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Long-Term Immunological Effects of Cancer Vaccines in Breast Cancer Patients

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Abstract This study discusses the future directions of cancer vaccines for breast cancer, with a focus on personalized and multi-antigen vaccines, combination with immune checkpoint inhibitors, and vaccine development for metastatic breast cancer. Personalized neoantigen vaccines leverage tumor-specific mutations to elicit a targeted immune response, while multi-antigen vaccines enhance immune efficacy by targeting multiple tumor antigens. Combining vaccines with checkpoint inhibitors can turn "cold" tumors into "hot" ones, thereby enhancing antitumor immunity. Dendritic cell vaccines and nanoparticle-based vaccines show promise for metastatic breast cancer. Future research should focus on optimizing vaccine formulations, modulating the tumor microenvironment, and developing personalized treatment strategies to improve the efficacy and long-term durability of cancer vaccines in breast cancer patients.

Keywords Breast cancer; Cancer vaccine; Personalized vaccine; Immune checkpoint inhibitors; Metastatic breast cancer

1 Introduction

Cancer vaccines represent a promising approach in the treatment of breast cancer, aiming to harness the body's immune system to target and eliminate cancer cells. Unlike traditional therapies, cancer vaccines are designed to induce a specific immune response against tumor-associated antigens. Recent advances have focused on various types of vaccines, including peptide-based, cell-based, and nucleic acid-based vaccines, which have shown potential in preclinical and early clinical trials. For instance, peptide-based vaccines targeting HER2, IGFBP-2, and IGF-IR have demonstrated safety and the ability to evoke cellular immune responses in patients with non-metastatic breast cancer. Despite these advancements, no breast cancer vaccine has yet received regulatory approval, highlighting the need for further research and larger clinical trials to establish their efficacy and safety (Schlom et al., 2014; Hosseini et al., 2023).

The long-term immunological effects of cancer vaccines are crucial for providing sustained protection against breast cancer recurrence. Effective cancer vaccines should not only induce an immediate immune response but also establish long-lasting immunological memory to prevent disease relapse (Zhou, 2024). Studies have shown that vaccines can generate durable immune responses, with some patients maintaining high levels of antigen-specific immunity for several months post-vaccination. For example, the E75 vaccine targeting HER2/neu has demonstrated a significant reduction in recurrence rates in patients who received booster inoculations, suggesting that maintaining immunity over time is essential for long-term clinical benefits (Perez et al., 2014). Additionally, the persistence of humoral immunity, as observed in patients receiving personalized peptide vaccinations, underscores the potential of vaccines to provide long-term protection.

This study explores the long-term immunological effects of cancer vaccines in breast cancer patients, focusing on their ability to provide continuous protection and prevent disease recurrence. By understanding the mechanisms underlying long-term immunity and identifying factors that contribute to durable immune responses, this study aims to inform the development of more effective cancer vaccines. This study is expected to improve clinical outcomes in breast cancer patients by reducing recurrence rates and improving overall survival. Given the promising results from early-phase clinical trials, this research could pave the way for the development of novel immunotherapeutic strategies that offer long-lasting protection against breast cancer.

2 Mechanisms of Cancer Vaccines in Breast Cancer

2.1 Antigen presentation and T-cell activation

Cancer vaccines aim to stimulate the immune system to recognize and attack cancer cells by presenting tumor-associated antigens (TAAs) to T cells. The process begins with the uptake of TAAs by antigen-presenting cells (APCs), such as dendritic cells (DCs). These APCs process the antigens and present them on their surface via major histocompatibility complex (MHC) molecules. For effective T-cell activation, the antigens must be cross-presented by DCs to CD8+ T cells, which are crucial for cytotoxic responses against tumor cells.

The stimulator of interferon genes (STING) pathway has been identified as a key player in enhancing antigen presentation. Activation of the STING pathway in DCs leads to the production of type I interferons and other cytokines, which enhance the cross-presentation of antigens and the activation of CD8+ T cells (Shae et al., 2020). Additionally, the use of adjuvants such as Toll-like receptor (TLR) agonists can further enhance the activation and maturation of DCs, leading to more effective T-cell priming.

Tumors, however, have developed mechanisms to evade immune recognition, such as downregulating antigen presentation machinery or altering the antigen repertoire presented on their surface. These evasion strategies can significantly impair the effectiveness of cancer vaccines. Therefore, understanding and overcoming these mechanisms is crucial for the development of more effective cancer vaccines.

2.2 Role of immune memory

The generation of long-term immune memory is a critical goal of cancer vaccination, as it ensures sustained surveillance and rapid response to tumor recurrence. Memory T cells, particularly memory CD8+T cells, play a pivotal role in this process. These cells can persist for extended periods and quickly expand upon re-exposure to the antigen, providing a robust and rapid immune response.

Interleukin-7 (IL-7) has been identified as a key cytokine in the maintenance and survival of memory T cells. IL-7 promotes the homeostatic proliferation of memory T cells and enhances their longevity, making it a promising adjuvant for cancer vaccines. Additionally, the bone marrow has been recognized as a critical niche for the survival of memory T cells, providing a supportive environment that helps maintain their long-term persistence. Recent studies have shown that cancer vaccines can induce durable memory T cell responses. For instance, a DNA vaccine targeting Fos-related antigen 1 (Fra-1) and coexpressing IL-18 was found to induce long-lived T memory cells capable of eradicating established tumors upon re-challenge . These findings highlight the potential of cancer vaccines to provide long-term protection against tumor recurrence.

