REVIEW ARTICLE

IJBCS
Indones J Basic Clin Stud. 2026; 1(2): 117-33
doi: 10.18585/ijbcs.v1i2.26

Utilizing Anti-Tumor Immunity Against Breast Cancer : Investigations of Anti-Tumor Immune Cells and Cytokines Escalation and Function Enhancement

Elsa Septiani Putri[1], Nuri Thobibatus Shofia Alfaruqi[2],Indah Fadhilah[3]

[1]*Department of Biomedical Sciences, Faculty of Medicine, Halu Oleo University,Indonesia*
[2]*Regional Research and Innovation Agency of Sumenep Regency, Indonesia*
[3]*Master Program of Biomedical Sciences, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University, Indonesia*

Breast cancer (BC) is one of the most common cancers in women, and it continues to be a key area of extensive basic and clinical study to understand its complexity. Immune cells significantly impact BC progression, with some promoting antitumor immunity and others facilitating tumor growth. Immunotherapy represents a promising approach to modifying the immune system for BC treatment. Immunotherapy works by enhancing the ability of the immune system to recognize and attack cancer cells. Future therapy utilizing anti-tumor immunity against breast cancer will be necessary to achieve a significant medical remission of the disease. Investigations involved in this review were limited in utilization of monotherapy and polytherapy against breast cancer which has been successful escalating and enhancing the function of CD8+ T lymphocytes, M1 macrophages, Natural Killer cells, and anti-tumor cytokines in pre-clinical and clinical trial. This review summarized recent investigations that reach their purpose of anti-tumor immune cells and cytokines escalation and function enhancement in breast cancer. This review also highlighted various approaches used as treatment in distinct molecular subtypes of breast cancer. In this review we show that utilization of monotherapy and polytherapy against breast cancer has been successful escalating and enhancing the function of anti-tumor immune cells such as $CD8^+$ T lymphocytes, M1 macrophages, Natural Killer cells, and anti-tumor cytokines in pre-clinical and clinical trials. The studies show potential for manipulating the immune system to eradicate the breast tumor and stimulate antitumor immunity.

Keywords: breast cancer, immunotherapy, anti-tumor immunity

Introduction

Breast cancer (BC) is a leading cancer in women, requiring extensive study due to its complexity.[1] BC is complicated by the varying levels of targetable receptors like Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) and immune-related markers such as Programmed Death-Ligand 1 (PD-L1) and Tumor-Associated Antigen (TAAs) across different subtypes.[2] Immune cells significantly impact BC progression, with some promoting antitumor immunity and others facilitating tumor growth.[3] Certain cells possess bilateral functions, either causing or preventing cancer. Inflammation, driven by proinflammatory cytokines, also plays a crucial role in tumor growth. The immune system actively participates in both preventing and progressing BC4 Research confirms the immune system's dual antitumor

Corresponding Author:
Elsa Septiani Putri
Department of Biomedical Science
Faculty of Medicine, Halu Oleo University
Jl. H.E.A. Mokodompit, Kendari, 93232, Indonesia
e-mail: elsaseptianiputri@uho.ac.id

Submission: 18 November 2025
Last Revision: 20 Maret 2026
Accepted for Publication: 8 April 2026

and pro-tumor activities. A deeper understanding of each immune component is essential to improve patient survival. This knowledge can guide strategies to suppress pro-tumor subsets, boost antitumor subsets, or use a combination.[5]

Immunotherapy is the use of drugs, biologicals, vitamins and minerals, transplantation, and immunizations to control immune responses. Immunotherapy is a type of cancer treatment that harnesses the power of the immune system to recognize and destroy cancer cells. The immune system is a complex network of cells, tissues, and organs that work together to protect the body from harmful pathogens and abnormal cells, including cancer cells. Normally, the immune system can recognize and destroy cancer cells, but sometimes cancer cells can evade the immune system and continue to grow and spread. Immunotherapy works by enhancing the ability of the immune system to recognize and attack cancer cells.[6]

Cancer immunotherapy has emerged as a superior alternative to traditional treatments like chemotherapy and radiotherapy due to its enhanced selectivity, reduced toxicity, and ability to provide long-lasting protection through immunological memory. The foundational concept of cancer immunosurveillance involves the immune system's capacity to recognize and destroy aberrant cells that disrupt tissue homeostasis, a process driven by natural killer (NK) cells and the detection of tumor-related neoantigens by the adaptive immune system. However, tumors often circumvent these defenses through a three-phase "immunoediting" process comprising eradication, equilibrium, and escape where selective pressure leads to the development of resistant, non-immunogenic phenotypes. This escape is facilitated by mechanisms such as the mutation of antigens, dysfunction of effector cells, and the imbalance of inhibitory signals within the tumor microenvironment. Central to this regulation are immune checkpoints like Programmed Cell Death Protein 1 (PD-1) / PD-L1 and Cytotoxic T-Lymphocyte-Associated Antigen 4 (CTLA-4), which normally prevent tissue damage but are exploited by malignancies to suppress T-cell activation and survival. By blocking these inhibitory interactions—such as preventing CTLA-4 from binding to CD80/86 or disrupting the PD-1/PD-L1 pathway—clinicians can restore the body's natural anti-tumor response. Consequently, current research is increasingly focused on activating the patient's innate and adaptive immunity through diverse modalities, including anticancer vaccines, oncolytic viruses, and adoptive cell therapies, positioning immunotherapy as a vital pillar alongside surgery and radiation in modern oncology.[7]

The use of immunotherapy for the treatment of breast cancer has expanded over the last two decades. Cancer immunotherapy represents one of the most significant advances in oncology in recent years. In particular, the utilization of Immune Checkpoint Inhibitors (ICIs) demonstrated impressive anti-tumor activity and a durable clinical benefit. The clinical research landscape of immunotherapy in BC is expanding with novel investigational therapies aimed at initiating, restoring, or triggering patients' immune responses against tumor cells8. It is a necessary to investigate mechanisms to enhance the T cell response.[9]

Immune status is vital for preventing BC recurrence. Strategies to enhance immune activation are needed for tumors with low Tumor-Infiltrating Lymphocytes (TILs) and a low neoantigen load. This includes using specific biomarkers or combination therapies that stimulate anti-tumor immunity without excessive toxicity. Increasing immune status post-treatment is likely to improve disease-free survival. Ongoing research is therefore necessary to ensure effective treatment modules for all forms of the illness.[10,11] Immunotherapy represents a promising approach to modifying the immune system for BC treatment.[12] It has emerged as the fourth primary modality for cancer management, alongside surgery, chemotherapy, and radiation therapy.[13] However, a significant number of patients do not respond to immunotherapy, or they relapse after an initial response. Efficacy is limited because the pro-tumorigenic tumor microenvironment (TME) restricts productive antitumor immune responses.[14,15] Consequently, the main therapeutic goals are to combat immunosuppression and T cell exhaustion. Traditional treatment approaches offer limited survival benefits16, highlighting the necessity of moving beyond these methods. Current techniques are often best at killing only the most selective cancer cells, leaving behind those responsible for tumor recurrence.[7,17] Future therapy utilizing anti-tumor immunity against breast cancer will be necessary to be safer, less toxic, and more effective at targeting cancer cells in order to achieve a significant medical remission of the disease. Many studies showed that utilizing innate immunity

provides potential therapeutic options for cancer control. Strategies exploiting innate immunity, such as agonists of stimulator of interferon genes, Chimeric Antigen Receptor (CAR)-macrophage or CAR-natural killer cell therapies, metabolic regulators, and novel immune checkpoint blockade, have exhibited potent antitumor activities in preclinical and clinical studies.[18] Another study also showed increased antitumor immunity using antiangiogenic agents.[19] However, those studies were conducted on different types of cancer and were not specific to a particular type of cancer.

Methods

This review will provide elaboration of recent investigations of anti-tumor immune cells and cytokines escalation and function enhancement in different molecular subtypes of breast cancer comprehensively. Investigations involved in this review were limited in utilization of monotherapy and polytherapy against breast cancer which has been successful escalating and enhancing the function of $CD8^+$ T lymphocytes, M1 macrophages, Natural Killer cells, and anti-tumor cytokines in pre-clinical and clinical trial. This is a non-structured narrative review that started with formulating a research question, drafting the review preparatory work, literature searching (Pubmed and Springer Nature Link Database) with key words used : "improve anti-tumor immunity in breast cancer", "improve breast cancer immunity", "enhance anti-tumor immunity in breast cancer", "improve anti-tumor immune response in breast cancer" within 2015-2025, full text, pre-clinical trial, clinical trial, and randomized controlled trial research articles.

