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Breast Cancer Vaccines and Combination Immunotherapy: Current Evidence, Limitations and Future Directions

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ABSTRACT

Background: Breast cancer is the most commonly diagnosed cancer in women worldwide and a leading cause of cancer mortality. Despite advances in targeted therapy, immunotherapy has yielded modest gains, constrained by the immunosuppressive tumour microenvironment (TME) and molecular heterogeneity across subtypes such as triple-negative breast cancer (TNBC) and HER2-positive disease. This review evaluated the clinical efficacy of current breast cancer vaccine platforms and examined whether combination immunotherapy strategies overcome TME-mediated immune suppression.

Methods: A PRISMA-ScR-guided scoping review was conducted across Scopus, PubMed, Google Scholar, Web of Science, and African Journals Online up to 30 April 2026. Of 2,334 records identified, 307 duplicates were removed, and remaining studies were screened by two independent reviewers. Following full-text assessment of 298 reports, 49 studies met eligibility criteria and were included. Quality was appraised using the CASP tool, and findings were synthesised thematically.

Results: Vaccine platforms showed limited durable efficacy as monotherapy. Key barriers included low tumour-infiltrating lymphocyte density, checkpoint upregulation, antigen escape, and TME-driven metabolic suppression. Regulatory approval remains restricted to TNBC in PD-L1-positive metastatic (KEYNOTE-355) and high-risk early-stage (KEYNOTE-522) settings. Combination regimens integrating checkpoint inhibitors, chemotherapy, HER2-directed agents, or PARP inhibitors improved outcomes, albeit with immune-related toxicity. Personalised neoantigen vaccines and biomarker-guided selection emerged as promising near-term strategies.

Conclusion: Vaccine monotherapy cannot overcome TME-mediated immunosuppression. Combination approaches pairing immune priming with checkpoint blockade, targeted therapy, or immunogenic chemotherapy offer the greatest clinical promise, contingent on refined biomarker selection, reduced toxicity, and equitable vaccine access.

Keywords: Breast Cancer; Cancer Vaccines; Immune Checkpoint Inhibitors; Immunotherapy; Tumor Microenvironment.

1.0 INTRODUCTION

Breast cancer comprises several molecularly distinct subtypes, including triple-negative breast cancer (TNBC), HER2-positive disease, and hormone receptor-positive/HER2-negative tumours, each with a distinct therapeutic sensitivity and prognostic profile [1]. Breast cancer vaccines fall into two categories: prophylactic vaccines, which prime immunity against tumour-associated antigens in high-risk individuals before disease onset, and therapeutic vaccines, which seek to enhance antigen-specific immune responses against established disease [2]. The shift toward

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immunotherapy, substituting precision-based biological treatment that harnesses the patient's own immune system for non-specific cytotoxic approaches, is underpinned by immune checkpoint inhibitors (ICIs) that block PD-1/PD-L1 to restore cytotoxic T-cell function against tumours that have acquired immune-evasion mechanisms. Despite this paradigm shift, breast cancer remains the most prevalent cancer diagnosed in women worldwide [3] and the second leading cause of cancer death in the United States [4], with rising incidence among women under 50. The overall effectiveness of immunotherapy in breast cancer, however, has lagged well behind that seen in immunogenically aggressive tumour types [5]. The FDA has authorised immunotherapy in breast cancer only for the TNBC subtype, in PD-L1-positive metastatic disease (KEYNOTE-355) and high-risk early-stage neoadjuvant disease (KEYNOTE-522) [3,6]. In IMpassion130, atezolizumab plus nab-paclitaxel improved progression-free survival only in PD-L1-positive metastatic TNBC, underscoring the narrow immunotherapy-responsive population [7]. This limited approval profile reflects the immunosuppressive tumour microenvironment (TME), long regarded as rendering breast cancer immunologically "cold". Higher stromal TIL density is strongly associated with improved invasive disease-free and overall survival in early-stage TNBC [7], and TIL levels independently predict pathological complete response and survival across subtypes after neoadjuvant therapy, though the magnitude of benefit varies with the tumour's immune landscape [8]. Because monotherapy, whether vaccine- or ICI-based, cannot overcome these layered suppressive mechanisms, this review critically examines the efficacy gap in breast cancer vaccines and evaluates the rationale, evidence base, and limitations of combination immunotherapy as the next frontier in this field [9,10].

2.0 METHODOLOGY

2.1 Search Strategy

A comprehensive literature search was conducted from database inception through 30 April 2026 to evaluate the efficacy of breast cancer vaccines and the role of combination therapy strategies in improving therapeutic outcomes among breast cancer patients. The search was restricted to English-language publications across Scopus, PubMed, Google Scholar, Web of Science, and African Journals Online, combining MeSH terms and free-text keywords for breast cancer vaccines, immunotherapy, vaccine efficacy, therapeutic vaccines, and combination therapy using the Boolean operators "AND" and "OR." Advanced filters were applied where available (disease condition: breast cancer; study type: interventional; intervention: vaccine-related therapies). Representative search strings (PubMed): ("breast cancer"[MeSH Terms] OR "breast neoplasms"[MeSH Terms] OR "breast cancer"[Title/Abstract]) AND ("cancer vaccines"[MeSH Terms] OR "cancer vaccine"[Title/Abstract] OR "therapeutic vaccine"[Title/Abstract] OR "vaccine therapy"[Title/Abstract] OR "active immunization"[Title/Abstract]) AND ("immunotherapy"[MeSH Terms] OR immunotherapy [Title/Abstract]) AND (efficacy [Title/Abstract] OR safety [Title/Abstract]). Equivalent strings, adapted to native syntax while preserving the same terms and Boolean logic, were used for Scopus, Web of Science, Google Scholar, and African Journals Online. The review team additionally hand-searched key oncology, immunology, and cancer-vaccine-focused journals and relevant conference proceedings, and searched grey literature via Google using the same keyword combinations; grey literature sources were eligible only where they met the same criteria applied to database records (Section 2.2.1).