2.3 Boosting immune responses

Boosting immune responses is essential for enhancing the efficacy of cancer vaccines. This can be achieved through various strategies, including the use of adjuvants, combination therapies, and heterologous boosting. Adjuvants such as TLR agonists, cytokines, and checkpoint inhibitors can enhance the activation and expansion of T cells, leading to more robust immune responses. Heterologous boosting, which involves using different vaccine platforms to deliver the same antigen, has been shown to enhance immune responses. For example, a study demonstrated that heterologous vaccination with different HER2-LAMP targeted vectors significantly augmented HER2-specific T and B cell responses, leading to more effective anti-tumor immunity (Marek et al., 2022). This approach can overcome the limitations of homologous boosting, where repeated use of the same vaccine platform may lead to diminished responses due to immune tolerance or vector-specific immunity.

Combination therapies that include cancer vaccines and immune checkpoint inhibitors have also shown promise. These combinations can enhance the overall immune response by simultaneously promoting T cell activation and preventing immune suppression. For instance, the co-delivery of peptide neoantigens and STING agonists in a nanovaccine platform significantly enhanced CD8+T cell responses, when combined with checkpoint blockade, led to complete tumor rejection in murine models. In summary, boosting immune responses through adjuvants, heterologous boosting, combination therapies is crucial for the success of cancer vaccines in breast cancer. These strategies can enhance the activation, expansion, and memory formation of tumor-specific T cells, leading to more effective and durable anti-tumor immunity.

3 Clinical Applications of Cancer Vaccines in Breast Cancer

Cancer vaccines represent a promising therapeutic approach in the treatment of breast cancer by stimulating the immune system to target and destroy cancer cells. These vaccines can be designed to target specific antigens expressed by breast cancer cells, thereby enhancing the body's immune response against the tumor. The clinical applications of cancer vaccines in breast cancer are diverse and include HER2/neu-based vaccines, dendritic cell vaccines, and multi-antigen vaccines. Each of these approaches has shown varying degrees of efficacy in preclinical and clinical studies, offering hope for improved treatment outcomes for breast cancer patients.

3.1 HER2/neu-based vaccines

HER2/neu-based vaccines target the HER2/neu protein, which is overexpressed in a significant subset of breast cancers. These vaccines aim to elicit a robust immune response against HER2/neu-expressing tumor cells. One of the most clinically advanced HER2/neu-based vaccines is the E75 peptide vaccine, which has shown promise in both preclinical and clinical settings. The E75 peptide, derived from the HER2/neu protein, has been demonstrated to induce specific CD8+ T cell responses that can target and kill HER2/neu-expressing tumor cells (Tran et al., 2015).

Recent studies have focused on optimizing the delivery of the E75 vaccine to enhance its efficacy. For instance, coupling the E75 peptide to the B-subunit of Shiga toxin (STxB) has been shown to improve the induction of multifunctional and high-avidity E75-specific CD8+ T cells, resulting in potent tumor protection in preclinical models. Additionally, combining the E75 vaccine with anti-HER2 monoclonal antibodies (mAbs) such as trastuzumab has been found to synergize in promoting tumor regression, particularly in tumors with low HER2/neu expression (Tran et al., 2015). These findings suggest that HER2/neu-based vaccines, especially when used in combination with other therapies, hold significant potential for improving outcomes in breast cancer patients.

3.2 Dendritic cell vaccines

Dendritic cell (DC) vaccines represent another promising approach in the immunotherapy of breast cancer. DCs are potent antigen-presenting cells that can be engineered to present tumor antigens, thereby stimulating a robust immune response. HER2/neu-loaded DC vaccines have shown efficacy in preclinical models, where they have been demonstrated to induce strong CD4+and CD8+T cell responses, as well as humoral immunity against HER2/neu (Özverel et al., 2020).

One innovative approach involves the intrathecal delivery of DC vaccines in models of leptomeningeal disease (LMD), a severe complication of breast cancer. Studies have shown that intrathecal administration of HER2/neu-pulsed DC vaccines can eradicate tumor growth and protect against disease re-inoculation in HER2+ and triple-negative breast cancer models. This method has been associated with prolonged survival and complete tumor regression in a significant proportion of treated mice, highlighting the potential of DC vaccines in managing advanced and metastatic breast cancer.

Furthermore, combining DC vaccines with other immunotherapeutic agents, such as anti-PD-L1 mAbs and adjuvants like QS-21, has been shown to enhance their efficacy. This combination therapy has resulted in decreased tumor sizes, increased cytotoxic activity of splenocytes, and significant infiltration of immune cells into the tumor microenvironment (Özverel et al., 2020). These findings underscore the potential of DC vaccines as part of a multi-modal immunotherapy strategy for breast cancer.

