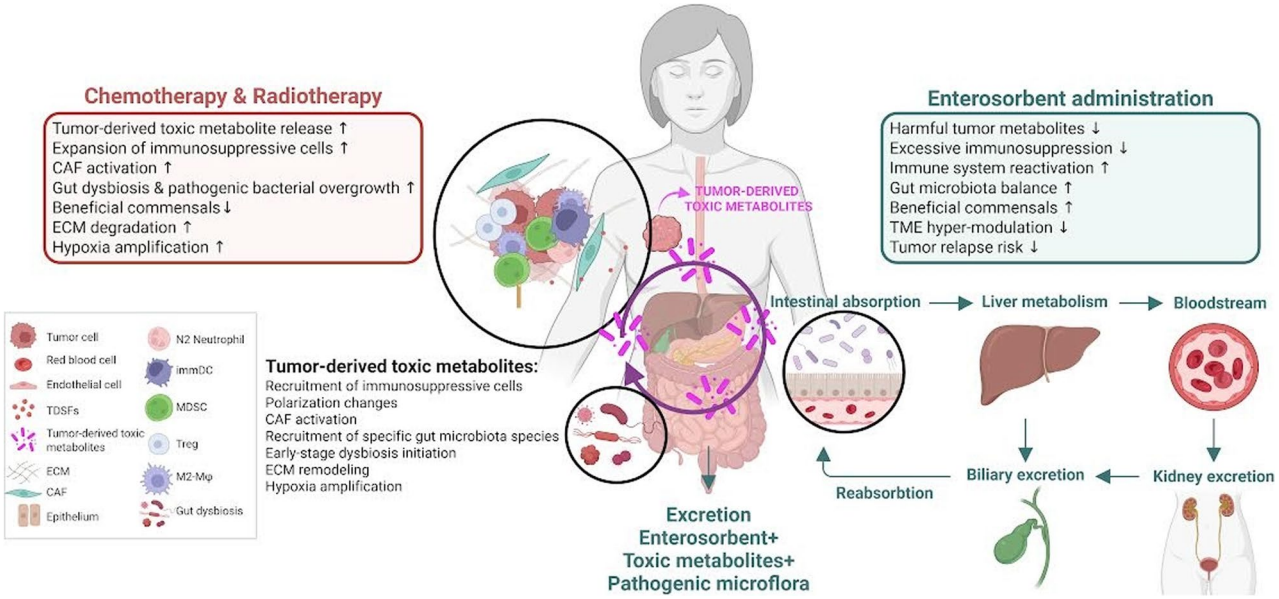

Fig. 9 Potential impact of enterosorption as an adjunct therapy in combination cancer therapy. Tumor cells produce toxic immunosuppressive metabolites, along with recruiting some species of gut microbiota, remodel their surrounding milieu to evade immune system control. Conventional chemo/radiotherapy may unintentionally increase the immunosuppression level and provoke gut microbiota dysbiosis, which can favor pathogenic overgrowth and increase susceptibility to tumor relapses. Enterosorption has no direct effect on the tumor; however, it can systemically reduce the burden of tumor-derived toxic metabolite and therapy-associated harmful components. In addition, enterosorption may contribute to immune system reactivation by limiting pathogenic microflora, reshaping host–microbiota interactions and promoting gut microbiota control. This indirect immunomodulatory effect has the potential to restore endogenous antitumor immunity, to decrease tumor relapse risk and enhance the efficacy of cell-based immunotherapies. *CAF, cancer-associated fibroblast; ECM, extracellular matrix; immDC, immature dendritic cell; Mø, macrophage; MDSC, myeloid-derived suppressor cell; TDSFs, tumor-derived soluble factors; TME, tumor microenvironment; Treg, regulatory T cell.* Created in BioRender. https://BioRender.com/9wzmzw2

paradigm from conventional cytotoxicity to the activation of durable, memory-based antitumor immunity. However, the clinical utility of these therapies is constrained by their unique safety profiles. Unlike the predictable, dose-dependent toxicities of chemotherapy, immunotherapy-induced adverse events result from off-target immune activation. Effectively navigating this therapeutic window requires a sophisticated understanding of immune-related adverse events (irAEs) to ensure that the gains in OS are not offset by severe morbidity or treatment-related mortality.

