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CANCER INNOVATION

REVIEW

Breast cancer immunotherapy: Realities and advances

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Abstract

Breast cancer (BC) is the most common malignant tumor and the main cause of death in women worldwide. With increased knowledge regarding tumor escape mechanisms and advances in immunology, many new antitumor strategies such as nonspecific immunotherapies, monoclonal antibodies, anticancer vaccines, and oncolytic viruses, among others, make immunotherapy a promising approach for the treatment of BC. However, these approaches still require meticulous assessment and readjustment as resistance and modest response rates remain important barriers. In this article, we aim to summarize the most recent data available in BC immunotherapy to include the results of ongoing clinical trials and approved therapies used as monotherapies or in combination with conventional treatments.

KEYWORDS

breast cancer, immunotherapy, metastatic disease, therapy combination, tumor microenvironment

1 | INTRODUCTION

According to the latest Global Cancer Statistics, in 2024, breast cancer (BC) is the most prevalent type of cancer and represents 11.6% of all cancers and represents 10% of total cancer deaths in 2022 [1]. It is estimated that in the United States alone in 2024, there will be 42,780 deaths (42,250 women and 530 men) [2]. Worldwide, BC is the leading overall cause of death in women with an estimated 666,103 deaths [1].

BC is highly heterogeneous and can be divided into four molecular subtypes: (1) Luminal A: estrogen receptor (ER+), progesterone receptor (PR+), human epidermal growth factor receptor 2 (HER-2+), and antigen Kiel 67 [Ki67 < 14%], which represents 53.1% of all BCs; (2) luminal B (ER+, PR+, HER-2+, and Ki67 > 14% or ER+, PR+ and HER-2+), accounting for 21.7%; (3) HER-2 positive (ER−, PR−, and HER-2+), representing 9%; and (4) triple-negative BC (TNBC: ER−, PR−, and HER-2−), accounting for 16.2% [3].

Despite advances in endocrine therapy and anti-HER-2 therapy in past decades, relapse and metastasis remain a great challenge in clinical practice. Metastatic BC (mBC) is most often an incurable disease with only modest responses

Abbreviations: APC, antigen-presenting cell; BC, breast cancer; CAR, chimeric antigen receptor; CTL, cytotoxic T lymphocyte; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; ER, estrogen receptor; FDA, Food and Drug Administration; HER-2, human epidermal growth factor receptor 2; HLA-I, human leukocyte antigen class I; HLA-II, human leukocyte antigen class II; ICI, immune checkpoint inhibitor; IFN-γ, interferon-gamma; IL-2, interleukin-2; mAb, monoclonal antibody; mBC, metastatic BC; NK, natural killer; OV, oncolytic virus; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PR, progesterone receptor; TIL, tumor-infiltrating lymphocyte; TME, tumor microenvironment; TNBC, triple-negative BC.

to available therapies [4]. Therefore, a need for innovative therapeutic approaches remains critical. Immunotherapy, also known as biologic therapy or biotherapy, uses the person's own immune system [5]. The main function of the immune system is to preserve the biological integrity of individuals, having the capacity to distinguish between the self and the nonself (foreign), to reject external invading agents (e.g., pathogens, molecules, etc.), and to destroy abnormal cells such as cancer cells. However, many tumors escape immune detection due to (1) lack of tumor-specific antigen recognition, (2) altered co-receptors that prevent their recognition, and (3) T-cell anergy or natural killer (NK) cells that allow or promote the development of cancer through "immunoediting" [6]. Although immune systems fight off bacteria, viruses, or parasites as foreign organisms, these processes can also be geared toward cancer cells [5]. To combat tumor recurrence, immunotherapy has emerged as a therapeutic approach to overcome immunosuppression [7]. Advances in molecular immunology have also led to the discovery of multiple tumor antigens and pathways, as well as other immunoregulatory aspects of BC [8].

As a result, many of the new anticancer strategies aim to rescue immune protection against these abnormal cells [9]. To improve the success of immunotherapy, there is a need to develop a deep understanding of the tumor microenvironment (TME), activation mechanisms of immune cells, and the delicate balance of cytokines in reaching cytotoxic T-cell reprogramming. Once established, the TME can be kept under control by regulatory mechanisms, such as immune checkpoint molecules (programmed death-1 [PD-1] or cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]), as well as other types of immunosuppressive cells such as regulatory T cells and T helper 17 cells (TH17). To induce an antitumor immune response, the immune system needs to recognize tumor antigens presented by tumor cells directly or by antigen-presenting cells (APCs) via a major histocompatibility complex on the cell surface [10, 11]. The advances achieved in the understanding of the complex interactions between the immune system and malignant tumors have given rise to numerous immunotherapeutic strategies against cancer.