3.3 Multi-antigen vaccines

Multi-antigen vaccines aim to target multiple tumor-associated antigens simultaneously, thereby broadening the immune response and reducing the likelihood of immune escape. These vaccines can be designed to include a combination of peptides, proteins, or whole-cell lysates that represent various tumor antigens. The rationale behind multi-antigen vaccines is to induce a more comprehensive and robust immune response that can target different aspects of tumor biology.

Preclinical studies have demonstrated the efficacy of multi-antigen vaccines in inducing potent antitumor immune

responses. For example, a dual-epitope DC vaccine targeting two different HER2 peptides has been shown to generate significant T cell responses and clinical benefits in patients with HER2-overexpressing breast cancer (Vincent et al., 2023). This approach has been associated with stable disease and partial responses in a subset of patients, indicating its potential for clinical application.

Moreover, targeting multiple antigens can also help in overcoming the limitations of single-antigen vaccines, such as antigen loss or mutation. By presenting a broader array of antigens, multi-antigen vaccines can enhance the likelihood of effective tumor recognition and destruction by the immune system. This strategy holds promise for improving the efficacy of cancer vaccines and providing durable clinical benefits for breast cancer patients. In conclusion, the clinical applications of cancer vaccines in breast cancer are diverse and evolving. HER2/neu-based vaccines, dendritic cell vaccines, and multi-antigen vaccines each offer unique advantages and have shown promising results in preclinical and clinical studies. Continued research and optimization of these vaccine strategies are essential for realizing their full potential in the treatment of breast cancer.

4 Long-Term Immunological Effects of Cancer Vaccines

Cancer vaccines have emerged as a promising strategy in the fight against breast cancer, particularly in enhancing the immune system's ability to recognize and destroy cancer cells. The long-term immunological effects of these vaccines are crucial for understanding their potential in providing sustained protection and preventing recurrence. This study delves into the persistence of T-cell responses, antibody-mediated immunity, and the role of these vaccines in recurrence prevention.

4.1 Persistence of T-cell responses

The persistence of T-cell responses is a critical factor in the long-term efficacy of cancer vaccines. Studies have shown that cancer vaccines can induce robust and durable T-cell responses in breast cancer patients. For instance, a study on a HER2/neu vaccine demonstrated that patients who were immunized showed persistent T-cell immunity years after the initial vaccination. Specifically, 75% of evaluable patients had long-term T-cell immunity to HER2 peptides, and 88% exhibited epitope spreading, which is the ability of the immune system to recognize and respond to multiple epitopes of the HER2 protein (Salazar et al., 2016). This long-term T-cell response is associated with improved overall survival, highlighting the potential of cancer vaccines to provide lasting immunological benefits.

Another study on personalized peptide vaccination (PPV) in breast cancer patients without active tumors at the time of vaccination found that while cytotoxic T lymphocyte (CTL) levels were initially boosted, they declined over time, indicating a transient nature of cellular immunity. However, the initial boost in CTL activity was significant, suggesting that periodic booster vaccinations might be necessary to maintain long-term T-cell responses (Suekane et al., 2022). These findings underscore the importance of understanding the dynamics of T-cell persistence and the potential need for booster doses to sustain immunity.

4.2 Antibody-mediated immunity

Antibody-mediated immunity plays a vital role in the long-term protection offered by cancer vaccines. The generation of specific antibodies against tumor-associated antigens can help in the continuous surveillance and elimination of cancer cells. In a phase I trial of a plasmid DNA vaccine encoding the ERBB2 intracellular domain, patients exhibited robust and long-lasting antibody responses against ERBB2. The study found that higher vaccine doses were associated with stronger antibody responses, which were maintained over time (Disis et al., 2022). This suggests that optimizing vaccine dosage is crucial for achieving sustained antibody-mediated immunity (Figure 1).

Similarly, a study on a multi-epitope HER2 vaccine combined with trastuzumab showed that the vaccine generated long-lasting T-cell and antibody responses in patients with HER2-positive breast cancer. The combination of the vaccine with trastuzumab not only enhanced the immune response but also contributed to better clinical outcomes (Chumsri et al., 2022). These findings highlight the potential of cancer vaccines to induce durable antibody responses, which are essential for long-term cancer control.

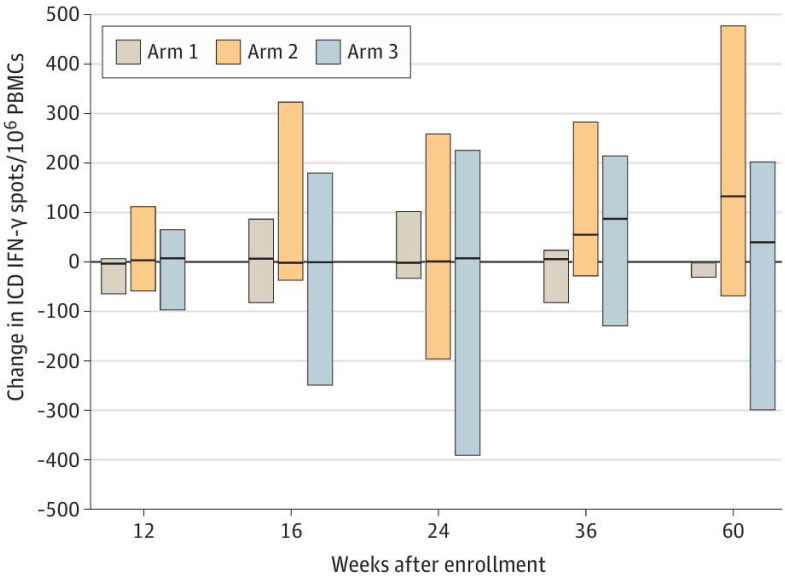

Figure 1 Association of magnitude and duration of vaccine-associated ERBB2 ICD T-Cell immunity with Dose (Adopted from Disis et al., 2022)