Result and Discussion

Monotherapy Approach in Order to Utilizing Anti-Tumor Immunity Against Breast Cancer

The landscape of breast cancer treatment has undergone a paradigm shift, moving away from viewing breast cancer as an "immunologically cold" tumor to recognizing its potential for targeted immune activation. Historically, breast cancer was thought to have low mutational burden and minimal lymphocyte infiltration. However, recent advancements in the monotherapy approach have demonstrated that the immune system can be precision-tuned to recognize and eliminate malignant cells. To provide a clear overview of how these single-agent strategies function across different breast cancer subtypes, **Table 1** summarizes the core descriptions, substance or strategy used in therapy, and current clinical standing of the primary monotherapy agents utilized in breast cancer care.

The treatment of triple-negative breast cancer (TNBC) increasingly relies on the synergistic combination of chemotherapy and immunotherapy to overcome tumor-driven immunosuppression and immune evasion. Recent research highlights how specific chemotherapeutic agents, such as eribulin, can directly enhance the proliferation of $CD8^+$ T cells and maintain them in a less-differentiated, more potent state compared to other treatments like paclitaxel. Furthermore, chemotherapy-induced stress in TNBC cells can trigger the upregulation of the cytokine InIL-23, which co-activates the PI3K-AKT signaling pathway in cytotoxic T lymphocytes (CTLs) to improve the efficacy of anti-PD-1 therapy. These therapeutic strategies aim to reverse "tumor editing," a process where late-stage tumors epigenetically repress innate and adaptive immune genes particularly interferon-stimulated genes to exclude immune cells and foster an exhausted T cell phenotype. By leveraging the immunomodulatory effects of chemotherapy, researchers are finding ways to restore immune control and enhance the long-term functionality of tumor-infiltrating lymphocytes.[20,21,57]

Beyond chemotherapy, a multifaceted approach to overcoming the immunosuppressive TME is being pursued through novel cellular activation, molecular engineering, and even biomechanical interventions. Direct enhancement of cytotoxic lymphocyte activity is a primary focus, achieved through the stimulation of NK-92 cells with anti-CD226 antibodies, the use of NK group 2 member D-bispecific antibodies to co-stimulate both NK and Cluster of Differentiation $(CD)8^+$ T cells, and the disruption of the CD6-CD318 axis to increase lymphocyte-mediated killing. Innovative delivery systems further augment these responses, such as ROR1-targeted bispecific T cell engagers that redirect T cells to lyse TNBC cells, and injectable supramolecular hydrogels that deliver abemaciclib and NLG919 to induce immunogenic cell death while inhibiting metabolic suppression. Additionally, reprogramming the immune environment through bacterial proteins like PepO

Indones J Basic Clin Stud. 2026; 1(2): 117-133

Print ISSN: XXXX-XXXX, Online ISSN: XXXX-XXXX

Table 1. Summary of monotherapy approach in order to utilizing anti-tumor immunity against breast cancer.

Therapy Category	Therapeutic Agent / Strategy	Effects on Anti-Tumor Immune Cells	Effects on Anti-Tumor Cytokines	Breast Cancer Molecular Subtype	Trial Phase	Research Model	Ref.
Chemotherapy	Eribulin + CD3/CD28-stimulated T cells	Increased proliferation of CD8+ T cells and inhibited TNBC cell growth	Increased IFN- γ+ CD8+ T cells	TNBC	Pre-clinical	TNBC cell lines	[20]
	Low-dose Decitabine	Restored immune gene expression and enhanced the quantity, function, and memory of tumor-infiltrating lymphocytes	Induced interferon-, pyroptosis-, and necroptosis-related genes	TNBC		Implanted TNBC tumors and GEMM mouse models	[21]
Targeted Therapy	Denosumab	Increased tumor-infiltrating lymphocytes (TILs), especially in luminal B-like tumors	–	Early HER2-negative	Clinical Trial (NCT03691311)	Human breast cancer tissue	[22]
Immunotherapy	UMCD6 (anti-CD6 monoclonal antibody)	Enhanced lymphocyte cytotoxicity, increased cytotoxic TILs with perforin expression, and upregulated the NKG2D-DAP10 complex essential for NK-cell activation	–	TNBC	Pre-clinical	Xenograft TNBC mouse models	[23]
	IgG-based bispecific CD3 T-cell engager targeting ROR1	Stimulated T-cell activation and proliferation and promoted selective killing of TNBC cells	–	TNBC		TNBC mouse models	[24]
	NKG2D costimulatory receptor-bispecifics (CRB) + T cell-dependent bispecific (TDB) antibody	Enhanced NK-cell and T-cell activation and promoted effector CD8+ T-cell differentiation	Increased cytokine production	HER2-positive		HER2-expressing cell lines and mouse models	[25]
	Streptococcus pneumoniae endopeptidase O (PepO)	Induced conversion of tumor-promoting M2 macrophages into anti-tumor M1 macrophages	Increased iNOS, Cxcl9, Cxcl10, TNF- α, and IL-6 while reducing Arg-1, Tgfb, Vegfa, and IL-10	TNBC		TNBC cell lines and mouse models	[26]
	LPS-stimulated bone marrow-derived dendritic cell vaccine	–	Slowed tumor growth and increased IFN- γ production in the tumor microenvironment	TNBC		TNBC cell lines and mouse models	[27]
	Supramolecular hydrogel co-loaded with Abemaciclib/NLG919	–	Increased IL-2 production by cytotoxic T lymphocytes	TNBC		TNBC cell lines and mouse models	[28]
	NK-92 cells stimulated with anti-CD226 antibodies (sNK-92)	Enhanced cytotoxicity and granzyme B release	–	TNBC		TNBC cell lines	[29]

Table 1. Summary of monotherapy approach in order to utilizing anti-tumor immunity against breast cancer (continue).

Therapy Category	Therapeutic Agent / Strategy	Effects on Anti-Tumor Immune Cells	Effects on Anti-Tumor Cytokines	Breast Cancer Molecular Subtype	Trial Phase	Research Model	Ref.
Genetic Engineering	Steroidogenesis inhibition	Reduced tumor-associated macrophages and enhanced dendritic- and T-cell-mediated anti-tumor immunity	–	TNBC	Pre-clinical	TNBC mouse models	[30]
	Lactate dehydrogenase C (LDHC) knockdown	Enhanced T-cell activation and cytolytic activity while reducing PD-1, CTLA-4, TIGIT, TIM3, and VISTA expression on CD8+ T cells	Increased IFN- γ, GM-CSF, MCP-1, and CXCL1 while reducing IL-6, Gal-9, IL-1 β, and IL-4	TNBC		TNBC cell lines	[31]
Phytotherapy	*Piper nigrum* extract	Increased dendritic cells and activated CD8+ T cells while reducing Tregs in the tumor microenvironment	–	TNBC		TNBC cell lines	[32]
	Chlorogenic acid (CGA)	Increased CD4+ and CD8+ T-cell proportions	–	TNBC		TNBC mouse models	[33]
	Auricularia polytricha extract	Promoted M1 macrophage polarization	Increased IL-6, IL-1 β, and TNF-α expression associated with M1 macrophages	TNBC and hormone receptor-positive		MDA-MB-231 and MCF-7 cell lines	[34]
	Coriolus versicolor extract	Increased M1 macrophage markers and decreased M2 macrophage markers	–	TNBC		TNBC cell lines	[35]
	Pachymic acid from *Poria cocos*	Promoted M1 macrophage infiltration	–	TNBC		CCLE database	[36]
Physical Therapy	Low-intensity pulsed ultrasound (LIPUS)	Enhanced CD4+ and CD8+ T-cell activation and promoted TIL accumulation	–	TNBC		TNBC mouse models	[37]
Chemical Compound	Shikonin	Increased CD8+ T-cell percentage	–	TNBC		TNBC mouse models	[38]
	Sodium chloride (NaCl)	Enhanced activation and effector function of human CD8+ T cells	–	Breast cancer (unspecified subtype)		KEGG database and human CD8+ T cells	[39]
	Yeast-derived β-(1,3)(1,6)-D-glucan	Promoted NK-cell proliferation	–	Luminal A		Luminal A cell lines	[40]
	Cordycepin	Increased expression of death ligands and NKG2D receptors on NK cells	–	Luminal A and TNBC		Luminal A and TNBC cell lines	[41]
	Hainanenin-1 (HN-1)	Increased infiltration of dendritic cells and T lymphocytes	Increased IL-2, IL-12, and IFN-γ secretion	TNBC		TNBC cell lines and mouse models	[42]
	Carbonic anhydrase inhibitor	Increased tumor pH and immune cell infiltration	–	HER2-positive		HER2-positive mouse models	[43]

Indones J Basic Clin Stud. 2026; 1(2): 117-133

Print ISSN: XXXX-XXXX, Online ISSN: XXXX-XXXX

Table 1. Summary of monotherapymApproach in order to utilizing anti-tumor immunity against breast cancer (continue).