An analysis of emerging BC immunotherapies reveals specific toxicity challenges that distinguish them from traditional systemic treatments. E-TCR and CAR-T therapies present a dual temporal risk profile linked to their in vivo kinetics. Immediate toxicities include cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), both driven by rapid T-cell expansion, cytokine surges, and endothelial blood–brain barrier disruption in the first days after infusion. Delayed toxicities predominantly arise from "on-target, off-tumor" recognition of antigens shared with healthy tissues, as well as true off-target cross-reactivity revealed only in patients. Notable clinical examples include severe and fatal cardiac toxicity from an affinity-enhanced MAGE-A3-specific TCR, in which engineered T cells cross-recognized a titin-derived peptide in cardiomyocytes (off-target cardiotoxicity), and acute, sometimes lethal, pulmonary injury when highly active ERBB2/HER2- or mesothelin-directed T cells engaged physiological antigen on lung epithelium, triggering diffuse lung damage via on-target, off-tumor mechanisms. Collectively, these cases illustrate how early, expansion-linked CRS/ICANS and later tissue-localized toxicities both mirror the pharmacokinetic and biodistribution patterns of adoptively transferred T cells, underscoring the need to balance receptor affinity, antigen selection, and persistence when designing next-generation ACT products.

CAR-NK cells are a lower-risk alternative to CAR-T cells, showing markedly reduced rates of CRS, neurotoxicity, and graft-versus-host disease, and thus offer a safer platform for clinical translation in BC and other solid tumors [375, 376].

Systemic blockade of the TGF-β pathway is constrained by its essential roles in tissue repair, immune tolerance, and vascular homeostasis [377, 378] such that broad inhibition can provoke fibrotic, inflammatory, and immune dysregulation in multiple organs [379, 380]. To mitigate these toxicities, current efforts focus on spatially restricted or context-selective blockade in the tumor microenvironment [55, 381, 382], including including nanoparticle-based delivery of TGF-β inhibitors and bifunctional or bispecific molecules such as anti-PD-L1/TGF-β 'trap' antibodies (e.g., bintrafusp alfa and anti-TGF-β/PD-L1 bispecifics in TNBC models) [383, 384].

Dysbiosis induced by chemotherapy and radiotherapy in BC patients significantly increases the risk and severity of colitis during subsequent or concurrent ICI therapy [385, 386]. To counteract these adverse effects, enterosorption serves as a non-invasive intervention to preserve gut homeostasis by selectively adsorbing therapy-derived metabolites and pro-inflammatory mediators within the intestinal lumen, thereby attenuating the systemic toxicity associated with the BC treatment-microbiota-immune axis [372].

4.7.2 Safety engineering

Current research highlights the necessity of "suicide switches" and "logic-gated TCRs" to terminate immune activity in the event of high-grade, unmanageable toxicity. Modern engineering strategies have evolved beyond simple "on-off" mechanisms to address the antigen heterogeneity and "on-target, off-tumor" toxicities inherent in BC subtypes, particularly TNBC. Next-generation logic gating strategies are rapidly reshaping the safety architecture of engineered T cells, with recent clinical frameworks such as the LogiCAR designer using patient-specific single-cell transcriptomics to build "AND," "OR," and "NOT" logic circuits that restrict activation to combinations of breast-specific markers, including ROR1, B7-H3, and HER2, thereby tightening the therapeutic window and preventing lethal systemic cross-reactivity [387]. Building on the foundational 'prime-and-kill' synNotch architectures originally validated in glioblastoma [388], recent advancements have integrated computational platforms like LogiCAR to identify BC-specific logic gates. These circuits utilize tissue-specific cues to induce secondary CAR expression only within the malignant niche, thereby minimizing systemic CRS and overcoming the immunosuppressive breast tumor microenvironment. In parallel, dynamic safety systems continue to evolve beyond classical inducible Caspase-9 suicide switches, introducing chimeric switch receptors (CSRs) that not only provide emergency shutdown capability but also convert inhibitory cues such as PD-1 or TIGIT engagement into activating signals, preserving effector-to-target ratios without driving systemic immune exhaustion [389]. Finally, remote-controlled termination platforms, including photothermal and ultrasound-activated switches now being tested in preclinical BC models, offer a non-pharmacological, externally tunable layer of safety by enabling localized, pulsatile CAR-T activation that can be instantly halted when the external stimulus is withdrawn [390].