4.3 Recurrence prevention

Preventing cancer recurrence is a primary goal of cancer vaccines. Several studies have demonstrated the potential of these vaccines in reducing the risk of breast cancer recurrence. For instance, a phase II study of HER2 vaccines (WOKVAC and DC1) in patients with residual invasive disease after neoadjuvant therapy showed promising results in terms of recurrence-free survival. The study found that both vaccines were well-tolerated and induced significant immune responses, which correlated with a reduced risk of recurrence (Han et al., 2023).

Another study on the E75 vaccine, which targets the HER2/neu protein, reported a lower recurrence rate in vaccinated patients compared to controls. Although the difference in recurrence rates lost significance over time, the pattern of recurrence remained significantly different, suggesting a potential long-term benefit of the vaccine in preventing recurrence (Peoples et al., 2008). These studies underscore the importance of cancer vaccines in providing long-term protection against breast cancer recurrence, thereby improving patient outcomes. In conclusion, cancer vaccines have shown significant promise in inducing long-term immunological effects, including persistent T-cell responses, durable antibody-mediated immunity, and reduced recurrence rates. Continued research and optimization of these vaccines are essential to fully harness their potential in the fight against breast cancer.

5 Case Study: HER2/neu Vaccine in Breast Cancer Patients

5.1 HER2-targeted vaccines

HER2-targeted vaccines have emerged as a promising therapeutic strategy for breast cancer patients, particularly those with HER2/neu overexpression. These vaccines aim to stimulate the immune system to recognize and attack HER2-positive cancer cells. Various approaches have been explored, including peptide-based vaccines, plasmid DNA vaccines, and whole-cell vaccines. Peptide-based vaccines, such as those targeting the HER2 intracellular domain, have shown potential in clinical trials. For instance, a Phase I/II trial demonstrated that HER2-specific T-cells could be expanded ex vivo after in vivo priming with a multiple peptide-based HER2 vaccine, leading to significant T-cell responses and epitope spreading in patients (Disis et al., 2023). Another study reported the safety and immunogenicity of a HER2 plasmid DNA vaccine administered with low doses of GM-CSF and IL-2, which induced long-lasting HER2-specific antibodies and T-cell responses in metastatic breast cancer patients .

Whole-cell vaccines, which use genetically modified cells to express HER2 and other immunostimulatory molecules, have also been investigated. These vaccines aim to provide broad antigenic coverage and stimulate robust immune responses. For example, a tri-antigen vaccine targeting HER2, IGFBP-2, and IGF-IR was shown to

be safe and immunogenic in non-metastatic breast cancer patients, generating high levels of antigen-specific T-cells (Stanton et al., 2023). Overall, HER2-targeted vaccines represent a promising avenue for enhancing anti-tumor immunity in breast cancer patients, with ongoing research focused on optimizing vaccine formulations and delivery methods to improve clinical outcomes.

5.2 T-cell and antibody responses

The efficacy of HER2-targeted vaccines largely depends on their ability to elicit robust T-cell and antibody responses. T-cells, particularly CD8+ cytotoxic T lymphocytes (CTLs), play a crucial role in directly killing cancer cells, while antibodies can mediate antibody-dependent cellular cytotoxicity (ADCC) and other immune mechanisms. Several studies have demonstrated the potential of HER2-targeted vaccines to induce strong T-cell responses. For instance, a Phase I/II trial showed that HER2-specific T-cells could be significantly augmented in patients receiving HER2 vaccine-primed T-cell infusions, with 82% of patients exhibiting enhanced T-cell responses to at least one immunizing epitope (Disis et al., 2023). Another study reported that a HER2 plasmid DNA vaccine induced significant MHC class II-restricted T-cell responses, which were detectable for several years after vaccination .

In addition to T-cell responses, HER2-targeted vaccines can also stimulate the production of HER2-specific antibodies. A pilot clinical trial demonstrated that a HER2 plasmid DNA vaccine, administered with GM-CSF and IL-2, induced long-lasting HER2-specific antibodies in a subset of patients. Furthermore, combining HER2-targeted vaccines with monoclonal antibodies, such as trastuzumab, has been shown to enhance CD8+ T-cell effector function and improve tumor-free survival in preclinical models (Wolpoe et al., 2003). Overall, the ability of HER2-targeted vaccines to elicit both T-cell and antibody responses is critical for their therapeutic efficacy, with ongoing research aimed at optimizing vaccine formulations to maximize these immune responses.