Therapy Category	Therapeutic Agent / Strategy	Effects on Anti-Tumor Immune Cells	Effects on Anti-Tumor Cytokines	Breast Cancer Molecular Subtype	Trial Phase	Research Model	Ref.
Nanotherapy	RDPNs@diABZIs nanoparticles	Triggered de novo T-cell responses, enhanced CTL-mediated tumor killing, and induced durable immune memory	–	TNBC	Pre-clinical	TNBC cell lines and mouse models	[44]
	Ultrasound-responsive spherical nucleic acid	Reduced PD-1+ effector T cells and converted tumor-associated macrophages into anti-tumor phenotypes	–	TNBC		TNBC cell lines and mouse models	[45]
Enzyme Inhibitor	Stearoyl-CoA desaturase inhibitor (SCDi)	Improved dendritic-cell antigen presentation and promoted cytotoxic T-cell infiltration	Enhanced interferon signaling	TNBC		TNBC cell lines and mouse models	[46]
	Acetyl-CoA synthetase 2 inhibitor	Increased T-cell activation markers and dendritic-cell antigen presentation and enhanced CD8+ T-cell proliferation and polyfunctionality	–	TNBC		TNBC cell lines and mouse models	[47]
Epigenetic Therapy	HDAC inhibitor Trichostatin A (TSA)	Restored MHC-I antigen-presentation machinery genes, although invasion- and metastasis-related genes were also increased	–	Luminal A		Luminal A cell lines	[48]
	Dual DNMT/HDAC inhibitor 15a	–	Increased expression of antigen-presentation genes (B2M, HLA-C) and chemokines (CCL5, CXCL10)	TNBC, Luminal A, HER2-positive		Cell lines and mouse models	[49]

can transform tumor-promoting M2 macrophages into tumor-inhibitory M1 cells, while optimizing dendritic cell maturation with lipopolysaccharide (LPS) enhances the potency of DC-based vaccines. Emerging biomechanical strategies, such as supramolecular polyrotaxane-based nano-theranostics, aim to stiffen cancer cells to physically facilitate T-cell-mediated destruction, offering a unique avenue to bypass immune evasion.[23–29, 44]

A critical parallel strategy involves the strategic reprogramming of the metabolic and biochemical landscape within the TME to enhance antitumor immunity. Strategic interventions targeting various metabolic pathways have shown significant potential: blocking acetyl-CoA synthetase 2 (ACSS2) can flip cancer cells from acetate consumers to producers, thereby providing acetate as a fuel source that metabolically bolsters T-cell effector functions and proliferation. Similarly, targeting stearoyl-CoA desaturase (SCD) induces lipotoxicity in cancer cells and reshapes the lipidome, which enhances antigen presentation by dendritic cells and promotes the infiltration of cytotoxic T cells while reducing immunosuppressive regulatory T cells. Further immune-modulatory effects are seen through the inhibition of local steroidogenesis, which restricts tumor progression by impeding glucocorticoid signaling and reducing immunosuppressive components like tumor-associated macrophages. Additionally, the expression of Lactate Dehydrogenase C (LDHC) serves as a tumor-intrinsic factor that influences immune cell infiltration and T-cell dysfunction, while the presence of carbonic anhydrases can reduce the acidity of the TME, thereby promoting immune infiltration and improving overall survival in specific breast cancer subtypes. Together, these studies illustrate that by perturbing the metabolic and endocrine landscape of the TME, it is possible to reverse immune evasion and significantly improve the efficacy of cancer immunotherapies.[30,31,43,46,47]

Parallel to these targeted biological and metabolic approaches, research into natural extracts and chemical compounds underscores their potential as immunomodulatory agents. Polysaccharides derived from mushrooms, such as *Auricularia polytricha* and *Coriolus versicolor*, have demonstrated a significant ability to polarize macrophages toward a tumor-inhibitory M1-like phenotype by upregulating pro-inflammatory markers and activating the NF-κB signaling pathway. Similarly, Piper nigrum (black pepper) extract exhibits direct cytotoxic and pro-oxidant effects on breast cancer cells while simultaneously enhancing the systemic antitumor immune response by increasing the frequency of activated dendritic cells and T cells.[32,34,35] At the molecular level, compounds like yeast-derived beta-(1,3)(1,6)-D-glucan significantly boost NK cell proliferation and cytotoxicity, while Hainanenin-1 (HN-1), a host defense peptide, induces immunogenic cell death (ICD) in TNBC cells through the cGAS-STING pathway, promoting dendritic cell maturation and increasing CD8+ T cell tumor infiltration.[38–42] These studies converge on the concept that natural bioactive compounds can potentiate anti-tumor immune responses through complementary mechanisms, including innate immune cell activation, ICD induction, and metabolic reprogramming of cytotoxic T cells.

The principles of metabolic and immune reprogramming are also being elegantly integrated into the design of advanced nanotherapies. For instance, redox-responsive supramolecular polyrotaxane nanoparticles (RDPNs@diABZIs) have been developed to simultaneously deliver methyl-β-cyclodextrin (MeβCD) and STING agonists to the TME. The released STING agonists activate the cGAS-STING pathway in antigen-presenting cells to prime de novo T-cell responses, while MeβCD depletes membrane cholesterol from cancer cells, mechanically stiffening them and thereby enhancing cytotoxic T lymphocyte (CTL)-mediated killing. Complementing this, an ultrasound-responsive spherical nucleic acid (USNA) has been engineered to deliver siRNA targeting PD-L1 and an antisense oligonucleotide targeting the oncogene c-Myc. Upon ultrasound activation, it simultaneously suppresses cancer cell proliferation while remodeling the TME by repolarizing M2-like tumor-associated macrophages toward the anti-tumoral M1 phenotype.[44,45] Complementing these strategies, innovative physical therapies such as low-intensity pulsed ultrasound (LIPUS) have demonstrated the ability to activate anti-tumor immunity by remotely targeting the spleen, leading to enhanced $CD4^+$ and $CD8^+$ T cell activation, increased pro-inflammatory cytokine production, and reduced immunosuppressive myeloid-derived suppressor cells (MDSCs) in murine breast cancer models.[37] These studies highlight synergistic approaches that mechanically reprogram cancer cells, activate innate immunity, and re-educate macrophages to overcome the immunosuppressive TME.

Furthermore, the role of epigenetic dysregulation in immune evasion has emerged as a critical target. Epigenetic alterations, particularly aberrant DNA methylation and histone deacetylation, play a critical role in breast cancer

pathogenesis by suppressing tumor suppressor genes and downregulating key immune recognition molecules. Studies have shown that DNMT1 and HDAC1 are overexpressed in breast cancer, and their simultaneous inhibition using a novel dual inhibitor induces a potent antitumor effect by triggering a viral mimicry response. This response elevates intracellular double-stranded RNA levels, activating the RIG-I–MAVS–JAK–STAT signaling cascade, and ultimately enhancing the production of type I/III interferons and chemokines, which sensitizes tumors to anti-PD-L1 immunotherapy. While histone deacetylase (HDAC) inhibition can restore antigen presentation machinery gene expression, it also presents a dual-edged nature, as it can concurrently upregulate PD-L1 and metastatic markers, highlighting the need for careful consideration when such agents are used in isolation rather than as part of rational combination regimens.[48,49]

Finally, the strategic inhibition of key metabolic enzymes has emerged as a powerful approach to simultaneously impair tumor cell survival and reprogram the immune landscape. Targeting enzymes such as carbonic anhydrases (CAs) can modulate tumor pH to promote immune infiltration, while inhibition of acetyl-CoA synthetase 2 (ACSS2) liberates acetate as an alternative fuel source to bolster T cell and NK cell effector functions. Similarly, blocking stearoyl-CoA desaturase (SCD) not only induces lipotoxicity in cancer cells but also remodels the tumor microenvironment by enhancing antigen presentation, increasing cytotoxic T cell infiltration, and weakening immunosuppressive checkpoint interactions.[43,46,47]

While monotherapy approaches have established the foundational understanding of immune modulation in breast cancer—demonstrating that agents can directly enhance T cell proliferation, polarize macrophages, activate NK cells, and induce cytokine production—their effects are often transient, limited in magnitude, and insufficient to fully overcome the multifaceted immunosuppressive tumor microenvironment.