BC has traditionally been considered one of the cancers with the least immune responses [12, 13]. In the last 20 years, BC immunotherapy research has increased our knowledge of the crosstalk between immune cells and BC cells. There are many cells and cytokines involved in the BC immune environment, some with antitumorigenic roles and others with protumorigenic or immunosuppressive functions. These cells and secreted cytokines can also promote the progression of BC through chronic inflammation [14]. An improved understanding of the interactions between the immune system and BC can enable the creation of predictive models for a better understanding of BC biology, as well as improved prognostic accuracy and treatment options for BC patients [11].

Scientists have begun to use the immune response to BC to their advantage, such as vaccinating against BC, helping enrich the immune system to fight BC, or working in conjunction with chemotherapy to reduce BC mortality. In a recent study, tumor-infiltrating lymphocytes (TILs) from the resected lesions of 42 patients with mBC were isolated and grown in culture; and a median number of 112 (range: 6–563) nonsynonymous mutations per patient were identified. Twenty-eight of the 42 (67%) patients had TILs that recognized at least one immunogenic somatic mutation, indicating that most patients with BC generate a natural immune response targeting the expressed products of their cancer mutations. Adoptive transfer of TILs in patients with mBC was shown in a pilot trial to mediate objective responses [15]. With the acceptance of the heterogeneity observed in BC subtypes and the molecular mechanisms that contribute to the emergence of treatment resistance and metastatic disease, the implementation of more effective therapeutics is going to be needed to increase the rate of survival of patients with BC. As a result, many of the new anticancer strategies aim to rescue immune protection against these abnormal cells [9].

Currently, all types of BCs are considered for immunotherapy treatments, and according to clinicaltrials.gov, there are at least 23 ongoing phases 2 and 3 studies focused on each ER+ and PR + BC patients, 31 phases 2 and 3 studies for HER-2+ BC patients, and 57 phases 2 and 3 studies for TNBC patients [16]. This means that the majority of immunotherapies, more than 50%, are targeted toward TNBC patients.

2 | BC IMMUNOTHERAPY: REALITIES AND ADVANCES

In both developed and developing countries, BC remains the most frequently diagnosed and the main cause of cancer death in women. Therefore, the development of new treatment strategies that, individually or in combination, might help to combat this disease has become the focus of researchers [17]. Immunotherapy is one of the leading strategies to be evaluated as a cancer therapy and has already been approved by health agencies worldwide with very prominent and positive results [18].

Although the beginnings of immunotherapy date back to 1891 with the studies of William Bradley Coley in his attempts to treat bone cancer, it was not until 1998, with the approval of trastuzumab for the treatment of certain types of BC, that immunotherapies began to be used for this disease. While some researchers do not categorize

monoclonal antibodies (mAbs) as immunotherapies, in this review, we will include them as such [19].

BC immunotherapy can be divided into two broad categories: (1) specific stimulation of the immune system by active immunization, with cancer vaccines or (2) passive immunization, such as tumor-specific antibodies (including immune modulators) or adoptive cell therapy that inhibit the function of, or directly kill, tumor cells [20].

The treatment options utilized depend largely on the stage, subtype, and invasiveness of the disease [21, 22]. Usually, for nonmetastatic disease, the eradication of tumors from the breast and regional lymph nodes is indicated, with postoperative radiation to prevent local recurrence. In those cases, systemic therapy may involve the use of neoadjuvant preoperative or postoperative, or both. In contrast, mBC on the other hand, remains theoretically incurable in all affected patients, and the therapeutic goals are centered around prolonging life and symptom palliation [21–23]. More recently, with several studies in tumor escape mechanisms and advances in immunology, many new antitumor strategies aim to make immunotherapy a promising new treatment for all types of BC [22–24]. Initially, BC was not considered a target for immunotherapy due to poor immunogenicity. However, favorable research results have been found in the use of immunotherapies, particularly, in patients with TNBC and HER-2+ BC [25].

The TME is the milieu or ecosystem that surrounds cancer cells, including immune cells, the extracellular matrix, blood vessels, and various other cells, such as fibroblasts. TME is remarkably important in the establishment of cancer. Any significant alteration of this stromal tissue surrounding cancer cells could lead to tumor progression [26]. Thus, the immune system's response to cancer constitutes a dynamic process between stromal tissue cells and tumor cells [27].