5.3 Patient survival and immunity maintenance

The long-term benefits of HER2-targeted vaccines in breast cancer patients are reflected in improved survival rates and sustained immune responses. Clinical trials have provided evidence that these vaccines can enhance overall survival and maintain immunity over extended periods. A Phase I/II trial reported that patients receiving HER2 vaccine-primed T-cell infusions had a median survival of 45.0 months for responders, compared to 20.5 months for those with progressive disease (Figure 2) (Disis et al., 2023). Another study demonstrated that HER2-specific T-cell immunity elicited by a HER2 peptide vaccine was durable, with 75% of evaluable patients maintaining T-cell responses to HER2 peptides more than a decade after vaccination. This long-term immunity was associated with improved overall survival, with patients who developed epitope spreading showing a median survival of 84 months compared to 25 months for those who did not (Salazar et al., 2016).

The combination of HER2-targeted vaccines with other therapies, such as trastuzumab, has also shown promise in extending patient survival. A study evaluating concurrent trastuzumab and HER2/neu-specific vaccination reported prolonged, robust immune responses and a median overall survival that had not been reached at a median follow-up of 36 months. In conclusion, HER2-targeted vaccines have demonstrated the potential to improve survival and maintain long-term immunity in breast cancer patients. Continued research and clinical trials are essential to further elucidate the mechanisms underlying these benefits and to optimize vaccine strategies for broader clinical application.

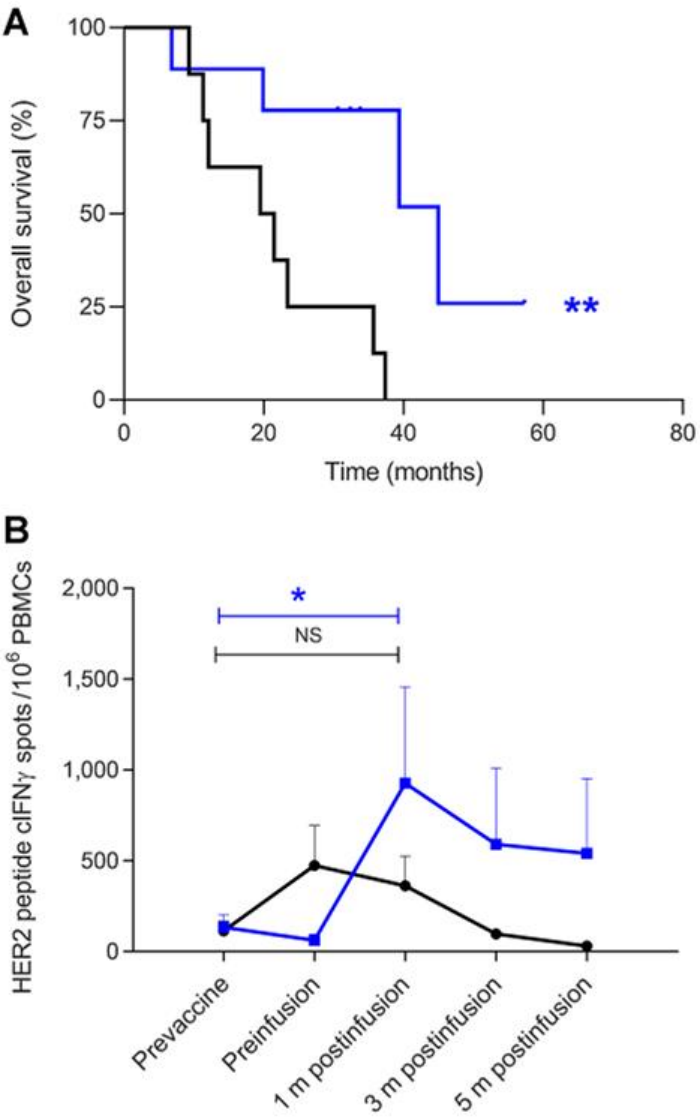

Figure 2 HER2-specific T cells persisted in patients with a PR or SD (Adopted from Disis et al., 2023)

Image caption: A, Kaplan–Meier curves of the OS inmonths from enrollment for responding patients (PRþSD, n ¼9) in blue and nonresponders (PD, n ¼ 8) in black. B, Sum of stimulating HER2 peptide (p776, 927, and p1166) specific T-cell responses (y axis) in pre vaccine, preinfusion (postvaccine), and 1, 3, and 5 months post T-cell infusion for responders (blue, n ¼ 9) versus nonresponders (black, n ¼ 8) during the treatment. Each dot represents mean (SE) at the time point in the group. NS, not significant, $P<0.05$, $P<0.01$ (Adopted from Disis et al., 2023)

6 Immune Escape Mechanisms in Breast Cancer

6.1 Tumor immune evasion

Breast cancer cells have developed sophisticated mechanisms to evade the immune system, which significantly hampers the efficacy of immunotherapies. One primary method of immune evasion is the downregulation of antigen presentation. Tumor cells often reduce the expression of major histocompatibility complex (MHC) molecules, which are crucial for presenting tumor antigens to T cells. This downregulation prevents the immune system from recognizing and attacking the tumor cells effectively. Additionally, breast cancer cells can secrete immunosuppressive cytokines such as TGF-β and IL-10, which inhibit the activation and proliferation of effector T cells and promote the development of regulatory T cells (Tregs) that suppress immune responses (Knudson et al., 2018).