Polytherapy Approach in Order to Utilizing Anti-Tumor Immunity Against Breast Cancer

While monotherapies have paved the way for modern oncology, the complex landscape of the breast TME often presents multiple layers of immune evasion. The polytherapy approach represents a strategic evolution in treatment. This multi-pronged strategy is designed not only targets the cancer cells directly but also "re-educates" the patient's immune system to recognize and destroy residual tumor cells, significantly reducing the risk of relapse, and transform the TME from a suppressive environment into an active battleground for anti-tumor immunity. The following section explores these combinations in detail, focusing on how they enhance anti-tumor immunity. **Table 2** summarizes the description of these polytherapy regimens.

The intersection of chemotherapy and immunotherapy has been extensively explored across different disease settings, revealing the complexity of immune modulation and the critical role of predictive biomarkers. In early-stage TNBC patients receiving neoadjuvant chemotherapy plus durvalumab, post-treatment B-cell clonal expansion was significantly lower in patients who developed immune-related adverse events, while elevated pre-treatment sCD40L, EGF, and IL-10 were associated with residual disease, underscoring the potential of serum cytokines as predictive biomarkers for both response and toxicity. In the metastatic setting, metronomic VEX chemotherapy combined with toripalimab achieved the longest median progression-free survival, with post-treatment systemic immune reprogramming—including reduction in $CD4^+$ central memory T cells and increases in activated NK cells—uniquely associated with treatment efficacy, implicating the chemotherapy backbone as a key driver of immunotherapy synergy. The first invasive lobular carcinoma-specific trial demonstrated that low-dose carboplatin followed by atezolizumab achieved clinical benefit predominantly in the triple-negative subgroup, with combination therapy significantly increasing $CD8^+$ T cell infiltration and exhausted T cell signatures, suggesting systemic reinvigoration of tumor-reactive T cells. These studies converge on the theme that treatment-induced dynamic changes in both the tumor microenvironment and systemic immune compartment are more informative predictors of efficacy than baseline immune parameters alone.[50,51,83]

Beyond immunotherapy combinations, chemotherapy agents can be meaningfully augmented by adjunct strategies that reshape immune responses. Albumin-bound paclitaxel combined with Sophora subprostrate polysaccharide reduced myeloid-derived suppressor cells (MDSCs) and elevated $CD8^+$ T and NK cell populations in tumor-bearing rats. Both paclitaxel and doxorubicin can trigger GSDME-mediated pyroptosis in breast cancer cells with high GSDME expression, releasing damage-associated molecular patterns that activate immunogenic cell death and enhance T cell activation. Combining low-dose doxorubicin with metformin significantly

Table 2. Summary of polytherapy approach in order to utilizing anti-tumor Immunity against breast cancer.

Therapy	Substance or Strategy Used in Therapy	Escalation and Function Enhancement – Anti-Tumor Immune Cells	Escalation and Function Enhancement – Anti-Tumor Cytokines	Molecular Subtype of Breast Cancer	Trial Phase	Research Object	Ref.
Chemotherapy combined with immunotherapy	Metronomic chemotherapy combined with PD-1 blockade	Reprogrammed systemic immune characteristics toward an immunotherapy-favorable profile by reducing $CD4^+$ Tcm cells and increasing classic monocytes and NK cells	–	Metastatic HER2-negative	Clinical Trial (NCT04389073)	Human tumor biopsies and blood	[50]
	Weekly carboplatin (AUC 1.5 mg ml–1 min–1) for 12 weeks combined with atezolizumab (PD-L1 blockade; triweekly) from week 3 until progression	Increased $CD8^+$ T-cell infiltration, immune checkpoint expression, and exhausted T cells	–	Invasive lobular breast cancer (ILC)	Clinical Trial (NCT03147040)	Human tumor biopsies and blood	[51]
Chemotherapy combined with another chemotherapy	Combination of paclitaxel and doxorubicin inducing pyroptosis and GSDME cleavage	Enhanced macrophage phagocytosis	Increased IFN- γ and IL-2 secretion	TNBC and Luminal A	Pre-clinical Trial	Human tumor biopsies and breast cancer cell lines	[52]
Chemotherapy combined with phytotherapy	Albumin-bound paclitaxel combined with Sophora subprostrata polysaccharide (SSP)	Increased $CD8^+$ T cells and NK cells, enhanced cytotoxic function, reduced MDSCs and immunosuppression	Increased perforin and granzyme B expression	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[53]
Chemotherapy combined with bacteriotherapy	Doxorubicin (DOX) combined with probiotics: Bifidobacterium breve BBr60, Pediococcus pentosaceus PP06, and Bifidobacterium longum subsp. longum BL21	Recruited M1 macrophages and $CD3^+CD8^+$ T cells; improved tumor microenvironment and immune response	Upregulated IL-6, TNF- α, IFN-γ, and IFN- β	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[54]
Chemotherapy combined with certain chemical compound	Cyclophosphamide combined with Minnelide	Significantly increased CTL infiltration in residual tumors and spleens	–	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[55]
	Doxorubicin combined with metformin	Increased percentage of $CD8^+$ T cells	–				[56]
Immunotherapy combined with targeted therapy	Rucaparib + atezolizumab	Enhanced $CD8^+$T-cell activity and STING pathway activation	–	TNBC	Clinical Trial (NCT03101280)	Human tumor biopsies and blood	[57]
	CBL0137 combined with NKG2A blockade in MYC-high TNBC	Increased activated $CD8^+$ T cells and NK-cell infiltration; enhanced tumor apoptosis after anti-NKG2A treatment	–		Pre-clinical Trial	TNBC cell lines and mouse models	[58]
	RBMS1 depletion combined with CTLA4 blockade or CAR-T therapy	Promoted CTL activity and $CD8^+$ T-cell infiltration	–			TNBC mouse models	[59]

Print ISSN: XXXX-XXXX, Online ISSN: XXXX-XXXX

Table 2. Summary of polytherapy approach in order to utilizing anti-tumor immunity against breast cancer (continue).