2.2 Eligibility Criteria

Studies were eligible if they met all of the following: (i) Population — human breast cancer patients, or preclinical/in silico models of breast cancer; (ii) Concept — evaluation of a cancer vaccine platform (peptide, DNA/mRNA, or dendritic cell-based) and/or combination immunotherapy strategies; (iii) Study design — clinical trials, cohort studies, comparative or narrative reviews, and computational/in silico studies reporting original data or analyses; (iv) Publication type — peer-reviewed journal articles; (v) Language — English. At title and abstract screening, records were excluded for: not reported in English; not focused on breast cancer; case reports; retrospective designs; ineligible publication type (e.g., conference abstracts, editorials, non-peer-reviewed material); or wrong population. Full-text reports were then assessed against the same criteria. Papers published in journals considered predatory as not indexed in Scopus, PubMed/MEDLINE, or Web of Science, or listed in Cabells' Predatory Reports were excluded at either stage.

2.3 Study Selection and Data Synthesis

A total of 2,334 records were retrieved and imported into Rayyan for management; 307 duplicates were removed, leaving 2,027 unique records for title/abstract screening. Screening was conducted independently by two reviewers

(Toheeb and Mustaqeem); 1,729 records were excluded, and discrepancies were resolved by Abdulameen and Abdulwarith. The remaining 298 reports were assessed in full text, of which 249 were excluded, yielding 49 included studies (Figure 1). Data were extracted by Mustaqeem using a standardised form capturing study details (author, year, location), population/sample size, immunotherapy and chemotherapy category, and vaccine efficacy metrics, and reviewed by Toheeb for consistency. Findings were synthesised thematically around "breast cancer," "immunotherapy," "survival," and "vaccine efficacy," with descriptive statistics where applicable. Methodological quality was appraised using the Critical Appraisal Skills Programme (CASP) checklist appropriate to each study design (randomised controlled trial, cohort, or systematic review), independently by two authors (Abdulameen and Abdulwarith), with disagreements resolved by discussion. No study was excluded on the basis of quality score, consistent with scoping review methodology; appraisal findings were instead incorporated narratively to contextualise the strength of the evidence for each theme.

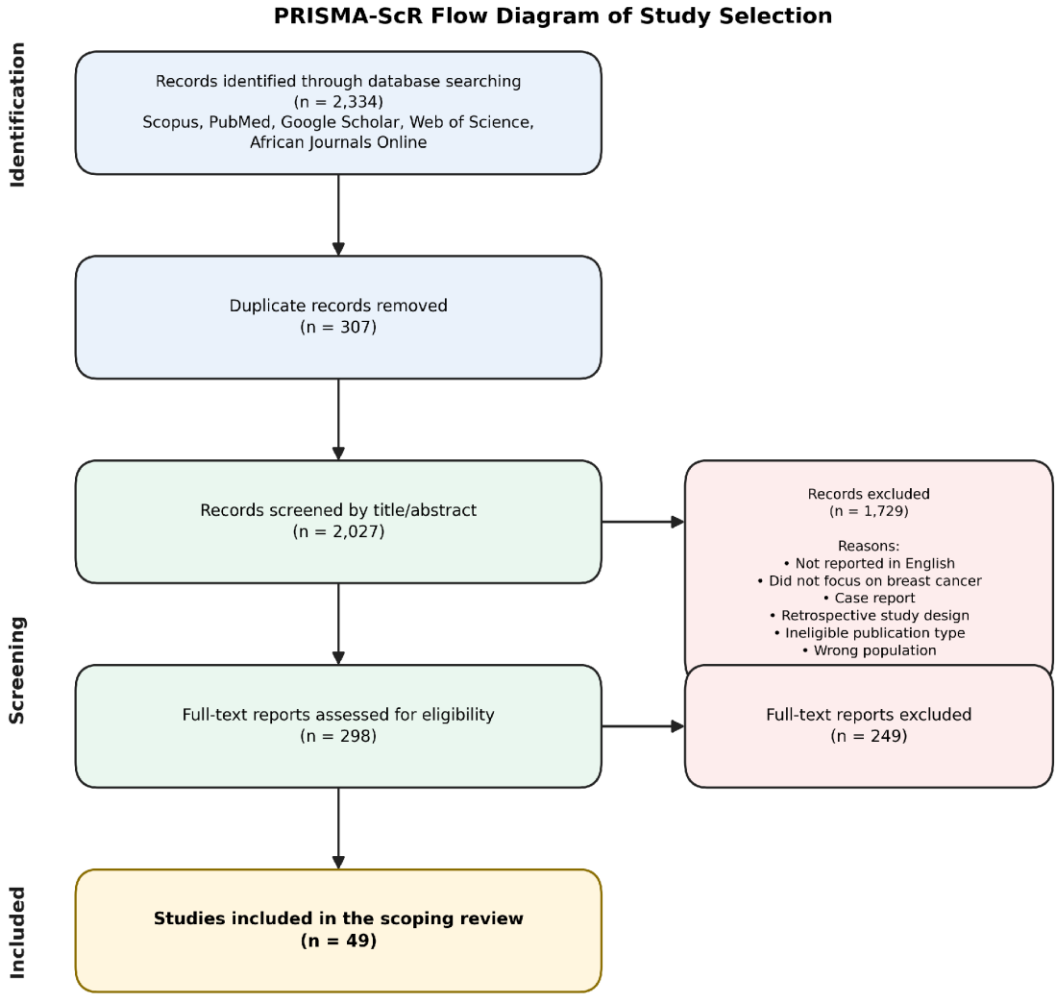

Figure 1. PRISMA-ScR flow diagram of the study identification, screening, eligibility, and inclusion process.

3.0 THE EFFICACY GAP IN BREAST CANCER VACCINES

3.1 Technical and Biological Limitations

A fundamental challenge in breast cancer vaccine development is the inability to generate immune responses of sufficient amplitude, specificity, and duration for clinically relevant tumour clearance, since central and peripheral

tolerance actively suppress T-cell activation against self-derived or marginally altered proteins [2]. Extensive inter- and intra-tumoural heterogeneity across molecular subtypes further complicates the search for universal, cross-patient tumour-associated antigens [1]. HER2-targeted peptide vaccines illustrate this limitation directly: E75 (nelipepimut-S) showed acceptable safety and antigen-specific immunogenicity in Phase I/II [2], and AE37 showed a benign toxicity profile with documented immune responses in Phase II [11], yet the E75 Phase III trial was stopped at interim analysis after failing to show a significant disease-free survival benefit [9].