Given the key role of TME and that immunotherapies seek to affect the tumor-supporting role of the TME, the success of immunotherapies might depend on an improved understanding of its role.

The immunosuppressive nature of the TME may alter the immune response by interfering with dendritic cell maturation and T-cell activation, thus allowing transformed cells to survive and progress into solid tumors [26]. Additionally, when patients are treated with conventional chemotherapy, most of the drugs used have severe immunosuppressive effects, whereas, for a more efficient treatment response, it is necessary to change the TME by increasing the activation of the immune cells [21].

The process of response to the malignant cell involves several molecular, hormonal, and immunological events, including infiltration of immune cells such as phagocytes, cytotoxic cells like NK and CD8+ cytotoxic T lymphocytes (CTLs), and secretion of cytokines and growth factors, which result in an inflammatory microenvironment and intense immunological response [18]. Additionally, if neoantigens enter the TME, they will be recognized, processed, and presented to CD4+ helper T cells by APCs in association with human leukocyte antigen class II (HLA-II), which will then develop an adaptive immune response through maturation, activation, and proliferation of both T cells and B cells [26].

Recent studies about the TME suggest an alternative route to neoantigen presentation directly involving CTL participation. This mechanism is called trogocytosis, in which CTLs extract the human leukocyte antigen class I (HLA-I) from the APC membrane to present it to another CTL and thus initiate a new activation cascade [27]. High levels of CTLs seem to correlate with a better prognosis in BC, due to their participation in tumor elimination [26, 28]. On the other hand, most cancerous tissues do not express HLA-II, which interferes with the antigen presentation via APCs, and a proper costimulation for a successful activation of naive T cells. Nevertheless, dendritic cells are capable of mediating antigen presentation through cross-presentation of internalized tumor antigens on HLA-I, thus activating naive T cells in the tumor-draining lymph nodes [29]. This is when some cytokines, such as interferon-gamma (IFN-γ), play a key role in the upregulation of HLA-I expression at the cell surface, which increases antigen processing [30].

New anticancer immunotherapy modalities have been developed to target different levels of the immune system, as well as to complement and improve the effectiveness of conventional therapies. Recent clinical trials have demonstrated the success of immunotherapies against primary tumors and in the prevention of metastatic cancer. These offer more promising options for cancer treatment with fewer side effects than conventional chemotherapy and radiotherapy [31]. Several types of immunotherapies used in cancer treatment include nonspecific immunotherapies, mAbs, adoptive cell immunotherapies, anticancer vaccines, tumor-targeting immunotherapies, oncolytic viruses (OVs), and various other combinations [7]. Below, we describe these different approaches and highlight related clinical data.

2.1 | Nonspecific immunotherapies

Nonspecific immunotherapies such as interleukin-2 (IL-2), IFN-γ, tumor necrosis factor, and interleukin-12 (IL-12) do not specifically target cancer cells, although they generally trigger the immune system by stimulating immune cells like NK cells and CTLs, plus inducing

foreign antigen presentation, thus enhancing the immune response against cancer cells [18, 21].

Cytokines have been shown to be effective when administered in large amounts to patients with metastatic cancers. In 1991, the Food and Drug Administration (FDA) approved the use of aldesleukin (a synthetic form of IL-2) for the treatment of metastatic kidney cancer and later in 1998 for metastatic melanoma [19]. Currently, there are several ongoing studies of cytokines in BC. Recent results of a study utilizing a murine model demonstrated that the combination of IFN-γ with anti-HER-2 agents seems to decrease the expression of this tyrosine kinase receptor, inhibiting tumor growth [32]. Additionally, according to numerous preclinical studies, IL-12 stands out as one of the most potent antitumor cytokines and might be used in the near future as a neoadjuvant treatment in early stage BC [33]. Also, the combination of these nonspecific treatments with conventional and/or developing treatments is now often utilized in BC therapeutic approaches and will be mentioned in the following sections of this article [19].