Another significant mechanism is the upregulation of immune checkpoint molecules like PD-L1, which binds to

PD-1 receptors on T cells, leading to T cell exhaustion and anergy. This interaction effectively "turns off" the T cells, preventing them from attacking the tumor cells (Knudson et al., 2018; Dutta et al., 2023). Furthermore, breast cancer cells can induce the expression of indoleamine 2,3-dioxygenase (IDO), an enzyme that depletes tryptophan in the tumor microenvironment, leading to T cell anergy and apoptosis (Wei and Taskén, 2022). These immune evasion strategies collectively create a hostile environment for immune cells, allowing the tumor to grow and metastasize unchecked.

6.2 Immune suppression by the tumor microenvironment

The tumor microenvironment (TME) in breast cancer is a complex and dynamic milieu that plays a critical role in immune suppression. The TME consists of various cell types, including cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs), all of which contribute to an immunosuppressive environment. CAFs secrete extracellular matrix components and cytokines that physically and biochemically shield the tumor from immune cell infiltration. MDSCs, on the other hand, inhibit T cell activation and proliferation through the production of reactive oxygen species (ROS) and nitric oxide (NO) (Salemme et al., 2021).

Hypoxia within the TME further exacerbates immune suppression by stabilizing hypoxia-inducible factors (HIFs), which promote the expression of immunosuppressive molecules like VEGF and adenosine. These molecules not only inhibit the function of effector T cells but also attract Tregs and MDSCs to the tumor site, enhancing the immunosuppressive environment. Additionally, the TME can induce metabolic reprogramming in immune cells, leading to a state of metabolic exhaustion where immune cells are unable to function effectively (Kim and Cho, 2022). This multifaceted suppression by the TME creates significant barriers to effective immunotherapy in breast cancer.

6.3 Combining vaccines with other therapies

Given the complex immune evasion and suppression mechanisms in breast cancer, combining cancer vaccines with other therapeutic modalities holds promise for enhancing anti-tumor efficacy. Cancer vaccines aim to stimulate the immune system to recognize and attack tumor cells by presenting tumor-specific antigens. However, their efficacy is often limited by the immunosuppressive TME and immune evasion strategies employed by the tumor. Combining vaccines with immune checkpoint inhibitors (ICIs) such as anti-PD-1/PD-L1 or anti-CTLA-4 antibodies can help to overcome T cell exhaustion and enhance the immune response against the tumor (Knudson et al., 2018; Dutta et al., 2023).

Additionally, combining vaccines with therapies that target the TME, such as TGF-β inhibitors or IDO inhibitors, can help to reduce the immunosuppressive environment and improve vaccine efficacy (Knudson et al., 2018). Metabolic therapies that modulate the nutrient availability in the TME can also enhance the function of effector T cells and improve the overall anti-tumor response. Furthermore, integrating cancer vaccines with conventional therapies like chemotherapy or radiation can help to release tumor antigens and enhance the immunogenicity of the tumor, providing a synergistic effect. These combination strategies hold significant potential for improving the clinical outcomes of cancer vaccines in breast cancer patients.

7 Safety and Toxicity of Long-Term Cancer Vaccination

7.1 Tolerability of cancer vaccines

Cancer vaccines have shown promising results in terms of tolerability among breast cancer patients. For instance, the E75 vaccine, which targets HER2/neu, has been extensively studied in phase I/II clinical trials. These studies have demonstrated that the vaccine is generally well-tolerated, with most adverse events being of low grade. Specifically, local toxicities were predominantly grade 1 (85%) and grade 2 (15%), with no grade 3 local toxicities reported. Systemic toxicities were also mostly grade 1 (71%) and grade 2 (14%), with only a small percentage (3%) experiencing grade 3 systemic toxicities (Vreeland et al., 2011).

Similarly, the nelipepimut-S (NP-S) vaccine, another HER2-targeting vaccine, was well-tolerated in phase I/II studies, with the most common adverse events being injection site reactions such as erythema, induration, and

pruritus (Mittendorf et al., 2019). These findings are consistent with other studies that have evaluated the safety of cancer vaccines in breast cancer patients, indicating that these vaccines are generally well-tolerated with manageable side effects (Hosseini et al., 2023; Dafni et al., 2020; Singer et al., 2020).

7.2 Long-term safety data

Long-term safety data for cancer vaccines in breast cancer patients are encouraging. The E75 vaccine has shown sustained safety over a median follow-up period of 60 months. Booster inoculations, administered every six months after the primary vaccine series, were also well-tolerated, with only grade 1 and 2 local and systemic toxicities reported. Notably, delayed urticarial reactions were observed in 13% of boosted patients, but these were grade 2 and well-tolerated. Another study on a plasmid DNA vaccine encoding the ERBB2 intracellular domain reported that the majority of vaccine-related toxic effects were grade 1 and 2, with no significant differences between dose arms. Long-term follow-up indicated that the vaccine was safe, with no severe adverse events reported. These findings are corroborated by a systematic review and meta-analysis, which found that therapeutic cancer vaccines generally display low toxicity, even over extended periods (Dafni et al., 2020).