Therapy	Substance or Strategy Used in Therapy	Escalation and Function Enhancement – Anti-Tumor Immune Cells	Escalation and Function Enhancement – Anti-Tumor Cytokines	Molecular Subtype of Breast Cancer	Trial Phase	Research Object	Ref.
Immunotherapy combined with another immunotherapy	Bevacizumab + nivolumab	Strongly promoted $CD8^+$ T-cell infiltration and activation	–	TNBC	Pre-clinical Trial	Humanized TNBC mouse models	[60]
	Nivolumab + ipilimumab	Immune activation observed in 60% of patients; high TIL levels correlated with response	–		Clinical Trial (NCT03815890)	Human tumor biopsies	[61]
Immunotherapy combined with nanotherapy	Macrophage membrane-coated nanoparticles loaded with SD-208 (MΦ-SDNP)	Blocked M2 macrophage differentiation and increased CTL population	–	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[62]
	Polyaniline-coated iron oxide nanoparticles (Pani/γ-Fe2O3 NPs)	Increased NK cells and CD86 macrophages	Enhanced IL-12p70 and TNF-α production				[63]
	Ad-hTERT oncolytic adenovirus delivered using folate-modified liposomes	Increased tumor apoptosis and T-cell infiltration; reduced proliferation	–				[64]
	PD-1 membrane-coated ferroptosis nanoinducer (PD-1@RSL3 NPs)	Enhanced $CD8^+$ T-cell infiltration and dendritic cell maturation	–				[65]
	Lipid nanoparticles delivering IL-21, IL-7, and 4-1BB ligand mRNA (Triplet LNP)	Increased tumor-infiltrating CD8 T cells	Increased granzyme B and IFN-γ production				[66]
	Cancer cell membrane-coated MOF platform delivering TLR7/8 agonist and epigenetic inhibitor	Activated $CD8^+$ T cells, enhanced lymphocyte infiltration, induced ICD, and reduced Tregs	–				[67]
Immunotherapy combined with certain chemical compound	CAR-T stimulation using DSF/Cu + IR-stressed cancer cells	Increased CAR-T and T-cell infiltration; enhanced CAR-T function in TME	Elevated pro-inflammatory cytokines and chemokines	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[68]
	Intratumoral injection of S. aureus spent culture media containing α-hemolysin prior to ICB	Recruited TILs and increased $CD8^+$ T cells and PD-L1 expression	–				[69]
Immunotherapy combined with photodynamic therapy	MOFs loaded with PD-L1 inhibitors and HA-PEG outer coating irradiated by 660 nm laser	Stimulated dendritic cell maturation, T-cell activation, and intratumoral infiltration	–	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[70]
Radiotherapy combined with certain chemical compound	Radiotherapy combined with dimethyl-α-ketoglutarate (DM- αKG)	Increased $CD8^+$ T-cell infiltration and reduced Treg composition	–	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[71]
Radiotherapy combined with nanotherapy	CeO_2 nanoparticles combined with bacterial outer membrane vesicles (CeO_2@OMV)	Enhanced macrophage polarization and systemic immune responses	–	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[72]
Nanotherapy combined with phytotherapy	Platycodon grandiflorum -derived extracellular vesicles (PGEVs)	Promoted TAM polarization toward M1 phenotype and CTL infiltration	–	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[73]
	CUR/miR155@DssD-Hb NPs co-delivering curcumin and miR155	Stimulated DC maturation, activated $CD8^+$ T cells, reduced MDSCs/Tregs/M2 TAMs/exhausted T cells	Triggered DAMP release and long-term immunity				[74]
	Curcumin and ginsenoside Rg3-loaded zwitterionic micelles (PPH@CR)	Promoted DC maturation and increased $CD4^+$ and $CD8^+$ T cells	Reduced PD-L1 expression				[75]

Table 2. Summary of polytherapy approach in order to utilizing anti-tumor immunity against breast cancer (continue).

Therapy	Substance or Strategy Used in Therapy	Escalation and Function Enhancement – Anti-Tumor Immune Cells	Escalation and Function Enhancement – Anti-Tumor Cytokines	Molecular Subtype of Breast Cancer	Trial Phase	Research Object	Ref.
Targeted therapy combined with another targeted therapy	Olaparib + Adavosertib	Increased $CD8^+$ TCR $\beta^+$and $CD4^+$ TCR β^+cells; enhanced MHC-I expression	Increased IFN β and CXCL10 mRNA levels	TNBC	Pre-clinical Trial	TNBC cell lines with wild-type BRCA1/2	[76]
Nanotherapy combined with targeted therapy	CRISPR/Cas9 nanoplatform targeting methionine metabolism and STING pathway via SLC43A2 transporter	Increased $CD8^+$ T-cell infiltration	Increased IFN- β expression	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[77]
	CRISPR-Cas9 with FCPCV nanoparticles targeting CCL5	Enhanced $CD8^+$T-cell activity and improved $CD8^+$ /$CD4^+$ ratio	Increased IFN- γ, TNF-α, and GZMB production	Breast cancer (no subtype classification)	Pre-clinical Trial	Breast cell lines and mouse models	[78]
Nanotherapy combined with sonodynamic therapy	Tin monosulfide nanoparticles (SnSNPs) as nano-sonosensitizers	Enhanced CTL infiltration and antitumor immunity	–	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[79]
Nanotherapy combined with certain chemical compound	HER2-targeted pH-sensitive nanoliposomes encapsulating TKD and IP-10p peptides with NK-cell therapy	Enhanced NK-cell infiltration and function; improved trastuzumab efficacy	–	HER2-positive	Pre-clinical Trial	HER2-positive trastuzumab-resistant cell lines and mouse models	[80]
Nanotherapy combined with chemotherapy	Gemcitabine-celecoxib nano-assembled carrier-free nanoparticles (GEM-CXB NPs)	Activated cytotoxic T cells and NK cells; inhibited Tregs; promoted M2-to-M1 repolarization	–	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[81]
Chemical compound combined with certain therapy	2-deoxy-D-glucose (2DG) combined with microwave ablation (MWA)	Enhanced differentiation of tumor-specific $CD44^{hi}CD62L^+$ $CD8^+$ TCM cells	–	TNBC	Pre-clinical Trial	TNBC cell lines and mouse models	[82]

increased $CD8^+$ T cell frequencies while downregulating immunosuppressive HIF-1α and STAT3 expression. Minnelide, a prodrug of triptolide, when combined with cyclophosphamide, reprogrammed the immunosuppressive TME by reducing granulocytic MDSCs and enhancing cytotoxic T cell infiltration, ultimately eradicating residual tumor cells following surgical resection. Extending the adjunct strategy to the gut-tumor axis, specific probiotic strains enhanced the anti-tumor efficacy of doxorubicin by promoting immune cell infiltration and enriching beneficial gut microbiota including Akkermansia. Collectively, these studies demonstrate that chemotherapy efficacy is deeply intertwined with the immune landscape, and combination strategies can meaningfully reverse immunosuppression and amplify cytotoxic immune responses.[52–56]

Numerous innovative therapeutic strategies have been developed specifically for TNBC, focusing on overcoming its immunosuppressive TME and resistance to conventional therapies. Lipid nanoparticle-formulated mRNA encoding IL-21, IL-7, and 4-1BBL for intratumoral delivery synergistically promotes $CD8^+$ T cell infiltration and IFN-γ production, leading to tumor eradication and long-term immunological memory. Exposing CAR T cells to disulfiram/copper and stressed tumor cells reprograms them into early memory-like T cells with enhanced persistence and cytotoxicity. A biomimetic metal-organic framework nanoplatform co-delivering a TLR7/8 agonist and BRD4 inhibitor induced immunogenic cell death and dendritic cell maturation, while macrophage membrane-coated nanoparticles loaded with a TGF-β inhibitor specifically targeted tumor-associated macrophages and synergized with anti-PD-1 therapy. The phase 2 BELLINI trial demonstrated that neoadjuvant nivolumab with or without ipilimumab induced immune activation in early-stage TNBC, with patients harboring high tumor-infiltrating lymphocytes achieving pathological complete responses.Rucaparib combined with atezolizumab showed that PARP inhibition primes tumors for immunotherapy response through cGAS-STING pathway activation. Additional strategies include photodynamic therapy with PD-L1 inhibition, bacterial products serving as immune-priming agents, ferroptosis inducers disrupting the PD-1/PD-L1 axis, polyaniline-coated nanoparticles reprogramming tumor-associated macrophages, curaxin drugs downregulating MYC and inducing Type I interferon responses, liposome-encapsulated oncolytic adenovirus preventing lung metastasis, and bispecific T-cell engagers fused to sialidase removing immunosuppressive sialic acids. Additional mechanistic insights include identification of RBMS1 as a key regulator of PD-L1 stability and demonstration that neoadjuvant nivolumab combined with bevacizumab normalizes tumor vasculature and promotes $CD8^+$ T cell infiltration.[58–70,84,85] Collectively, these studies establish multiple complementary strategies addressing the major barriers to effective TNBC immunotherapy: insufficient T cell infiltration, immunosuppressive myeloid populations, checkpoint upregulation, and the physical barriers posed by the TME.