2.2 | mAb-based cancer immunotherapy

mAbs are man-made proteins and the first BC immunotherapy implemented, which were designed to bind and neutralize a targeted altered molecule expressed on the surface of cancer cells [18, 34]. The approval of trastuzumab (Herceptin®), the first anti-HER-2 mAb used for the treatment of mBC patients with overexpression and/or gene amplification of this molecule, represented a significant event in the history of immunotherapy for BC. This approval transformed the approach in the treatment of mBC, as response rates increased from 7% to 35%, with only a 15% relapse rate posttherapy [18]. Moreover, according to an ongoing phase 3 trial, trastuzumab in combination with pertuzumab, also an anti-HER-2 mAb, and a taxane (like paclitaxel or docetaxel) might result in further improvement of the median survival rate of these patients, and a remarkable decrease of cardiac dysfunctions risk, thus transforming the therapeutic landscape of this condition [18, 35].

In another randomized phase 3 clinical trial in patients with HER-2+ invasive BC, the use of conventional chemotherapy in combination with or without trastuzumab after surgery has shown several adverse effects, with no efficacy results yet available [36]. Also, different anti-HER-2 tyrosine kinase inhibitors (TKIs) such as lapatinib, neratinib, gefitinib, and afatinib or the mAb bevacizumab have been added to the list of therapeutic options for BC, both as monotherapy or in combination with other therapies [18, 30].

Neratinib has shown an 84% response rate in HER-2+ and HR+ BC, compared with a 59% response rate in HER-2+ and HR− BC. Lapatinib, a reversible dual TKI, has shown a response rate of 24% in trastuzumab-naive patients and <10% in trastuzumab-refractory breast tumors, as well as a partial response rate in 39% of patients with relapsed or refractory HER-2+ inflammatory BC. Additionally, gefitinib has not shown any responses in patients with advanced, previously treated BC, while afatinib has shown partial response in 10% and progressive disease in 39% of extensively pretreated HER-2+ patients with mBC progressing after trastuzumab [18].

Even though it remains unclear if the combination of paclitaxel, trastuzumab, and lapatinib is more effective than paclitaxel with trastuzumab alone, according to some ongoing studies, this combination given before surgery may shrink tumor size, reducing the amount of normal tissue removed [37].

Three phase 3 trials have demonstrated that the addition of bevacizumab to chemotherapy reduces overall progression and is well tolerated. In other clinical trials, the combination of bevacizumab with albumin-bound paclitaxel (nab-paclitaxel [Abraxane®]) showed remarkable activity in metastatic TNBC [38, 39]. Although bevacizumab has been used as a neoadjuvant in cases of HER-2+ and TN tumors, so far, it has not demonstrated a significant benefit in overall survival [38–40]. Another ongoing phase 3 trial compares the effect of tamoxifen citrate in combination with bevacizumab in patients with HER-2+ mBC and non-mBC, resulting, up to now, in better overall prognosis [41]. Currently, there are no completed or ongoing phase 4 clinical trials using mAbs for BC treatment.

Recently, margetuximab, a new-generation mAb, has been approved for use in combination with chemotherapy for the treatment of patients with HER-2+ mBC. Margetuximab is a chimeric Immunoglobulin G1 mAb targeting the HER-2 pathway, and in preclinical studies, relative to trastuzumab, it demonstrated an increased capacity to mediate antibody-dependent cellular cytotoxicity through effector cells such as NK cells, macrophages, and neutrophils [42, 43].

The FDA has approved new therapeutic approaches known as antibody-drug conjugates such as ado-trastuzumab emtansine and T-cell bispecific antibodies, which could be among the most promising immunotherapy strategies for BC [18]. Additionally, Enhertu (fam-trastuzumab-deruxtecan-nxki), an intravenous infusion for the treatment of patients with unresectable or metastatic HER-2-low BC, was also approved becoming the first therapy for patients with the HER-2-low BC subtype [42–44].

As demonstrated in the clinical trial, trastuzumab significantly improved the prognosis of BC associated

with HER-2 amplification. However, resistance to trastuzumab remains a significant challenge. The presence of primary or acquired resistance is, therefore, worth some consideration. Several mechanisms of resistance to trastuzumab have been described [45]. Some have been evaluated as prognostic factors and others as predictors associated with treatment benefits in clinical trials performed in early and advanced disease. The epidermal growth factor receptor (EGFR/HER1) and HER3 hold a significant role in trastuzumab resistance [46, 47]. Coexpression of EGFR in HER-2 overexpressed BC has been associated with poor survival in several retrospective series, suggesting that the expression of other members of the HER-2 family interferes with the inhibitory activity of HER-2 by trastuzumab. Another intrinsic alteration of HER-2 is located in the p95HER-2 fragments, a subtype of HER-2 receptors that are characterized by the lack of extracellular domain, the binding epitope for trastuzumab [45, 47].