3.2 Tumour Microenvironment-Mediated Suppression

The breast cancer TME acts as an immunological sink, neutralising vaccine-primed effector cells before meaningful antitumour activity is achieved. Each 10% increase in stromal TIL density was associated with better invasive and distant disease-free survival and overall survival in early-stage TNBC [7], yet average stromal TIL infiltration in TNBC is only 15–25% even in this most immunologically permissive subtype. A pooled analysis of 3,771 patients confirmed that TIL levels independently predict pathological complete response and survival across subtypes, but the suppressive TME limits immune effector function even in TIL-enriched tumours, and IMpassion130 showed that PD-L1 positivity was required for significant benefit from ICI combination therapy [3].

3.3 Antigen Escape

Tumour cells evade immune recognition chiefly through loss of surface HLA class I expression, arising from loss of heterozygosity at chromosome 6p, β2-microglobulin or HLA class I mutations, or defective antigen-processing machinery [8]. In HER2-targeted approaches, selective outgrowth of HER2-low or HER2-negative subclones under immune pressure may render the vaccine clinically ineffective [9]. Neoantigen-directed strategies such as the α-lactalbumin vaccine (targeting an antigen expressed in >70% of TNBCs) and the multi-peptide PVX-410 vaccine target tumour-specific somatic mutations that are less susceptible to immunoediting.

3.4 Inconsistencies Across Clinical Trials

The dominant pattern in this literature is early-phase immunogenicity that fails to translate into Phase III survival benefit: Phase I/II trials evaluate safety and immunogenicity endpoints that support biological proof-of-concept but do not predict survival-level efficacy [2,11]. Dendritic cell vaccines targeting HER2/HER3 in TNBC brain metastases remain at Phase IIa [12]; PVX-410 remains at Phase Ib [10]; and the Globo H antigen vaccine, despite reaching Phase III initiation, lacks mature efficacy data [13]. These recurring discrepancies rooted in inadequate immune activation, TME-mediated suppression, antigen escape, and surrogate-endpoint limitations — define the efficacy gap that rationally designed combination immunotherapy is best positioned to address.

4.0 OVERVIEW OF VACCINE PLATFORMS

4.1 Peptide, DNA/mRNA, and Dendritic Cell Vaccines

Peptide vaccines are precise and safe but exhibit MHC restriction and limited immunogenicity [2,14]. DNA/mRNA vaccines enable stronger immune activation and in situ antigen expression, with mRNA platforms showing encouraging early results despite delivery challenges [15]. Dendritic cell (DC) vaccines are highly efficient antigen-presenting platforms capable of robust T-cell priming but are constrained by cost and manufacturing complexity [16].

4.2 Comparative Efficacy Across Platforms

Read across trials, the three platforms differ systematically rather than incidentally. Peptide vaccines consistently show low immunogenicity and minimal effect on progression-free survival, driven largely by immunological tolerance and antigen loss [2]. DNA/mRNA vaccines generate broader and more durable T-cell responses, with early-phase trials showing improved immunogenicity in personalised neoantigen contexts [17]. DC vaccines achieve the strongest immune activation and occasional durable responses, but clinical benefit remains patient-specific and unpredictable [18]. The ordering peptide < DNA/mRNA < DC for depth of immune activation, and DC > DNA/mRNA > peptide for cost and manufacturing complexity, explains why no single platform has yet dominated clinical development, and why platform selection is increasingly paired with a combination partner (Section 6) rather than pursued as monotherapy.

4.3 Tumour Heterogeneity as a Driver of Inconsistency

Variable vaccine effectiveness is driven substantially by tumour heterogeneity: subclonal populations within a single tumour may display divergent antigenic patterns, allowing non-targeted clones to persist under vaccine-induced immune pressure. Dynamic antigen expression as disease progresses further erodes long-term immune recognition, an effect most pronounced in aggressive subtypes and a major contributor to inconsistent, non-durable vaccine responses [19].

4.4 Subtype-Specific Responses (TNBC vs HER2-Positive)

HER2-positive tumours are comparatively more vulnerable to antigen-specific vaccination because they express a distinct, immunogenic target [2]. TNBC carries a higher mutational burden and greater TIL infiltration features that favour immunotherapy response, including neoantigen-based vaccination but lacks a single consistent targetable antigen [20]. The two subtypes therefore represent complementary rather than interchangeable vaccine development strategies: antigen-directed vaccination is better matched to HER2-positive disease, while neoantigen and combination approaches are better matched to TNBC.

4.5 Delivery System Limitations

Suboptimal immune activation frequently reflects delivery rather than antigen selection: peptide vaccines are rapidly cleared in vivo, and mRNA vaccines require protective carriers such as lipid nanoparticles for stability and effective distribution [15]. Limited trafficking to lymphoid organs further reduces contact with antigen-presenting cells, and these pharmacokinetic constraints contribute materially to the uneven clinical results described above [21].

5.0 TARGET CLASSIFICATION AND CLINICAL SPECTRUM

5.1 Tumour-Associated Antigens (TAAs)

Standardised vaccines exploit overexpression of self-proteins such as CEA, MUC1, and HER2, the last overexpressed in 20–25% of breast cancers [1]. E75 (nelipepimut-S) showed a favourable Phase I/II safety profile [2] and GP2/AE37 were tested in Phase II adjuvant trials [11], but the E75 Phase III trial was halted early for lack of disease-free survival benefit [10]. Allogeneic whole-cell platforms offer an alternative: Bria-IMT with low-dose cyclophosphamide and interferon-alpha produced HLA-matched clinical benefit, improving progression-free survival (4.1 vs 1.8 months) alongside declining cancer-associated macrophage-like cells [22], with a 13% objective response rate and 61% disease control rate reported [23]. PVX-410 with durvalumab was assessed in TNBC [11]; α-lactalbumin vaccination is under evaluation for adjuvant therapy and BRCA1-carrier prevention [13]; and an alpha-DC1 vaccine targeting HER2/HER3 with pembrolizumab has been reported in brain metastases [14]. Immune tolerance remains the principal limitation of TAA-directed vaccines.