Table 5 Clinical manifestations of immune-related adverse events (irAEs) across major organ systems and their therapeutic management

Organ system	Common irAE subtypes	Clinical indicators	Management tier
Dermatologic	Rash, Pruritus, Vitiligo	Erythema, maculopapular eruptions, skin depigmentation	Grade 1: Topical steroids; Grade 2+: Oral Prednisone
Gastrointestinal	Colitis, Diarrhea	Increase in stool frequency, abdominal pain, hematochezia	Grade 2: Hold therapy, oral steroids; Grade 3+: IV Methylprednisolone
Endocrine	Thyroiditis, Hypophysis	TSH/T4 imbalance, fatigue, headache, pituitary enlargement on MRI	All Grades: Hormone replacement; usually permanent
Pulmonary	Pneumonitis	New-onset cough, dyspnea, ground-glass opacities on CT	Grade 2+: Permanent hold or discontinuation; high-dose steroids
Hepatic	Hepatitis	Asymptomatic elevation of ALT/AST or bilirubin	Grade 2: Hold therapy; Grade 3+: Discontinue, IV steroids

4.7.3 Clinical framework of organ-system subtypes and management tiers

Clinical manifestations of irAEs across major organs are categorized below, requiring vigilant monitoring of specific indicators and adherence to hierarchical management tiers (Table 5).

The standard clinical approach to managing irAEs follows a strict hierarchical protocol:

1. Severity grading: Clinicians must apply the Common Terminology Criteria for Adverse Events (CTCAE) to grade toxicities from 1 (mild/asymptomatic) to 5 (death).
2. Corticosteroid intervention: Systemic steroids (e.g., prednisone at 0.5–1 mg/kg/day for Grade 2, or methylprednisolone at 1–2 mg/kg/day for Grade 3+) remain the primary intervention to suppress the aberrant inflammatory response.
3. Treatment suspension vs. discontinuation:

– Moderate (Grade 2–3): Temporary suspension of immunotherapy until the event resolves to Grade 1 or baseline.
– Severe (Grade 4): Permanent discontinuation is mandatory for most Grade 4 toxicities, with the notable exception of manageable endocrinopathies.

The critical challenge in BC immunotherapy remains the optimization of the therapeutic window. While "biomarker-guided patient selection" to enhance efficacy is widely advocated, a significant "Standardization dilemma" exists regarding toxicity prediction. Currently, while PD-L1 and TMB serve as surrogates for efficacy, clinicians lack validated, standardized biomarkers for predicting irAE risk. Standardizing these metrics is essential to move beyond reactive management and toward a predictive model of safety. Integrating multi-omics profiling with a critical understanding of the TME will be necessary to identify patients at higher risk for severe irAEs, fulfilling the clinical mandate for safer, personalized BC care.

5 Conclusion and future perspectives

BC remains a major global health challenge due to its biological complexity and heterogeneity, which critically affect therapeutic responses and clinical outcomes. Although advances in immunotherapy have markedly improved patient survival, major challenges persist, particularly in aggressive subtypes such as TNBC and immunologically "cold" tumors. Future progress will depend on the development of personalized, synergistic, and innovative immunotherapeutic strategies that enhance antitumor immunity and yield durable clinical benefits.