Overall, the long-term safety profile of cancer vaccines in breast cancer patients appears to be favorable, with most adverse events being mild to moderate in severity (Hosseini et al., 2023; Mittendorf et al., 2019; Singer et al., 2020).

7.3 Risk of immune-related adverse events

The risk of immune-related adverse events (irAEs) associated with cancer vaccines is an important consideration. While most cancer vaccines have been shown to be safe, there is a potential for irAEs, particularly when used in combination with other immunotherapies such as immune checkpoint inhibitors (ICIs). A systematic review and meta-analysis on the safety of influenza vaccination in cancer patients treated with ICIs found that the incidence of irAEs was not significantly increased following vaccination. However, another study highlighted that late-onset and long-lasting irAEs are common but often underreported. This study emphasized the need for long-term monitoring to fully capture and characterize these events (Ghisoni et al., 2021).

In the context of cancer vaccines, the E75 vaccine study reported delayed urticarial reactions in a subset of patients, indicating a potential for irAEs (Vreeland et al., 2011). Similarly, the NP-S vaccine study noted that while most adverse events were mild, there was a need for ongoing surveillance to monitor for any late-onset irAEs (Mittendorf et al., 2019). These findings underscore the importance of vigilant monitoring and reporting of irAEs to ensure the long-term safety of cancer vaccines in breast cancer patients.

8 Challenges in Sustaining Long-Term Immunity

8.1 Waning immunity

Waning immunity is a significant challenge in the context of long-term immunological effects of cancer vaccines in breast cancer patients. Over time, the immune response elicited by a vaccine can diminish, leading to a reduced ability to recognize and combat cancer cells. This phenomenon has been observed in various vaccine studies, including those targeting HER-2/neu in breast cancer. For instance, a study demonstrated that HER-2/neu peptide-specific CD8+ T-cell responses were short-lived, with a noticeable decline in immune response five months post-vaccination . This waning immunity can be attributed to several factors, including the nature of the antigen, the adjuvant used, and the patient's immune status.

Moreover, the tumor microenvironment (TME) plays a crucial role in the persistence of immune responses. The TME can exert immunosuppressive effects that hinder the long-term efficacy of cancer vaccines. For example, the presence of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) within the TME can suppress the activity of effector T cells, leading to a decline in vaccine-induced immunity. Additionally, the continuous exposure to tumor antigens without adequate immune stimulation can lead to T-cell exhaustion, further contributing to the waning of immunity.

To address this challenge, combination therapies that include immune checkpoint inhibitors (ICIs) have shown

promise. ICIs can reinvigorate exhausted T cells and enhance the durability of the immune response. Studies have indicated that combining cancer vaccines with ICIs can sustain and even boost the antitumor immune response, thereby mitigating the effects of waning immunity (Burg et al., 2016). Therefore, ongoing research is focused on optimizing vaccine formulations and exploring combination strategies to sustain long-term immunity in breast cancer patients.

8.2 Immunosenescence

Immunosenescence, the gradual deterioration of the immune system associated with aging, poses a significant challenge in sustaining long-term immunity in breast cancer patients. As the immune system ages, there is a decline in the production of naive T cells and an accumulation of memory T cells, which can lead to a reduced ability to respond to new antigens, including those presented by cancer vaccines. This age-related decline in immune function can compromise the efficacy of cancer vaccines in elderly breast cancer patients, who represent a substantial proportion of the patient population. Several studies have highlighted the impact of immunosenescence on cancer immunotherapy. For instance, research has shown that elderly patients have lower levels of naive T cells and higher levels of senescent T cells, which can impair the generation of robust and long-lasting immune responses. Additionally, the presence of age-related chronic inflammation, or "inflammaging," can further exacerbate immune dysfunction and contribute to an immunosuppressive TME.

Despite these challenges, there is evidence that elderly patients can still benefit from immunotherapy. Clinical experience with immune checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-1/PD-L1 antibodies, has shown that advanced age does not necessarily result in poorer responses or greater toxicity. This suggests that with appropriate strategies, it is possible to overcome the effects of immunosenescence.

To enhance the efficacy of cancer vaccines in the elderly, researchers are exploring various approaches, including the use of adjuvants that can boost immune responses, the development of vaccines targeting multiple antigens, and the combination of vaccines with other immunotherapies (Burg et al., 2016). These strategies aim to counteract the effects of immunosenescence and improve the long-term immunological outcomes for elderly breast cancer patients.

8.3 Overcoming immune suppression

Overcoming immune suppression is a critical challenge in sustaining long-term immunity in breast cancer patients receiving cancer vaccines. The TME is often characterized by various immunosuppressive mechanisms that can inhibit the effectiveness of cancer vaccines. These mechanisms include the presence of Tregs, MDSCs, and immunosuppressive cytokines, all of which can dampen the antitumor immune response.

One approach to overcoming immune suppression is the use of combination therapies that target multiple aspects of the immune response. For example, the NANT Cancer Vaccine (NCV) combines low-dose chemotherapy, radiotherapy, and multifaceted immunotherapy to reverse the immunosuppressive TME, induce immunogenic tumor cell death, and reengage NK and T-cell responses . This coordinated approach has shown promise in early clinical trials, suggesting that it is possible to overcome immune suppression and achieve sustained antitumor immunity.