5.2 Neoantigens and Tumour-Specific Antigens (TSAs)

TSAs arise from tumour-specific somatic mutations that bypass central tolerance. A Phase I trial (NCT05269381) used the REAL-neo approach to identify class I/II HLA-bound neoantigens for a personalised neoantigen peptide vaccine (PNeoVCA) combined with pembrolizumab [24]. Updated KEYNOTE-522 results, combining a checkpoint inhibitor with (neo)antigen-rich chemotherapy-induced cell death, demonstrated 5-year event-free survival of 81.3% (HR 0.63), supporting the rationale for pairing vaccination or antigen release with checkpoint blockade [3].

5.3 Comparative Synthesis: Immunogenicity vs Survival Benefit Across Trials

Placed side by side rather than described sequentially, the vaccine trials in Sections 5.1–5.2 separate into two clear tiers. Antigen-directed monotherapies (E75, AE37) achieved immunogenicity and safety endpoints but not durable survival benefit; combination or neoantigen-based approaches (Bria-IMT, PNeoVCA/KEYNOTE-522) achieved both immune activation and measurable disease-free or event-free survival benefit. Table 1 summarises this pattern.

Table 1. Comparative immunogenicity and survival outcomes across representative breast cancer vaccine trials.

Vaccine / regimen	Platform	Immunogenicity	Pathological / disease-free response	Survival outcome
E75 (nelipepimut-S)	Peptide (TAA)	Confirmed, Phase I/II	No significant DFS benefit at Phase III interim analysis	Trial halted — no OS benefit shown
AE37	Peptide (TAA)	Confirmed, Phase II	Benign toxicity; recurrence data limited to Phase II	Not yet established (no Phase III)
Bria-IMT + cyclophosphamide/IFN-α	Allogeneic whole-cell	Confirmed, Phase I/IIa	13% objective response, 61% disease control	PFS improved: 4.1 vs 1.8 months
PNeoVCA + pembrolizumab	Personalised neoantigen	Confirmed, Phase I	Combined with KEYNOTE-522 backbone	5-yr EFS 81.3% (HR 0.63) in the KEYNOTE-522 population

5.4 Subtype Variation: HR+ versus TNBC

TNBC is the most immunologically active subtype: ~5% of breast tumours carry TMB ≥10 mutations/Mb, and high TMB independently predicts checkpoint-inhibitor response [25]. KEYNOTE-522 established pembrolizumab plus chemotherapy as standard of care, achieving pCR of 64.8% versus 51.2%, with residual cancer burden significantly influencing event-free survival [26]. IMpassion031 showed higher pCR with atezolizumab (58% vs 41%) [27]. KEYNOTE-355 improved survival in PD-L1 CPS ≥10 patients (median 23.0 vs 16.1 months; HR 0.73), whereas IMpassion131 showed no benefit in advanced disease [7,28]. In HR+/HER2− disease, KEYNOTE-756 increased pCR with pembrolizumab (24.3% vs 15.6%) [29] and CheckMate 7FL showed improvement with nivolumab (24.5% vs 13.8%) [30]; pembrolizumab also improved I-SPY2 pCR rates (30% vs 13%) [31]. Combining immunotherapy with CDK4/6 inhibitors remains constrained by toxicity [32,33].

6.0 COMBINATION IMMUNOTHERAPY STRATEGIES

6.1 Vaccine + Immune Checkpoint Inhibitors

ICIs and cancer vaccines form a logical pairing: anti-PD-1/PD-L1 and anti-CTLA-4 agents prevent T-cell exhaustion and restore effector function, while vaccines prime and expand tumour-specific T cells [34]. Preclinical and early clinical data show that this combination improves T-cell infiltration and cytokine production relative to monotherapy [35], overcoming tumour-induced suppression particularly in immunologically "cold" breast tumours.

6.2 Vaccine + Chemotherapy/Radiation (Immunogenic Cell Death)

Combining vaccines with chemotherapy or radiation improves antitumour immunity through immunogenic cell death: conventional treatment releases tumour antigen, enhances antigen presentation, and activates dendritic cells [36], broadening the antigen repertoire available for T-cell recognition, while radiation can additionally remodel the TME by reducing immunosuppressive signalling [37]. Clinical evidence indicates these combinations produce a stronger and more durable immune response than monotherapy [38].

6.3 Vaccine + Targeted Therapies

Anti-HER2 antibodies such as trastuzumab both inhibit tumour growth and enhance vaccine-induced immunity via antibody-dependent cellular cytotoxicity and antigen presentation [39]. PARP inhibitors similarly raise tumour mutational burden and neoantigen accessibility, improving immunogenicity and T-cell recognition, particularly relevant to BRCA- and HER2-mutant breast cancer [40]. Clinical results, however, remain inconsistent, and further optimisation of combination strategy is required.

6.4 Computational and Network Pharmacology Approaches

Network pharmacology and in silico modelling increasingly support the rational design of vaccine combinations by mapping relationships between immune responses, tumour pathways, and therapeutic agents, while in silico docking predicts antigen–adjuvant interactions, epitope-binding affinity, and immune activation potential [17,19]. These approaches accelerate development and reduce cost, but require experimental and clinical validation before translation.

6.5 Standard Care versus Combination Immunotherapy

Table 2 contrasts current standard-of-care monotherapy with emerging combination immunotherapy across the dimensions most relevant to clinical decision-making.

Table 2. Standard care versus combination immunotherapy in breast cancer.

Parameter	Current standard care / monotherapy	Emerging combination immunotherapy
Therapeutic examples	Chemotherapy, endocrine therapy, HER2-targeted agents (e.g., trastuzumab), radiotherapy	Vaccine + ICI; ICI + chemotherapy; vaccine + targeted therapy (HER2, PARP inhibitors)
Clinical trial status	Established standard; multiple Phase III approvals; routine use	Numerous ongoing Phase I–III trials; some combinations approved (e.g., pembrolizumab + chemotherapy in TNBC)
Mechanism of action	Direct tumour cytotoxicity or inhibition of oncogenic signalling	Synergistic immune activation: antigen release, improved T-cell priming, checkpoint blockade
Tumour microenvironment effect	Limited immune modulation; often fails to overcome suppression	Reprogrammes TME; increases immune infiltration and antigen presentation
Observed efficacy	Moderate response rates; resistance and relapse common	Improved PFS and response rates in trials (e.g., TNBC combinations)
Durability of response	Often short-lived due to resistance	More durable, reflecting sustained immune activation and memory formation
Key limitations	Drug resistance, tumour heterogeneity, systemic toxicity	Immune-related adverse events, high cost, variable patient response
Overall outcome	Effective for disease control; limited long-term remission	Promising for enhanced efficacy and durable control; still under optimisation