Conclusions

The utilization of monotherapy and polytherapy against breast cancer has been successful escalating and enhancing the function of anti-tumor immune cells such as $CD8^+$ T lymphocytes, M1 macrophages, Natural Killer cells, and anti-tumor cytokines in pre-clinical and clinical trials. Various approaches used as treatment in distinct molecular subtypes of breast cancer but especially the most common is the TNBC subtype. There are various substances or strategies used in monotherapy and polytherapy. The synergistic effects observed in chemotherapy-immunotherapy combinations, nanotherapy platforms, targeted therapy combinations, and multimodal approaches consistently demonstrate enhanced $CD8^+$ T cell infiltration, comprehensive myeloid compartment reprogramming, robust dendritic cell maturation, and significantly elevated and sustained pro-inflammatory cytokine production while effectively suppressing immunosuppressive factors. The collective evidence strongly supports that polytherapy approaches, despite their increased complexity, offer superior immunomodulatory effects across all parameters examined, with the potential for durable antitumor immunity and prevention of recurrence outcomes that remain elusive with most monotherapy strategies. Although many of these therapies have a ways to go before becoming viable treatment options, the studies show potential for manipulating the immune system to eradicate the breast tumor and stimulate antitumor immunity. While immunotherapy has made remarkable achievement in treating various cancers, its application in breast cancer has presented both opportunities and challenges. Meanwhile, real world data from these

regimens will provide a better understanding of the risks and benefits. Special attention should be paid to recognizing and mitigating the additional toxicity of these combinations while maintaining a favorable risk-benefit ratio.

Authors' Contributions

ESP was involved in concepting and planning the research. ESP drafted and critically revised the manuscript. IF edited and critically revised the manuscript. NTSA revised and gave critical suggestions to the final draft. All authors took parts in giving critical revision of the manuscript. All authors have agreed with the final revisions of the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest associated with this publication.

References

1. Xiong X, Zheng LW, Ding Y, Chen YF, Cai YW, Wang LP, *et al*. Breast cancer: pathogenesis and treatments. Signal Transduct Target Ther. 2025;10(1): 49. doi: 10.1038/s41392-024-02108-4.
2. Gatti-Mays ME, Balko JM, Gameiro SR, Bear HD, Prabhakaran S, Fukui J, *et al*. If we build it they will come: targeting the immune response to breast cancer. NPJ Breast Cancer. 2019;5: 37. doi: 10.1038/s41523-019-0133-7.
3. Nakasone ES, Hurvitz SA, McCann KE. Harnessing the immune system in the battle against breast cancer. Drugs Context. 2018;7: 212520. doi: 10.7573/dic.212520.
4. Amens JN, Bahçecioglu G, Zorlutuna P. Immune system effects on breast cancer. Cell Mol Bioeng. 2021;14(4): 279-92.
5. Edechi CA, Ikeogu N, Uzonna JE, Myal Y. Regulation of immunity in breast cancer. Cancers. 2019;11(8): 1–18.
6. Said SS, Ibrahim WN. Cancer resistance to immunotherapy: comprehensive insights with future perspectives. Pharmaceutics. 2023;4;15(4): 1143. doi: 10.3390/pharmaceutics15041143.
7. Anayyat U, Ahad F, Muluh TA, Zaidi SAA, Usmani F, Yang H, *et al*. Immunotherapy: Constructive Approach for Breast Cancer Treatment. Breast Cancer Targets Ther. 2023;15: 925-51.
8. Debien V, De Caluwé A, Wang X, Piccart-Gebhart M, Tuohy VK, Romano E, *et al*. Immunotherapy in breast cancer: an overview of current strategies and perspectives. NPJ Breast Cancer. 2023;9(1): 7. doi: 10.1038/s41523-023-00508-3.
9. Heater NK, Warrior S, Lu J. Current and future immunotherapy for breast cancer. J Hematol Oncol. 2024;17(1): 131. doi: 10.1186/s13045-024-01649-z.
10. Bondhopadhyay B, Hussain S, Kasherwal V. The differential effect of the immune system in breast cancer. Explor Med. 2023;4: 1094–108.
11. Imani S, Farghadani R, Roozitalab G, Maghsoudloo M, Emadi M, Moradi A, *et al*. Reprogramming the breast tumor immune microenvironment: cold-to-hot transition for enhanced immunotherapy. J Exp Clin Cancer Res. 2025;44(1): 1–51.
12. Badiu DC, Zgura A, Gales L, Iliescu L, Anghel R, Haineala B. Modulation of immune system - strategy in the treatment of breast cancer. In Vivo. 2021;35(5):2889–94.
13. Prové A, Dirix L. Neratinib for the treatment of breast cancer. Expert Opin Pharmacother. 2016;17(16): 2243–8.
14. Henriques B, Mendes F, Martins D. Immunotherapy in breast cancer: when, how, and what challenges? Biomedicines. 2021;9(11): 1687. doi: 10.3390/biomedicines9111687.
15. Jallah JK, Dweh TJ, Anjankar A, Palma O. A Review of the Advancements in Targeted Therapies for Breast Cancer. Cureus. 2023;15(10): e47847. doi: 10.7759/cureus.47847.
16. Wang J, Wu SG. Breast cancer: an overview of current therapeutic strategies, challenge, and perspectives. Breast Cancer Targets Ther. 2023;15: 721–30.
17. Burguin A, Diorio C, Durocher F. Breast cancer treatments: updates and new challenges. J Pers Med. 2021;11(8): 808. doi: 10.3390/jpm11080808.
18. Yi M, Li T, Niu M, Mei Q, Zhao B, Chu Q, *et al.* Exploiting innate immunity for cancer immunotherapy. Mol Cancer. 2023;22(1): 1–55.
19. Li SJ, Chen JX, Sun ZJ. Improving antitumor immunity using antiangiogenic agents: Mechanistic insights, current progress, and clinical challenges. Cancer Commun. 2021;41(9): 830–50.
20. Shimizu T, Oba T, Oshi M, Ito K ichi. Eribulin promotes

proliferation of CD8+ T cells and potentiates T cell-mediated anti-tumor activity against triple-negative breast cancer cells. Breast Cancer Res Treat. 2024;203(1): 57–71.

21. Zhang Y, Naderi Yeganeh P, Zhang H, Wang SY, Li Z, Gu B, *et al*. Tumor editing suppresses innate and adaptive antitumor immunity and is reversed by inhibiting DNA methylation. Nat Immunol. 2024;25: 1858-70.
22. Vethencourt A, Trinidad EM, Dorca E, Petit A, Soler-Monsó MT, Ciscar M, *et al.* Denosumab as an immune modulator in HER2-negative early breast cancer: results of the window-of-opportunity D-BIOMARK clinical trial. Breast Cancer Res. 2025;27(1): 68. doi: 10.1186/s13058-025-01996-w.
23. Gurrea-Rubio M, Wu Q, Amin MA, Tsou PS, Campbell PL, Amarista CI, *et al*. Activation of cytotoxic lymphocytes through CD6 enhances killing of cancer cells. Cancer Immunol Immunother. 2024;73(2): 1–12.
24. Wang F, Li W, Han G, Xie J, Bai X. A ROR1 targeted bispecific T cell engager shows high potency in the pre-clinical model of triple negative breast cancer. Breast Cancer Res. 2025;27(1): 47. doi: 10.1186/s13058-025-02005-w.
25. Herault A, Mak J, de la Cruz-Chuh J, Dillon MA, Ellerman D, Go MA, *et al*. NKG2D-bispecific enhances NK and CD8+ T cell antitumor immunity. Cancer Immunol Immunother. 2024;73(10): 1–16.
26. Liu B, Huang J, Xiao J, Xu W, Zhang H, Yuan Y, *et al.* The Streptococcus virulence protein PepO triggers anti-tumor immune responses by reprograming tumor-associated macrophages in a mouse triple negative breast cancer model. Cell Biosci. 2023;13(1): 1–19.
27. Lopes AMM, Vieira JF, da Silva SFM, Murta EFC, Michelin MA. Dendritic cell immunotherapy has its antitumor action improved by the LPS in the maturation process. Clin Transl Oncol. 2025;27(8): 3501-10.
28. Zhu B, Cai Y, Zhou L, Zhao L, Chen J, Shan X, *et a*l. Injectable supramolecular hydrogel co-loading abemaciclib/NLG919 for neoadjuvant immunotherapy of triple-negative breast cancer. Nat Commun. 2025;16(1): 687. doi: 10.1038/s41467-025-55904-z.
29. Dastouri M, Kilic N, Yilmaz H. The apoptotic effects of NK-92 cells stimulated with an anti-CD226 antibody on MDA-MB-231 triple-negative breast cancer cells. Med Oncol. 2023;40(8): 1–11.
30. Zhao Q, Pramanik J, Lu Y, Homer NZM, Imianowski CJ, Zhang B, *et al*. Perturbing local steroidogenesis to improve breast cancer immunity. Nat Commun. 2025;16(1): 3945. doi: 10.1038/s41467-025-59356-3.
31. Naik A, Thomas R, Al-Khalifa A, Qasem H, Decock J. Immunomodulatory effects of tumor lactate dehydrogenase c (LDHC) in breast cancer. Cell Commun Signal. 2025;23(1): 145. doi: 10.1186/s12964-025-02139-6.
32. Lasso P, Rojas L, Arévalo C, Urueña C, Murillo N, Nossa P, *et al*. Piper nigrum extract suppresses tumor growth and enhances the antitumor immune response in murine models of breast cancer and melanoma. Cancer Immunol Immunother. 2023;72(10): 3279–92.
33. Zeng A, Liang X, Zhu S, Liu C, Wang S, Zhang Q, *et al*. Chlorogenic acid induces apoptosis, inhibits metastasis and improves antitumor immunity in breast cancer via the NF-κB signaling pathway. Oncol Rep. 2021;45(2): 717–27.
34. Nilkhet S, Mongkolpobsin K, Sillapachaiyaporn C, Wongsirojkul N, Tencomnao T, Chuchawankul S. M1 macrophages polarized by crude polysaccharides isolated from Auricularia polytricha exhibit anti-tumor effect on human breast cancer cells. Sci Rep. 2024;14(1): 1–13.
35. Jędrzejewski T, Sobocińska J, Maciejewski B, Spisz P, Walczak-Skierska J, Pomastowski P, *et al*. In vitro treatment of triple-negative breast cancer cells with an extract from the coriolus versicolor mushroom changes macrophage properties related to tumourigenesis. Immunol Res. 2025;73(1): 14. doi: 10.1007/s12026-024-09574-6.36.
36. Liu M, Zheng L, Zhang Y, Tian J. Mechanistic insights into pachymic acid's action on triple-negative breast cancer through TOP2A targeting. Sci Rep. 2025;15(1): 2856. doi: 10.1038/s41598-025-87286-z.
37. Xia Y, Yang M, Xiao X, Tang W, Deng J, Wu L, *et al.* Low-intensity pulsed ultrasound activated the anti-tumor immunity by irradiating the spleen of mice in 4 T-1 breast cancer. Cancer Immunol Immunother. 2024;73(3): 1–12.
38. Yu C, Xing H, Fu X, Zhang Y, Yan X, Feng J, *et al.* Effect and mechanisms of shikonin on breast cancer cells in vitro and in vivo. BMC Complement Med Ther. 2024;24(1): 389. doi: 10.1186/s12906-024-04671-3.