Another strategy involves the use of immune checkpoint inhibitors to block inhibitory signals and enhance T-cell activation. Checkpoint inhibitors, such as anti-PD-1/PD-L1 and anti-CTLA-4 antibodies, have been shown to reinvigorate exhausted T cells and improve the efficacy of cancer vaccines (Burg et al., 2016). By blocking the inhibitory pathways, these agents can enhance the immune response and help maintain long-term immunity. Additionally, targeting specific components of the TME, such as Tregs and MDSCs, can also help overcome immune suppression. Agents that deplete Tregs or inhibit their function, as well as those that target MDSCs, are being investigated to enhance the effectiveness of cancer vaccines. These approaches aim to create a more favorable immune environment that supports sustained antitumor responses. In conclusion, overcoming immune suppression is essential for sustaining long-term immunity in breast cancer patients receiving cancer vaccines. Combination therapies, immune checkpoint inhibitors, and targeted approaches to modulate the TME are

promising strategies that are being actively explored to achieve this goal.

9 Future Directions in Cancer Vaccines for Breast Cancer

9.1 Next-generation vaccines: personalized and multi-antigen vaccines

The advent of next-generation sequencing and bioinformatics has revolutionized the development of personalized cancer vaccines. These vaccines are designed to target neoantigens, which are unique to each patient's tumor, thereby eliciting a robust and specific immune response. Personalized neoantigen-based vaccines have shown promise in early clinical trials, demonstrating safety, immunogenicity, and preliminary evidence of antitumor activity in various cancers, including melanoma and glioblastoma. The process involves sequencing the tumor's DNA to identify mutations, predicting which neoantigens will be most immunogenic, and then creating a vaccine tailored to these targets. This approach aims to broaden the endogenous repertoire of tumor-specific T cells, thereby enhancing the immune system's ability to recognize and destroy cancer cells (Blass and Ott, 2021).

Multi-antigen vaccines, which target several tumor-associated antigens simultaneously, are another promising avenue. These vaccines aim to overcome tumor heterogeneity and reduce the likelihood of immune escape by targeting multiple pathways involved in tumor growth and survival. Combining personalized and multi-antigen approaches could potentially offer a more comprehensive and effective immunotherapy strategy for breast cancer patients. The integration of these next-generation vaccines with other immunotherapeutic modalities, such as immune checkpoint inhibitors, could further enhance their efficacy by overcoming the immunosuppressive tumor microenvironment (Kim et al., 2021).

9.2 Combining vaccines with checkpoint inhibitors

Combining cancer vaccines with immune checkpoint inhibitors (ICIs) represents a promising strategy to enhance antitumor immunity. ICIs, such as anti-PD-1 and anti-CTLA-4 antibodies, have revolutionized cancer treatment by unleashing the immune system to attack tumors. However, their efficacy is often limited by the lack of pre-existing T-cell responses in many cancers, including breast cancer (Collins et al., 2018; Thomas et al., 2021). Cancer vaccines can prime and expand tumor-specific T cells, turning "cold" tumors into "hot" ones, thereby making them more susceptible to ICIs (Collins et al., 2018; Wang, 2024).

Preclinical and early clinical studies have shown that combining vaccines with ICIs can lead to synergistic antitumor effects. For instance, a study combining a MUC1 mRNA nano-vaccine with CTLA-4 blockade demonstrated significant inhibition of tumor growth in triple-negative breast cancer (TNBC) models (Liu et al., 2018). This combination therapy enhanced the activation and expansion of tumor-specific T cells, leading to a more robust and durable immune response compared to either treatment alone (Liu et al., 2018). Additionally, personalized cancer vaccines combined with ICIs have shown acceptable safety profiles and minimal additional toxicity, making them a viable option for enhancing clinical outcomes in breast cancer patients (Zhao et al., 2019).

9.3 Vaccine development in metastatic breast cancer

Metastatic breast cancer (MBC) remains a significant clinical challenge due to its aggressive nature and poor prognosis. Developing effective vaccines for MBC requires overcoming several hurdles, including the immunosuppressive tumor microenvironment and the heterogeneity of metastatic lesions. Recent advances in vaccine technology, such as the use of dendritic cell (DC)-based vaccines and nanoparticle delivery systems, offer new avenues for targeting metastatic disease.

DC-based vaccines have shown potential in inducing strong antitumor immune responses by presenting tumor antigens to T cells and activating them. Combining DC vaccines with ICIs, such as PD-1 blockade, has been proposed as a strategy to enhance their efficacy by overcoming immune evasion mechanisms. Additionally, nanoparticle-based mRNA vaccines targeting specific tumor antigens have demonstrated promising results in preclinical models of TNBC, suggesting their potential for treating metastatic disease (Liu et al., 2018).

Ongoing clinical trials are exploring the efficacy of various vaccine platforms in combination with standard therapies and ICIs in MBC patients. These studies aim to identify optimal combinations and treatment regimens

that can improve survival and quality of life for patients with metastatic breast cancer. The development of effective biomarkers to predict response to vaccine-based therapies will also be crucial for personalizing treatment and maximizing clinical benefits (Zhao et al., 2022).

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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