Integrating comprehensive multi-omics profiling into treatment planning is expected to become a cornerstone of precision oncology in BC. Combining genomic, transcriptomic, and proteomic data with established biomarkers such as PD-L1 expression, TMB, and TILs will enable more accurate prediction of therapeutic responses and rational selection of treatment combinations. Such biomarker-guided precision strategies will facilitate patient stratification and optimize clinical outcomes.

Emerging therapeutic modalities are expanding the treatment landscape, particularly for TNBC. Bispecific antibodies targeting dual immune checkpoints or tumor antigens and oncolytic viruses designed to enhance tumor antigen release and immune priming have shown significant promise. Further refinement of viral delivery, intratumoral replication, and immune activation is key to maximizing their immunostimulatory potential. Similarly, therapeutic cancer vaccines, particularly when combined with chemotherapy, radiotherapy, or ICIs, represent an important direction for future research. Semi-synthetic vaccine prototypes have demonstrated high safety, robust immunogenicity, and potent antitumor activity in preclinical studies, promoting their clinical translation.

Overcoming therapeutic resistance remains a fundamental challenge in BC management. A deeper

understanding of both intrinsic and acquired resistance to ICIs and combination regimens will aid in identifying novel druggable targets and developing more effective strategies. Promising approaches include combining ICIs with HER2-targeted therapies, chemotherapy, or small-molecule inhibitors of immunosuppressive signaling pathways. Next-generation immunotherapies such as CAR-M therapy and T-cell engagers are also expanding the immunotherapeutic landscape for BC.

The discovery of reliable predictive biomarkers remains critical for advancing precision immunotherapy. In addition to established markers, novel candidates, such as immune checkpoint-associated lncRNAs, the tumor microbiome, and spatial immune architecture, are gaining importance, particularly in TNBC. In addition, CB2 receptor expression may serve as a potential biomarker for immunologically "cold" BC subtypes, complementing conventional indicators and refining patient selection.

AI-based analytical tools are expected to play a transformative role in immuno-oncology. Machine learning and deep learning models can integrate complex tumor–immune datasets to predict therapeutic responses, identify biomarkers, and uncover previously unrecognized therapeutic targets, thereby accelerating translational progress.

Future clinical studies should emphasize inclusivity and diversity in patient recruitment to ensure the generalizability of immunotherapy outcomes. Long-term follow-up is essential for evaluating the durability of immune responses and detecting delayed adverse effects.

By tackling tumor heterogeneity, improving biomarker-guided patient selection, and designing rational multimodal combinations, future research has the potential to fundamentally transform BC therapy, achieving more effective, durable, and truly individualized clinical outcomes.