7.0 CHANGES IN CLINICAL MANAGEMENT

7.1 Persistent Resistance

Resistance to checkpoint blockade in TNBC operates at two levels. At the burden level, residual disease after neoadjuvant immunotherapy occurs in >35% of patients [3] and correlates directly with event-free survival by residual cancer burden class [26], implying that surviving cells largely reflect an innately resistant subpopulation rather than resistance acquired de novo during therapy. At the receptor-signalling level, resistance is driven substantially by compensatory checkpoint activation: PD-1/PD-L1 positivity co-occurs with LAG-3 expression on tumour-infiltrating lymphocytes [41], and LAG-3 signalling converges mechanistically with the CTLA-4 and PD-1/PD-L1 pathways [42]. A third, convergent pattern across trials confines clinical benefit to PD-L1-positive disease: KEYNOTE-355 benefit was concentrated in the PD-L1-positive advanced TNBC subgroup [7], and IMpassion130 demonstrated an overall survival benefit restricted to PD-L1-positive patients (median 25.4 vs 17.9 months; HR 0.67) [43]. Read together, these three patterns identify baseline PD-L1 status as a marker of intrinsic susceptibility to checkpoint blockade, distinct from the acquired resistance produced by checkpoint diversification during treatment.

7.2 Immune-Related Adverse Events

Combination immunotherapy carries a materially higher toxicity burden. In KEYNOTE-522, immune-mediated adverse events occurred in 43.6% of patients versus 21.9% of controls, with permanent discontinuation in 22.8% versus 11.8%, and Grade ≥3 events in 82% versus 79% [3]. In IMpassion031, 81% of atezolizumab-treated patients experienced major adverse events, 17% Grade 3/4 [27]. I-SPY2 identified pembrolizumab-induced adrenal insufficiency, and real-world data from 233 patients showed 34% developing immune-related adverse events, chiefly endocrine and gastrointestinal [44]; fulminant type 1 diabetes with ketoacidosis has also been reported after pembrolizumab [45]. This toxicity profile is the principal counterweight to the survival gains described in Section 5.4 and must be weighed explicitly in patient selection.

7.3 Biomarker Landscape: Predictive, Prognostic, and Exploratory Classes

Predictive biomarkers forecast benefit from a specific therapy and directly inform patient selection. PD-L1 CPS ≥10 predicts benefit from pembrolizumab in metastatic TNBC (KEYNOTE-355) [3,7], while KEYNOTE-522 showed benefit in early-stage disease independent of PD-L1 status indicating that predictive value is stage-dependent. Tumour mutational burden (TMB ≥10 mutations/Mb, present in ~5% of breast tumours) independently predicts checkpoint-inhibitor benefit [46], and TMB together with immune infiltration independently predicts response to neoadjuvant immunotherapy [47]. Prognostic biomarkers indicate disease trajectory irrespective of therapy choice. Higher TIL density is associated with improved pathological complete response and survival [9], and stage I TNBC patients with stromal TILs ≥50% show a 95% 10-year survival rate without chemotherapy [48] a prognostic signal rather than a treatment-selection tool. Exploratory biomarkers are candidate signatures awaiting prospective validation, including the 27-gene immunomodulatory signature [49], Immune+, and Imprint. To date, no biomarker has been prospectively validated for predicting benefit from a specific breast cancer vaccine [50], which remains the most consequential gap separating vaccine development from routine clinical application.

7.4 Cost and Accessibility

Personalised vaccines require custom GMP production, bioinformatic prediction, and genomic sequencing largely restricted to specialised centres [24]. Allogeneic vaccines such as Bria-IMT reduce per-patient manufacturing cost but still require checkpoint inhibitors, intradermal administration, cyclophosphamide pre-dosing, and interferon-alpha [22]. Without scalable manufacturing and sustainable implementation strategies, these therapies risk widening global disparities in cancer care.

8.0 GAPS AND FUTURE DIRECTIONS

8.1 Biomarker Development Beyond PD-L1

Section 7.3 shows that PD-L1 remains the only biomarker with routine predictive use, and that no biomarker has been prospectively validated for breast cancer vaccine response specifically. Multi-omics profiling, integrating genomic, transcriptomic, and proteomic data with machine learning which is the most direct route to closing this gap, moving beyond single-marker correlation toward predictive models of vaccine and combination-therapy response [51,52]. Table 3 summarises the omics layers with the clearest near-term application to breast cancer vaccine development;

layers with evidence confined to unrelated indications (e.g., haematologic malignancies) have been excluded, consistent with the breast-cancer-vaccine focus of this review.

Table 3. Omics layers most directly applicable to breast cancer vaccine and combination-immunotherapy biomarker development

Omics layer	Key biomarkers	Application to breast cancer vaccines	Limitations
Genomics	TMB, HLA diversity, neoantigen load	Guides neoantigen selection for personalised vaccine design; supports ICI/vaccine co-selection	Low predictive power in low-TMB, HR+/HER2− tumours
Transcriptomics	T-cell exhaustion markers (LAG3, TIM3); immune deconvolution	Classifies “hot” vs “cold” breast TME to prioritise vaccine + ICI combinations	Requires single-cell resolution for spatial insight
Proteomics / spatial omics	Soluble PD-L1, cytokine panels, spatial immune architecture	Monitors on-treatment immune activation; maps TIL distribution relative to tumour	Dynamic range variability; limited clinical validation to date

8.2 Personalised Neoantigen Vaccine Engineering

Therapeutic cancer vaccines aim to train the adaptive immune system, typically via a Th1-biased response characterised by cytotoxic T-cell activation and pro-inflammatory cytokine release. AI-assisted vaccine design depends on access to curated epitope and neoantigen datasets; Table 4 lists the databases most directly relevant to breast cancer neoantigen and epitope selection, reduced from the broader dataset inventory considered during manuscript preparation to those with demonstrated application to peptide- or neoantigen-based vaccine design.