39. Soll D, Chu CF, Sun S, Lutz V, Arunkumar M, Gachechiladze M, *et al.* Sodium chloride in the tumor microenvironment enhances T cell metabolic fitness and cytotoxicity. Nat Immunol. 2024;25(10): 1830-44.
40. Boulifa A, Raftery MJ, Franzén AS, Radecke C, Stintzing S, Blohmer JU, *et al*. Role of beta-(1→3) (1→6)-D-glucan derived from yeast on natural killer (NK) cells and breast cancer cell lines in 2D and 3D cultures. BMC Cancer. 2024;24(1): 1–12.
41. Thepmalee C, Jenkham P, Ramwarungkura B, Suwannasom N, Khoothiam K, Thephinlap C, *et al.* Enhancing cancer immunotherapy using cordycepin and Cordyceps militaris extract to sensitize cancer cells and modulate immune responses. Sci Rep. 2024;14(1): 1–17.
42. Li X, Su N, Yu H, Li X, Sun SL. Hainanenin-1, an oncolytic peptide, triggers immunogenic cell death via STING activation in triple-negative breast cancer. Cell Commun Signal. 2024;22(1): 1–16.
43. Lee S, Toft NJ, Axelsen T V, Espejo MS, Pedersen TM, Mele M, *et al*. Carbonic anhydrases reduce the acidity of the tumor microenvironment, promote immune infiltration, decelerate tumor growth, and improve survival in ErbB2/HER2-enriched breast cancer. Breast Cancer Res. 2023;25(1): 1–27.
44. Luo H, Lv J, Wen P, Zhang S, Ma W, Yang Z. Supramolecular polyrotaxane-based nano-theranostics enable cancer-cell stiffening for enhanced T-cell-mediated anticancer immunotherapy. Nat Commun. 2025;16(1):1–13.
45. Wang R, Li G, Gao F, Xu F, Li X, Zhang J, *et al.* Ultrasound-responsive spherical nucleic acid against c-Myc/PD-L1 to enhance anti-tumoral macrophages in triple-negative breast cancer progression. Sci China Life Sci. 2024;67(4): 698–710.
46. Sammarco A, Guerra G, Eyme KM, Kennewick K, Qiao Y, Hokayem J El, *et al*. Targeting SCD triggers lipotoxicity of cancer cells and enhances anti-tumor immunity in breast cancer brain metastasis mouse models. bioRxiv Prepr Serv Biol. 2025;8(1):562. doi: 10.1038/s42003-025-07977-1.
47. Miller KD, O'Connor S, Pniewski KA, Kannan T, Acosta R, Mirji G, *et al*. Acetate acts as a metabolic immunomodulator by bolstering T-cell effector function and potentiating antitumor immunity in breast cancer. Nat Cancer. 2023;4(10): 1491–507.
48. Murtadha AH, Sharudin NA, Azahar IIM, Has ATC, Mokhtar NF. Upregulation of mhc i antigen processing machinery gene expression in breast cancer cells by trichostatin a. Mol Biol. 2023;57(6): 1212–27.
49. Huang W, Zhu Q, Shi Z, Tu Y, Li Q, Zheng W, *et al.* Dual inhibitors of DNMT and HDAC induce viral mimicry to induce antitumour immunity in breast cancer. Cell Death Discov. 2024;10(1). doi: 10.1038/s41420-024-01895-7.
50. Mo H, Yu Y, Sun X, Ge H, Yu L, Guan X, *et al.* Metronomic chemotherapy plus anti-PD-1 in metastatic breast cancer: a Bayesian adaptive randomized phase 2 trial. Nat Med. 2024;30: 2528-39.
51. Voorwerk L, Isaeva OI, Horlings HM, Balduzzi S, Chelushkin M, Bakker NAM, *et al*. PD-L1 blockade in combination with carboplatin as immune induction in metastatic lobular breast cancer: the GELATO trial. Nat Cancer. 2023;4(4): 535–49.
52. Fu C, Ji W, Cui Q, Chen A, Weng H, Lu N, *et al.* GSDME-mediated pyroptosis promotes anti-tumor immunity of neoadjuvant chemotherapy in breast cancer. Cancer Immunol Immunother. 2024;73(9): 1–15.
53. Ding C, Li Z, Zheng Y, Li K, Yu W, Kong L, *et al.* Effects of albumin-bound paclitaxel combined with sophora subprostrate polysaccharide on inflammatory factors and immune function in breast cancer rats. Discov Oncol. 2025;16(1): 716. doi: 10.1007/s12672-025-02539-7.
54. Ye Z, Liang L, Xu Y, Yang J, Li Y. Probiotics influence gut microbiota and tumor immune microenvironment to enhance anti-tumor efficacy of doxorubicin. Probiotics Antimicrob Proteins. 2024;16(2): 606–22.
55. Korkaya H, Koksalar AF, Caglayan A, Alkan H, Benson E, Gunduz Y, *et al*. Dual activity of minnelide chemosensitize basal/triple negative breast cancer stem cells and reprograms immunosuppressive tumor microenvironment. Res Sq. 2024;14(1): 22487. doi: 10.1038/s41598-024-72989-6.
56. Hassani E, Mozzendizaji S, Shafiei-Irannejad V, Mohammadzadeh A. Metformin boosts doxorubicin efficacy and increases CD8 + T cell frequency in mouse breast cancer. Clin Transl Oncol. 2024;27(5): 2060–6.
57. Pan F, Liu J, Chen Y, Zhu B, Chen W, Yang Y, *et al.* Chemotherapy-induced high expression of IL23A enhances efficacy of anti-PD-1 therapy in TNBC by co-activating the PI3K-AKT signaling pathway of