The PI3K/Akt pathway can be activated by HER-2 and other TKR signaling. It can also be constitutively activated by amplification or mutation of the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform [48] or serine-threonine protein kinase 1 [49] or by mutation or loss of expression of tumor suppressors that inhibit the pathway, such as phosphatase and tensin homolog and inositol polyphosphate-4-phosphatase, type II [50]. Constitutive activation by one of these mechanisms has been associated with trastuzumabs' resistance.

2.3 | Immune checkpoint inhibitors (ICIs)

Several mechanisms of tumor evasion have been described, most of them resulting in a downregulation of HLA molecules at the cell surface. The diminution of the expression of HLA-I impairs the ability of CTLs to recognize the tumor cells as a threat [51]. Additionally, the diminution of HLA-II expression inhibits the function of the APCs, leading to an alteration of T-cell signal transduction and induction of T-cell apoptosis via the CD95/CD95L signaling pathway [51]. Other alterations may include the upregulation of inhibitory pathways, such as those triggered by immune checkpoints that can result in the overexpression of co-inhibitory molecules or the absence of costimulatory molecules. One explanation for the failure of immune responses is the dysfunction of TILs, caused by the expression of checkpoint receptors known as CTLA-4 and PD-1 on TILs [18, 26, 29].

The inhibition of programmed death-ligand 1 (PD-L1) and CTLA-4 has been targeted in cancer treatment so that the immune system can better recognize and attack these abnormal cells. Drugs known as ICIs have been included in more recent studies and have been demonstrated to increase survival rates when compared with standard therapies [18, 19]. More importantly, ICIs have been approved by the FDA for more than nine types of cancer, including melanoma, nonsmall cell lung cancer, bladder cancer, Hodgkin's lymphoma, and mismatch repair-deficient solid tumors [52].

After a study of atezolizumab (anti-PD-L1) plus nab-paclitaxel reported a 40% reduced risk of disease progression or death in patients with metastatic TNBC with PD-L1 overexpression, the FDA approved this therapy for these types of patients in 2019, but it was withdrawn in 2021. A randomized phase 3 trial is being developed to describe the effect of atezolizumab plus carboplatin and abraxane as neoadjuvant treatment with no reported results yet [53, 54]. Ipilimumab (anti-CTLA-4) and, more recently, pembrolizumab (anti-PD-1) have also been approved for patients with overexpression of these proteins. Unfortunately, according to some randomized trials for metastatic TNBC, none of them have yet led to a better prognosis than conventional chemotherapy alone [18, 40, 54, 55]. The combination of ipilimumab plus nivolumab (anti-PD-L1) is still under evaluation for the treatment of BC with no conclusive results yet reported [56–58].

Currently, the PD-L1 inhibitors mepolizumab and nivolumab are being compared in an ongoing clinical trial in TNBC patients, with 76% of TNBC patients not showing a promising response under mepolizumab therapy [40]. Additionally, ongoing phase 2 clinical trials are studying the benefits of the combination of ipilimumab and nivolumab, but these have not yet been completed [56].

In general, during treatment with ICIs, immune-mediated adverse events such as endocrinopathies and exacerbated inflammatory responses in some organs can lead to treatment discontinuation [18]. Modest response rates also remain as notable impediments for the broad use of ICIs. Both CTLA-4 and PD-1/PD-L1 inhibitors have broadly demonstrated their value in boosting potent and durable antitumor responses and in increasing the average life expectancy for patients with metastatic TNBC, although more studies are still needed [41]. There are no ongoing phase 4 clinical trials using ICIs for HER-2+ and HR+ BC patients. In a recently published review, Alturki discusses an updated analysis on the ICIs in the context of cancer treatment [59].

2.4 | CAR T-cells

Chimeric antigen receptor (CAR) T-cell therapy was first described in the 1990s and involves the isolation of

patient T-cells and NK cells, their modification and multiplication in the laboratory, and then reinjection back into the patient [60]. CAR T-cell therapy was first approved by the FDA in 2017 for relapsed B-cell acute lymphoblastic leukemia in children and later in 2018 for diffuse large B-cell lymphoma and other types of lymphoma [17]. Additionally, the use of HER-2-redirected CAR T-cells has shown great potential in eliminating tumor cells previously sensitized with trastuzumab in preclinical models. According to some clinical trials, HER-2-redirected CAR T-cells have seemed to cure patients treated with trastuzumab, recognizing that CAR T-cell therapy could be a promising option for patients in advanced stages of BC [61]. However, these studies have only shown a modest improvement in BC survival since despite the significant improvements after therapy with trastuzumab and CAR T-cells, a high proportion of patients eventually experience recurrence even after initially responding to the synergistic effects of the therapies [62, 63].