Table 4. Publicly available datasets most relevant to breast cancer neoantigen and epitope-based vaccine design

Database	Content	Relevance to breast cancer vaccine design	Ref.
IEDB	~1.6 million peptidic and ~3,200 non-peptidic epitopes, publicly available	Primary source for candidate peptide epitopes for HER2- and TAA-directed vaccines	[53]
dbPepNeo2.0	801 high-confidence and ~865,000 candidate neoantigen peptidomes with validated TCR/HLA data	Supports prediction and filtering of tumour-specific neoantigens for personalised vaccine design	[54]
SYFPEITHI / MHCBN	Curated peptide–MHC binding datasets (class I and II)	Supports MHC-binding prediction, a rate-limiting step in epitope selection	[55,56]

8.3 Translational and Implementation Challenges

Two further constraints must be resolved before biomarker-guided, personalised vaccines can reach routine practice. First, the metabolic profile of the breast TME aerobic glycolysis, lactate accumulation, and hypoxia which actively suppresses vaccine-primed T-cell function and should be considered alongside checkpoint status when selecting combination partners [57,58]. Second, personalised vaccine manufacturing remains concentrated in specialised, high-income centres; public–private partnerships such as the Imperial College London collaboration with sub-Saharan African universities have demonstrated that equitable access and capacity-building for complex biologics is achievable at scale in other disease areas and offer a template for extending breast cancer vaccine access to low- and middle-income settings, provided that digital infrastructure, regulatory alignment, and workforce training are addressed alongside funding [59].

9.0 CONCLUSION

This review demonstrates that breast cancer vaccine monotherapy whether peptide-based, DNA/mRNA, or dendritic cell-derived consistently fails to produce durable antitumour responses. The immunosuppressive TME, defined by low TIL infiltration, checkpoint upregulation, antigen escape, and metabolic competition, remains the central obstacle, evidenced by the recurring pattern of early-phase immunogenicity that does not translate into Phase III survival benefit. Combination strategies pairing vaccines or ICIs with chemotherapy, anti-HER2 agents, or PARP inhibitors represent the most clinically credible path forward, supported by outcome data from KEYNOTE-522 and IMpassion031; the accompanying immune-related toxicity burden nonetheless requires careful benefit-risk evaluation for each subtype and disease stage. Advancing the field will require prospectively validated, multi-parameter biomarkers beyond PD-L1 that distinguish predictive from prognostic value, accelerated investment in neoantigen-personalised vaccines and computational adjuvant design, and scalable, equitable manufacturing platforms so that therapeutic gains extend beyond high-income specialist settings. Well-powered, biomarker-stratified trials remain the most urgent priority.

DECLRATIONS

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Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Contribution of Authors

T.A.S.: Conceptualization, literature search, methodology, data curation, formal analysis, writing – original draft, visualization, and writing – review & editing. A.O.L.: Literature review, validation, critical revision of the manuscript, and writing – review & editing. M.A.A.: Data curation, investigation, methodology, and writing – review & editing. A.B.S.: Validation, critical revision of the manuscript, and writing – review & editing. All authors have read and approved the final version of the manuscript for submission.

Declaration of AI Generative Tools

During preparation of this manuscript, the author(s) used Claude (Anthropic) to assist with language editing and improving clarity of author-written text. The tool was not used to generate scientific content, data, or conclusions. All output was reviewed and verified by the author(s), who take full responsibility for the final content.

REFERENCES

[1] Loibl, S., Poortmans, P., Morrow, M., Denkert, C., & Curigliano, G. (2021). Breast cancer. The Lancet, 397(10286), 1750–1769. https://doi.org/10.1016/S0140-6736(20)32381-3

[2] Mittendorf, E. A., Clifton, G. T., Holmes, J. P., Schneble, E., van Echo, D., Ponniah, S., & Peoples, G. E. (2014). Final report of the phase I/II clinical trial of the E75 (nelipepimut-S) vaccine with booster inoculations to prevent disease recurrence in high-risk breast cancer patients. Annals of Oncology, 25(9), 1735–1742. https://doi.org/10.1093/annonc/mdu211

[3] Schmid, P., Cortes, J., Dent, R., Pusztai, L., McArthur, H., Kümmel, S., et al. (2021). KEYNOTE-522: Phase III study of neoadjuvant pembrolizumab + chemotherapy vs placebo + chemotherapy for early-stage TNBC. Annals of Oncology, 32(9), 1198–1200. https://doi.org/10.1016/j.annonc.2021.06.014

[4] Xu, S., Murtagh, S., Han, Y., Wan, F., & Toriola, A. T. (2024). Breast cancer incidence among US women aged 20 to 49 years. JAMA Network Open, 7(1), e2353331. https://doi.org/10.1001/jamanetworkopen.2023.53331

[5] Dvir, K., Giordano, S., & Leone, J. P. (2024). Immunotherapy in breast cancer. International Journal of Molecular Sciences, 25(14), 7517. https://doi.org/10.3390/ijms25147517

[6] Cortes, J., Cescon, D. W., Rugo, H. S., et al. (2020). KEYNOTE-355: Pembrolizumab plus chemotherapy for metastatic TNBC. The Lancet, 396(10265), 1817–1828. https://doi.org/10.1016/S0140-6736(20)32531-9

[7] Loi, S., Drubay, D., Adams, S., et al. (2019). Tumor-infiltrating lymphocytes and prognosis in early-stage TNBC. Journal of Clinical Oncology, 37(7), 559–569. https://doi.org/10.1200/JCO.18.01010

[8] Mehta, A. M., Jordanova, E. S., Kenter, G. G., Ferrone, S., & Fleuren, G. J. (2008). Antigen processing machinery and HLA class I defects in cervical carcinoma. Cancer Immunology, Immunotherapy, 57(2), 197–206. https://doi.org/10.1007/s00262-007-0362-8

[9] Mittendorf, E. A., Lu, B., Melisko, M., et al. (2019). Efficacy and safety of nelipepimut-S vaccine to prevent breast cancer recurrence: Phase III trial. Clinical Cancer Research, 25(14), 4248–4254. https://doi.org/10.1158/1078-0432.CCR-18-2867

[10] Isakoff, S. J., Adams, S., Soliman, H. H., et al. (2020). Phase 1b study of PVX-410 plus durvalumab as adjuvant therapy in early TNBC. Cancer Research, 80(4 Suppl.), P3-09-15. https://doi.org/10.1158/1538-7445.SABCS19-P3-09-15