CTLs. Sci Rep. 2024;14(1): 1–15.
58. Raninga P V., Zeng B, Moi D, Trethowan E, Saletta F, Venkat P, *et al*. CBL0137 and NKG2A blockade: a novel immuno-oncology combination therapy for Myc-overexpressing triple-negative breast cancers. Oncogene. 2025;44: 893-908.
59. Zhang J, Zhang G, Zhang W, Bai L, Wang L, Li T, *et al*. Loss of RBMS1 promotes anti-tumor immunity through enabling PD-L1 checkpoint blockade in triple-negative breast cancer. Cell Death Differ. 2022;29(11): 2247–61.
60. Zheng H, Wu L, Chen J, Na N, Lou G. Neoadjuvant nivolumab plus bevacizumab therapy improves the prognosis of triple-negative breast cancer in humanized mouse models. Breast Cancer. 2024;31(3): 371–81.
61. Kok M. Neoadjuvant nivolumab or nivolumab plus ipilimumab in early-stage triple-negative breast cancer: a phase 2 adaptive trial. Nat Med. 2024;30: 3223-35.
62. Kim J, Kim M, Yong SB, Han H, Kang S, Lahiji SF, *et al*. Engineering TGF-β inhibitor-encapsulated macrophage-inspired multi-functional nanoparticles for combination cancer immunotherapy. Biomater Res. 2023;27(1): 1–16.
63. Nascimento CS, Carvalho JG, Tavares NC, Lage ACP, Pascoal-Xavier MA, Melo CP de, *et al.* Polyaniline-coated iron oxide nanoparticles reprogram macrophages and modulate the tumor microenvironment to inhibit breast cancer progression and metastasis. Cancer Nanotechnol. 2025;16(1): 1-25.
64. Shah JR, Dong T, Phung AT, Khan S, Aisagbonhi O, Blair SL, *et al*. Liposomal oncolytic adenovirus as a neoadjuvant therapy for triple-negative breast cancer. Sci Rep. 2025;15(1): 1–18.
65. Mu Y, Fan Y, He L, Hu N, Xue H, Guan X, *et al.* Enhanced cancer immunotherapy through synergistic ferroptosis and immune checkpoint blockade using cell membrane-coated nanoparticles. Cancer Nanotechnol. 2023;14(1): 1–18.
66. Hamouda AEI, Filtjens J, Brabants E, Kancheva D, Debraekeleer A, Brughmans J, *et al*. Intratumoral delivery of lipid nanoparticle-formulated mRNA encoding IL-21, IL-7, and 4-1BBL induces systemic anti-tumor immunity. Nat Commun. 2024;15(1): 10635. doi: 10.1038/s41467-024-54877-9.
67. Jiang Z, Cai G, Liu H, Liu L, Huang R, Nie X, e*t al.* A combination of a TLR7/8 agonist and an epigenetic inhibitor suppresses triple-negative breast cancer through triggering anti-tumor immune. J Nanobiotechnology. 2024;22(1): 1–21.
68. Wang Y, Drum DL, Sun R, Zhang Y, Chen F, Sun F, *et al*. Stressed target cancer cells drive nongenetic reprogramming of CAR T cells and solid tumor microenvironment. Nat Commun. 2023;14(1): 5727. doi: 10.1038/s41467-023-41282-x.
69. Liu CC, Wolf M, Ortego R, Grencewicz D, Sadler T, Eng C. Characterization of immunomodulating agents from staphylococcus aureus for priming immunotherapy in triple-negative breast cancers. Sci Rep. 2024;14(1): 1–16.
70. Liang X, Mu M, Chen B, Fan R, Chen H, Zou B, *et al*. Metal-organic framework-based photodynamic combined immunotherapy against the distant development of triple-negative breast cancer. Biomater Res. 2023;27(1): 1–18.
71. Tan H, Liu J, Huang J, Li Y, Xie Q, Dong Y, *et al.* Ketoglutaric acid can reprogram the immunophenotype of triple-negative breast cancer after radiotherapy and improve the therapeutic effect of anti-PD-L1. J Transl Med. 2023;21(1): 1–16.
72. Chen SF, Ng PL, Lai CW, Wang FJ, Wang YC, Chen MH, *et al*. Bacterial membrane-modified cerium oxide nanoboosters enhance systemic antitumor effects of radiotherapy in metastatic triple-negative breast cancer. J Nanobiotechnology . 2025;23(1): 105. doi: 10.1186/s12951-025-03187-3.
73. Yang M, Guo J, Li J, Wang S, Sun Y, Liu Y, *et al.* Platycodon grandiflorum-derived extracellular vesicles suppress triple-negative breast cancer growth by reversing the immunosuppressive tumor microenvironment and modulating the gut microbiota. J Nanobiotechnology . 2025;23(1): 92. doi: 10.1186/s12951-025-03139-x.
74. Li K, Wang J, Xie Y, Lu Z, Sun W, Wang K, *et al.* Reactive oxygen species/glutathione dual sensitive nanoparticles with encapsulation of miR155 and curcumin for synergized cancer immunotherapy. J Nanobiotechnology. 2024;22(1): 1–23.
75. Zhao Y, Bai Y, Li M, Nie X, Meng H, Shosei S, *et al.* A pH-triggered N-oxide polyzwitterionic nano-drug loaded system for the anti-tumor immunity activation research. J Nanobiotechnology. 2024;22(1): 1–18.

76. Teo ZL, O'Connor MJ, Versaci S, Clarke KA, Brown ER, Percy LW, *et al*. Combined PARP and WEE1 inhibition triggers anti-tumor immune response in BRCA1/2 wildtype triple-negative breast cancer. npj Breast Cancer. 2023;9(1): 1–16.
77. Huang Y, Qin G, Cui TT, Zhao C, Ren J, Qu X. A bimetallic nanoplatform for STING activation and CRISPR/Cas mediated depletion of the methionine transporter in cancer cells restores anti-tumor immune responses. Nat Commun. 2023;14(1): 1–15.
78. Yan W, Wang S, Zhu L, Yu X, Li J. Targeted editing of CCL5 with CRISPR-Cas9 nanoparticles enhances breast cancer immunotherapy. Apoptosis. 2025;30(3-4): 912-35.
79. Li Y, Chen W, Kang Y, Zhen X, Zhou Z, Liu C, *et al*. Nanosensitizer-mediated augmentation of sonodynamic therapy efficacy and antitumor immunity. Nat Commun. 2023;14(1): 1–17.
80. Du R, Cao C, Fan D, Li G, Pu S, Xu X, *et al.* NK cell immunopotentiators-loaded nanoliposomes enhance ADCC effect for targeted therapy against HER2-positive breast cancer. Cell Commun Signal . 2025;23(1): 106. doi: 10.1186/s12964-024-02023-9.
81. Zhang X, Liang Q, Cao Y, Yang T, An M, Liu Z, *et al.* Dual depletion of myeloid-derived suppressor cells and tumor cells with self-assembled gemcitabine-celecoxib nano-twin drug for cancer chemoimmunotherapy. J Nanobiotechnology. 2024;22(1): 1–19.
82. Tang X, Mao X, Ling P, Yu M, Pan H, Wang J, *et al.* Glycolysis inhibition induces anti-tumor central memory CD8+T cell differentiation upon combination with microwave ablation therapy. Nat Commun. 2024;15(1): 4665. doi: 10.1038/s41467-024-49059-6.
83. Foldi J, Blenman KRM, Marczyk M, Gunasekharan V, Polanska A, Gee R, *et al*. Peripheral blood immune parameters, response, and adverse events after neoadjuvant chemotherapy plus durvalumab in early-stage triple-negative breast cancer. Breast Cancer Res Treat. 2024;208(2): 369–77.
84. Kristeleit R, Leary A, Oaknin A, Redondo A, George A, Chui S, *et al.* PARP inhibition with rucaparib alone followed by combination with atezolizumab: Phase Ib COUPLET clinical study in advanced gynaecological and triple-negative breast cancers. Br J Cancer. 2024;131(5): 820–31.
85. Yang Z, Hou Y, Grande G, Cho JH, Wang C, Shi Y, *et al*. Targeted desialylation and cytolysis of tumour cells by fusing a sialidase to a bispecific T-cell engager. Nat Biomed Eng. 2024;8(5): 499–512.
86. Gómez-Aleza C, Nguyen B, Yoldi G, Ciscar M, Barranco A, Hernández-Jiménez E, *et al*. Inhibition of RANK signaling in breast cancer induces an anti-tumor immune response orchestrated by CD8+ T cells. Nat Commun. 2020;11(1): 6335. doi: 10.1038/s41467-020-20138-8.