Lotfinejad et al., in 2020, studied the effects of combining CAR T-cells with PD-1 inhibitors to overcome TME immunosuppression in a murine model of HER-2+ BC [64]. They found a significant reduction in the tumor volume when combining HER-2-redirected CAR T-cells with PD-1 inhibitor antibodies, also observing that the levels of IFN-γ and granzyme-B were increased with this therapy, indicating an improved immune response [61, 63, 64].

A clear benefit of CAR T-cells is that they can cross the blood–brain barrier, which could help to avoid metastases to the central nervous system [61]. However, this therapy may lead to cytokine storms, which may also activate endothelial cells in the blood–brain barrier, disrupting barrier integrity and driving CAR-T therapy-associated neurotoxicity, a potentially lethal adverse effect if not quickly treated [57, 61]. Currently, there are no conclusive CAR-T studies on HR + BC and TNBC. It is important to consider that, as with other immunotherapies, CAR T-cell therapy works efficiently only in patients with fairly intact immune systems. Consequently, patients receiving conventional cytotoxic chemotherapy are not suitable for CAR T-cell therapy, as they will be immunosuppressed [17, 62].

2.5 | Therapeutic cancer vaccines

Therapeutic vaccines vary depending on the antigen used, dependent on sources like synthetic proteins or peptides of cancer antigens, DNA/RNA encoding cancer antigens, and cell-based delivery of tumor antigens. These vaccines may be used alone or as a complement to immune-stimulating molecules [17, 65–67].

In 1990, bacillus Calmette–Guérin was the first vaccine to be approved by the FDA for the treatment of bladder cancer. Then, in 2010, the sipuleucel-T vaccine was approved by the FDA for the treatment of patients with advanced prostate cancer [65–68].

Although still in the early stages, the combination of different kinds of vaccines with ICIs and/or standard treatments have been investigated as BC therapies. Some randomized trials are currently assessing the combination of drugs targeting PD-1, standard neoadjuvant or adjuvant chemotherapies, and other immunotherapies in early stage TNBC [68]. A human pilot study performed in 2015 by Convit et al. showed the effectiveness of a polyvalent vaccine in the inducement of antitumor cell infiltration [69].

A phase 2 trial is currently studying the efficacy of combining an allogeneic large multivalent immunogen BC vaccine with aldesleukin (IL-2) in women with stable mBC, with no results yet available [70].

A peptide-based vaccine with a single-agent E75 is also currently under study in a phase 3 clinical trial for managing HER-2+ BC patients. Its combination with trastuzumab is also being studied in a phase 2 clinical trial [71].

Additionally, the vaccines Theratope® (STn) applied in the metastatic setting and NeuVax™ [Nelipepimut-S, or E75] applied in the adjuvant setting have failed to bring clinical benefits in a phase 3 study despite their early success [72].

Another cancer vaccine approach, located conceptually between immunotherapy and biological therapies, called OV therapy has been in development for over a decade. It involves the modification of tumor cells by intratumoral administration of OVs. Various types of virotherapy have been tested in multiple cancer types at different clinical trial phases, either as monotherapy or in combination with other drugs, but it was not until 2015, that the T-VEC vaccine, a genetically modified herpes virus, was licensed for the treatment of patients with unresectable melanoma, becoming one of the first OV to be approved [11, 19, 73].

In 2017, Bernstein et al. assessed the effectiveness of pelareorep, an oncolytic reovirus, in combination with paclitaxel in patients with mBC through a phase 2 trial [74]. This combination resulted in a significant increase in the overall survival compared with paclitaxel alone, but there was no significant difference in the progression-free survival [74].

Bourgeois-Daigneault et al., in 2018, studied the neoadjuvant effect of an oncolytic Maraba virus for the treatment of advanced TNBC in a murine model [75]. In this study, 50% of the virus-treated mice were found to have no metastasis, and those that still had remnants of metastatic disease showed smaller and lesser amounts of lesions in the lung compared to control mice [75].

Although OVs increase tumor infiltration by cytotoxic T-cells and other immune cells, cancer cells seem to compensate for this by upregulating their expression of PD-L1 in response to OV intervention [74]. In response to this observation, Mostafa et al., in 2018 studied the combination of pelareorep with an anti-PD-1 antibody in BC human models, reporting that the overall antitumor efficacy of the OV was improved by this combination [76].