[11] Mittendorf, E. A., Ardavanis, A., Symanowski, J., et al. (2016). Phase II trial of AE37 vaccine in breast cancer patients. Annals of Oncology, 27(7), 1241–1248. https://doi.org/10.1093/annonc/mdw150

[12] Tuohy, V. K., Jaini, R., Johnson, J. M., et al. (2016). Targeted vaccination against α-lactalbumin for TNBC immunoprevention. Cancers, 8(6), 56. https://doi.org/10.3390/cancers8060056

[13] Gandhi, S., Forsyth, P., Opyrchal, M., et al. (2020). Phase IIa study of alpha-DC1 vaccine against HER2/HER3 with pembrolizumab in brain metastasis. Journal for ImmunoTherapy of Cancer, 8(Suppl. 3). https://doi.org/10.1136/jitc-2020-SITC2020.0320

[14] Disis, M. L., & Cecil, D. L. (2022). Breast cancer vaccines for treatment and prevention. Breast Cancer Research and Treatment, 191, 481–489. https://doi.org/10.1007/s10549-021-06459-2

[15] Pardi, N., Hogan, M. J., Porter, F. W., & Weissman, D. (2018). mRNA vaccines – a new era in vaccinology. Nature Reviews Drug Discovery, 17, 261–279. https://doi.org/10.1038/nrd.2017.243

[16] Palucka, K., & Banchereau, J. (2012). Cancer immunotherapy via dendritic cells. Nature Reviews Cancer, 12, 265–277. https://doi.org/10.1038/nrc3258

[17] Sahin, U., Derhovanessian, E., Miller, M., et al. (2017). Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature, 547, 222–226. https://doi.org/10.1038/nature23003

[18] Bol, K. F., Schreibelt, G., Gerritsen, W. R., De Vries, I. J. M., & Figdor, C. G. (2016). Dendritic cell-based immunotherapy. Clinical Cancer Research, 22, 1897–1906. https://doi.org/10.1158/1078-0432.CCR-15-1399

[19] Emens, L. A. (2018). Breast cancer immunotherapy: Facts and hopes. Clinical Cancer Research, 24, 511–520. https://doi.org/10.1158/1078-0432.CCR-16-3001

[20] Basu, A., Ramamoorthi, G., Jia, Y., et al. (2019). Immunotherapy in breast cancer: Current status and future directions. Advances in Cancer Research, 143, 295–349. https://doi.org/10.1016/bs.acr.2019.03.006

[21] Hirayama, M., & Nishimura, Y. (2016). Present status and future prospects of peptide-based cancer vaccines. International Immunology, 28, 319–328. https://doi.org/10.1093/intimm/dxw027

[22] Wiseman, C. L., Williams, W. V., & Somer, R. A. (2024). Phase I/IIa trial of SV-BR-1-GM with low-dose cyclophosphamide and interferon alpha (Bria-IMT) in metastatic breast cancer. Human Vaccines & Immunotherapeutics, 20(1), 2302161. https://doi.org/10.1080/21645515.2024.2379864

[23] Calfa, C. J., Nangia, C. S., Barve, M. A., et al. (2024). Outcomes of advanced/metastatic breast cancer treated with BRIA-IMT. Journal of Clinical Oncology, 42(Suppl 16), abstr 1022

[24] Lou, Y., Chumsri, S., Asmann, Y. W., et al. (2024). Phase I pilot study of personalized neoantigen peptide-based vaccine with pembrolizumab (PNeoVCA). Journal of Clinical Oncology, 42(Suppl 16), TPS2700.

[25] Barroso-Sousa, R., Jain, E., Cohen, O., et al. (2020). Prevalence and mutational determinants of high tumor mutation burden in breast cancer. Annals of Oncology, 31(3), 387–394. https://doi.org/10.1016/j.annonc.2019.11.010

[26] Pusztai, L., Denkert, C., O'Shaughnessy, J., et al. (2024). Event-free survival by residual cancer burden with pembrolizumab in early-stage TNBC (KEYNOTE-522). Annals of Oncology, 35(5), 429–436. https://doi.org/10.1016/j.annonc.2024.02.002

[27] Mittendorf, E. A., Zhang, H., Barrios, C. H., et al. (2020). Neoadjuvant atezolizumab with chemotherapy in early-stage TNBC (IMpassion031). The Lancet, 396(10257), 1090–1100. https://doi.org/10.1016/S0140-6736(20)31953-X

[28] Miles, D., Gligorov, J., André, F., et al. (2021). IMpassion131: Paclitaxel with or without atezolizumab for advanced TNBC. Annals of Oncology, 32(8), 994–1004. https://doi.org/10.1016/j.annonc.2021.05.801

[29] Cardoso, F., McArthur, H., Schmid, P., et al. (2023). KEYNOTE-756: Neoadjuvant pembrolizumab for early-stage ER+/HER2− breast cancer. Annals of Oncology, 34(Suppl 2), S1260–1

[30] Loi, S., Curigliano, G., Salgado, R. F., et al. (2023). Nivolumab versus placebo with neoadjuvant chemotherapy in high-risk ER+/HER2− breast cancer. Annals of Oncology, 34(Suppl 2), S1259–60.

[31] Nanda, R., Liu, M. C., Yau, C., et al. (2020). Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response. JAMA Oncology, 6(5), 676–684. https://doi.org/10.1001/jamaoncol.2019.6650

[32] Rugo, H. S., Kabos, P., Beck, J. T., et al. (2020). Phase Ib study of abemaciclib with pembrolizumab in HR+, HER2− breast cancer. Journal of Clinical Oncology, 38(Suppl 15), 1051.

[33] Masuda, J., Tsurutani, J., Masuda, N., et al. (2021). Phase II study of nivolumab with abemaciclib plus endocrine therapy (WJOG11418 NEWFLAME). Cancer Research, 81(Suppl 4), PS12-10.