Abbreviations

ACTs	Adoptive cell therapies
Bregs	Regulatory B cells
CAF	Cancer-associated fibroblast
CAR	Chimeric antigen receptor
CAR-MSCs	MSCs engineered to express CARs
CB	Cannabinoid receptor
CCR, C-C	Chemokine receptor
CEA	Carcinoembryonic antigen
COX-2	Cyclooxygenase-2
CSF-1R	Colony stimulating factor-1 receptor
CTL	Cytotoxic T lymphocyte
CTLA-4	Cytotoxic T-lymphocyte antigen-4
CPS	Combined positive score
DAMPs	Danger-associated molecular patterns
DCs	Dendritic cells
e-MDSCs	Early MDSCs
ECD	Extracellular domain
EGFR	Epidermal growth factor receptor
E-ACTs	Engineered adoptive T-cell therapies
ER^+	Estrogen receptor-positive
ERBB2	Tyrosine kinase receptor 2 for human epidermal growth factor
E-TCR	Engineered T-cell receptor
f-MDSCs	Fibrocytic MDSCs
FoxP3	Forkhead box P3
GARP	Glycoprotein A repetitions associated protein
GM-CSF	Granulocyte/macrophage colony-stimulating factor
GZMB	Granzyme B
HER2	Human epidermal growth factor receptor 2
HR-positive	Hormone receptor-positive
HSV	Herpes simplex virus
hTERT	Human telomerase reverse transcriptase
ICD	Intracellular domain
ICIs	Immune checkpoint inhibitors
IDO	Indoleamine-2,3-dioxygenase
IFN-γ	Interferon γ
IL	Interleukin
iPSC-Ms	Induced pluripotent stem cell-derived macrophages
iTILs	Intratumoral TILs
KK-LC1	Kita-kyushu lung cancer antigen 1
LAG-3	Lymphocyte activation gene-3 protein
LNP	Lipid nanoparticle
LN-14S	Long non-coding RNA 14S
lncRNAs	Long noncoding RNAs
mAb	Monoclonal antibody
MAGEA	Melanoma antigen gene A
MAL2	Myelin and lymphocyte protein 2
M-CSF	Macrophage colony-stimulating factor
MDSCs	Myeloid-derived suppressor cells
MDSC-LCs	MDSC-like cells
M-MDSCs	Monocytic MDSCs
MHC	Major histocompatibility complex
mRNA	Messenger RNA
miRNAs	microRNAs
MUC1	Mucin 1
ncRNAs	Noncoding RNAs
NK	Natural killer cell
NK1R	Neurokinin-1 receptor
NSAIDs	Nonsteroidal anti-inflammatory drugs
OS	Overall survival
OVs	Oncolytic viruses
PARP	Poly (ADP–ribose) polymerase
PD-1	Programmed cell death protein-1
PD-L1/L2	Programmed death ligand-1/-2
PI3K	Phosphoinositide 3-kinases
p-MHC	Peptide-MHC
PMN-MDSC	Polymorphonuclear MDSC
PR	Progesterone receptor
ROR1	Tyrosine kinase-like receptor orphan receptor 1
SCF	Stem cell factor
SNS	Sympathetic nervous system
STING	Stimulator of interferon genes
SP	Substance P
TAAs	Tumor-associated antigens
TACAs	Tumor-associated carbohydrate antigens
TAMs	Tumor-associated macrophages
TCR	T-cell receptor
TGF-β	Transforming growth factor β
Th	Helper T cells
TILs	Tumor-infiltrating lymphocytes
TIM-3	T-cell immunoglobulin and mucin domain-3
TIS	Tumor inflammation signature
TLSs	Tertiary lymphoid structures
TMB	Tumor mutational burden
TMD	Transmembrane domain
TME	Tumor microenvironment
TNBC	Triple-negative breast cancer
TNF-α	Tumor necrosis factor α
Treg	Regulatory T cell
TRPV1	Transient receptor potential vanilloid 1
T-VEC	Talimogene laherparepvec
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal peptide

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Authors' contributions
V.S. conceptualized the study, collected relevant literature, wrote the manuscript draft, Abstract, Introduction, and Subsections 2.4, 2.7, 2.8, 3.1-3.4, 3.6, 4.2-4.4, 4.5.2, 4.6, and 5, prepared drafts for Figs. 1, 3, 4, 6, 7 and 9, prepared Tables 3 and 4, edited the final manuscript and reference list, coordinated the manuscript preparation. A.M. wrote subsections 2.5, 2.6, and 4.5.1, collected relevant literature, prepared Figs. 2 and 8, prepared and edited all final figures in BioRender, edited the manuscript. V.U. wrote Subsections 2.2, 2.3, 4.1.2, 4.1.3, 4.7, contributed to Subsections 2.1 and 4.1.1, collected relevant literature, prepared Tables 1, 2 and 5, and edited the manuscript. N.E. wrote subsections 2.9, 2.10, 4.5.3, 4.5.4, 4.5.5, collected relevant literature, and prepared Figure 5. C.N. wrote subsection 4.3.2.2, collected relevant literature, prepared the abbreviation list, and edited the draft and final manuscript. S.K.B. wrote subsection 3.5, collected relevant literature, and edited the final manuscript. S.R. coordinated the project and essentially contributed to editing the final manuscript.

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