Despite the successful results of OV therapies, acquired immunity against the virus used is their most important disadvantage since it could disrupt any chance of repeated therapy in the same patient. Moreover, even though there are several ongoing preclinical and clinical trials, no OV vaccine has yet been approved for either BC treatment or its prevention [19, 73, 77].

3 | PROGNOSIS, CHALLENGES, AND DISADVANTAGES

The development of immunotherapies for BC continues to go through the hard process of assessment and readjustment, but, according to da Costa Vieira et al., the prognosis for BC is good, with 5-year survival rates of 73% in developed countries and 57% in countries with fewer resources [17]. However, as with other types of cancer, early diagnosis greatly increases the chances of successful treatments, allowing about a 20% reduction in overall mortality rates and helping lessen BC morbidity. Hence, the application of adequate health policies as well as preventive strategies directed to increase early detection are clearly needed [17, 18].

Incidence rates of BC have increased slightly by 0.3% per year. Recent statistics indicate that, beyond successful surgical removal, chemotherapy, radiotherapy, or a combination of both, about 30% of patients will develop metastatic disease even with a prompt diagnosis. This fact and the efficacy shown over the years by cancer immunotherapies have positioned immunotherapies as a promising option for BC treatment [18, 78].

Nevertheless, one of the most important challenges in immuno-oncology is to understand why some patients respond to immunotherapy, whereas others seem to have no sensitivity to these strategies. The extent and composition of immune infiltrates vary greatly between BC subtypes. Therefore, it is not expected that all BC patients will benefit from the same immunotherapeutic strategy to restore or elicit an antitumor immune response [25]. Moreover, it is suggested that levels of checkpoint expression may not be the sole contributing factors to the difficulty and resistance observed in immunotherapy. While previous research has primarily focused on understanding immune and tumor cell suppression mechanisms within tumors, there is growing recognition that tumor and immune suppressor cells interact with stromal cells to form a complex signaling network. This interaction may be crucial for T-cell exclusion. An increasing body of research has also shed light on the role of stromal cells in promoting immune evasion and supporting cancer progression and metastasis [79].

Complicating immunotherapeutic approaches is the fact that some patients are thought to develop cancer hyperprogression after immunotherapy treatment, and although this seems to be supported by some kind of acquired resistance, the specific reason for this response remains unknown. With that said, the appearance of severe immune-related adverse effects, requiring therapy discontinuation, remains the main drawback of immune-oncology therapies, especially those that include a combined regimen [16, 17]. Further research on combined therapies remains necessary to prevent these responses and to advance cancer immunotherapy approaches.

After reviewing the current BC immunotherapy data, Tables 1 and 2 were generated to summarize the results of the latest and ongoing clinical trials, as well as approved therapies used as monotherapies or in combination with conventional treatments. Additionally, we present a summary figure (Figure 1) of the immunotherapies currently approved by the FDA.

TABLE 1 Therapies.

Therapy name	Target	Status	Results	Side effects	References
Monoclonal antibodies					
Trastuzumab	HER-2+	Approved by the FDA	Response rates from 7% to 35%, and 15% relapse rates after therapy in patients with HER-2 overexpression.	Chills, asthenia, fever, pain, nausea, cardiac dysfunction.	[18]
Pertuzumab	HER-2+	Approved by the FDA	3.0%–7.6% complete response and 16.7% partial response.	Diarrhea, nausea, vomiting, fatigue, asthenia, back pain.	[18]

(Continues)

TABLE 1 (Continued)

Therapy name	Target	Status	Results	Side effects	References
Lapatinib	HER-2+	Approved by the FDA	Partial response in 39% of patients with relapsed or refractory HER-2+ inflammatory breast cancer.	Diarrhea, fatigue, nausea, rash, anorexia, dyspnea, vomiting, back pain.	[18]
Neratinib	HER-2+	Approved by the FDA	Response rate in 84% of HER-2+ HR+ patients, plus pathological complete response in 56% of HER-2+ HR- patients.	Diarrhea, nausea, abdominal pain.	[18]
Gefitinib	HER-2+	Approved by the FDA	No conclusive results for breast cancer.	Diarrhea, skin rash.	[18]
Afatinib	HER-2+	Approved by the FDA	Partial response in 10% and progressive disease in 39% of extensively pretreated HER-2+ patients with metastatic breast cancer progressing after trastuzumab. No complete response was observed.	Diarrhea, skin rash.	[18]
Margetuximab	HER-2+	Approved by the FDA	Response rates were 22% compared to a response rate of 16% in the control arm.	Fatigue/asthenia, nausea, diarrhea, vomiting, constipation, headache, pyrexia, alopecia, abdominal pain, peripheral neuropathy, arthralgia/myalgia, cough, decreased appetite, dyspnea, infusion-related reactions, palmar-plantar erythrodysesthesia, and extremity pain.	[43]
Immune checkpoints inhibitors					
Pembrolizumab	TNBC	Phase 3 trial	No conclusive results for breast cancer.	Anemia, fatigue, constipation.	[71]