[34] Torres, E. T. R., & Emens, L. A. (2022). Emerging combination immunotherapy strategies for breast cancer. Breast Cancer Research and Treatment, 191, 291–302. https://doi.org/10.1007/s10549-021-06423-0

[35] Liu, Z. B., Zhang, L., Bian, J., & Jian, J. (2020). Combination strategies of checkpoint immunotherapy in metastatic breast cancer. OncoTargets and Therapy, 2657–2666. https://doi.org/10.2147/OTT.S240655

[36] Hu, Z. I., & McArthur, H. L. (2018). Immunotherapy in breast cancer: The new frontier. Current Breast Cancer Reports, 10, 35–40. https://doi.org/10.1007/s12609-018-0274-y

[37] Fenton, M., Yoneyama, M., Wennerberg, E., et al. (2025). The untapped potential of radiation and immunotherapy for hormone receptor-positive breast cancer. NPJ Breast Cancer, 11, 77. https://doi.org/10.1038/s41523-025-00796-x

[38] Singh, K., Yadav, D., Jain, M., Singh, P. K., & Jin, J.-O. (2022). Immunotherapy for breast cancer treatment: Current evidence and therapeutic options. Endocrine, Metabolic & Immune Disorders – Drug Targets, 22, 212–224. https://doi.org/10.2174/1871530321666210426125904

[39] Costa, R. L. B., & Czerniecki, B. J. (2020). Clinical development of immunotherapies for HER2+ breast cancer. NPJ Breast Cancer, 6, 10. https://doi.org/10.1038/s41523-020-0153-3

[40] Heater, N. K., Warrior, S., & Lu, J. (2024). Current and future immunotherapy for breast cancer. Journal of Hematology & Oncology, 17, 131. https://doi.org/10.1186/s13045-024-01649-z

[41] Burugu, S., Gao, D., Leung, S. C., Chia, S., & Nielsen, T. O. (2017). LAG-3+ tumor infiltrating lymphocytes in breast cancer. Annals of Oncology, 28(12), 2977–2984. https://doi.org/10.1093/annonc/mdx557

[42] Liu, Q., Qi, Y., Zhai, J., et al. (2021). Molecular and clinical characterization of LAG3 in breast cancer. Frontiers in Immunology, 12, 599207. https://doi.org/10.3389/fimmu.2021.599207

[43] Emens, L. A., Adams, S., Barrios, C. H., et al. (2021). First-line atezolizumab plus nab-paclitaxel for metastatic TNBC (IMpassion130 final OS analysis). Annals of Oncology, 32(8), 983–993. https://doi.org/10.1016/j.annonc.2021.05.355

[44] Jayan, A., Sukumar, J. S., Fangman, B. D., et al. (2024). Real-world immune-related adverse events with pembrolizumab in early TNBC. Journal of Clinical Oncology, 42(Suppl 16), 1099.

[45] Ouyang, L., Liu, H., Tang, Z., et al. (2024). Use of pembrolizumab may cause acute and severe adverse reactions. International Journal of Surgical Oncology, 9(3), 40–44.

[46] Barroso-Sousa, R., Keenan, T. E., Pernas, S., et al. (2020). Tumor mutational burden and PTEN alterations as correlates of response to PD-1/L1 blockade in metastatic TNBC. Clinical Cancer Research, 26(11), 2565–2572. https://doi.org/10.1158/1078-0432.CCR-19-3507

[47] Karn, T., Denkert, C., Weber, K. E., et al. (2020). Tumor mutational burden and immune infiltration as predictors of response to neoadjuvant immune checkpoint inhibition (GeparNuevo). Annals of Oncology, 31(9), 1216–1222. https://doi.org/10.1016/j.annonc.2020.05.015

[48] Geurts, V. C. M., Balduzzi, S., Steenbruggen, T. G., et al. (2024). Tumor-infiltrating lymphocytes in stage I TNBC untreated with chemotherapy. JAMA Oncology, 10(8), 1077–1086. https://doi.org/10.1001/jamaoncol.2024.1917

[49] Iwase, T., Blenman, K. R. M., Li, X., et al. (2021). A novel immunomodulatory 27-gene signature to predict response to neoadjuvant immunochemotherapy in TNBC. Cancers, 13(19), 4839. https://doi.org/10.3390/cancers13194839

[50] Yee, D., Shatsky, R. A., Yau, C., et al. (2022). Improved pathologic complete response rates for TNBC in I-SPY2. Journal of Clinical Oncology, 40(Suppl 16), 591.

[51] Chen, M., et al. (2023). Divergent tumor and immune cell reprogramming underlying immunotherapy response and immune-related adverse events. Journal for ImmunoTherapy of Cancer, 11(10), e007305. https://doi.org/10.1136/jitc-2023-007305

[52] Pavlović, M., et al. (2021). The immuneML ecosystem for machine learning analysis of adaptive immune receptor repertoires. Nature Machine Intelligence, 3(11), 936–944. https://doi.org/10.1038/s42256-021-00413-z

[53] Vita, R., Mahajan, S., Overton, J. A., et al. (2019). The Immune Epitope Database (IEDB): 2018 update. Nucleic Acids Research, 47(D1), D339–D343. https://doi.org/10.1093/nar/gky1006

[54] Lu, M., Xu, L., Jian, X., et al. (2022). dbPepNeo2.0: A database for human tumor neoantigen peptides. Frontiers in Immunology, 13, 855976. https://doi.org/10.3389/fimmu.2022.855976

[55] Schuler, M. M., Nastke, M.-D., & Stevanović, S. (2007). SYFPEITHI. Methods in Molecular Biology, 409, 75–93. https://doi.org/10.1007/978-1-60327-118-9_5

[56] Lata, S., Bhasin, M., & Raghava, G. P. (2009). MHCBN 4.0: A database of MHC/TAP binding peptides and T-cell epitopes. BMC Research Notes, 2, 61. https://doi.org/10.1186/1756-0500-2-61

[57] Ohshima, K., & Morii, E. (2021). Metabolic reprogramming of cancer cells during tumor progression and metastasis. Metabolites, 11, 28. https://doi.org/10.3390/metabo11010028

[58] Sun, L., et al. (2020). Metabolic reprogramming in immune response and tissue inflammation. Arteriosclerosis, Thrombosis, and Vascular Biology, 40(9), 1990–2001. https://doi.org/10.1161/ATVBAHA.120.314037

[59] Imperial College London. (2023). Imperial opens new hub in Ghana with a commitment to boost science and innovation across Africa. https://www.imperial.ac.uk/news/258253/imperial-opens-ghana-with-commitment-boost/