Abbreviations: FDA, Food and Drug Administration; HER-2+, human epidermal growth factor receptor type 2 positive; PD-1, programmed cell death protein 1.

TABLE 2 Combined therapies.

Combined therapy	Target	Status	Results	Side effects	References
Monoclonal antibodies					
Trastuzumab plus conventional chemotherapy	HER+	Phase 3 trial	No conclusive result yet, although several adverse effects have been reported.	Cardiac disorders, anemia, nausea, fatigue, arthralgia, neuropathies, alopecia.	[36]
Pertuzumab plus trastuzumab plus taxane	HER-2+	Approved by the FDA	Improvement of the median survival and remarkable decrease in cardiac dysfunction risk. Overall response rate of 80%.	Asthenia, neuropathy, myelosuppression, febrile neutropenia, congestive heart failure.	[35]
Lapatinib plus trastuzumab and paclitaxel	HER-2+	Phase 3 trial	No conclusive results for breast cancer.	Anemia, diarrhea, nausea, fatigue, neuropathies, myalgia.	[37]
Bevacizumab plus nab-paclitaxel	TNBC	Phase 3 trial	Remarkable activity in metastatic TNBC without a significant benefit in overall survival.	Neutropenia, fatigue, and neuropathy.	[40]
Bevacizumab plus hormone therapy	HER-2+	Phase 3 trial	Better overall prognosis in patients with HER-2+	Arthralgia, hypertension, headache, fever.	[41]

TABLE 2 (Continued)

Combined therapy	Target	Status	Results	Side effects	References
			metastatic and nonmetastatic breast cancer.		
Pembrolizumab plus conventional chemotherapy and hormone therapy	ER+	Approved by the FDA	The addition of KEYNOTE-756 to chemotherapy significantly increased the pathological complete response rate in patients with early stage high-risk ER+/HER-2− breast cancer.	Safety was consistent with the known profiles of each regimen.	[80]
Margetuximab plus chemotherapy	HER-2+	Approved by the FDA	Results demonstrate a favorable benefit-risk profile for margetuximab plus chemotherapy.	Fatigue/asthenia, nausea, diarrhea, vomiting, constipation, headache, pyrexia, alopecia, abdominal pain, peripheral neuropathy, arthralgia/myalgia, cough, decreased appetite, dyspnea, Infusion-related reactions, palmar-plantar erythrodysesthesia, and extremity pain.	[44]
Nivolumab plus conventional chemotherapy and hormone therapy	ER+	Phase 3 trial	Not yet shown	Not yet reported	[81]
Pembrolizumab plus carboplatin and docetaxel	TNBC	Phase 2 trial	Neoadjuvant carboplatin and docetaxel plus pembrolizumab show encouraging pathological complete response and 3-year event-free survival.	The regimen was well tolerated, and immune enrichment, as identified by various biomarkers, was independently predictive of pathological complete response.	[82]
Pembrolizumab plus conventional chemotherapy	TNBC	Phase 3 trial	Among patients with early triple-negative breast cancer, the percentage with a pathological complete response was significantly higher among those who received pembrolizumab plus neoadjuvant chemotherapy than among those who received placebo plus neoadjuvant chemotherapy.	The incidence of treatment-related adverse events of grade 3 or higher was 78.0% in the pembrolizumab–chemotherapy group and 73.0% in the placebo–chemotherapy group.	[83]
Immune checkpoints inhibitors					
Atezolizumab plus nab-paclitaxel	HER-2	Approved by the FDA	40% reduced risk of disease progression or death.	Pneumonitis, hepatitis, colitis, and endocrinopathies.	[18]
Ipilimumab plus nivolumab	HER-2	Phase 2 trial	No conclusive results for breast cancer.	Respiratory disorders, hyperglycemia, hypertension.	[57]
Cancer vaccines					
Allogeneic large multivalent	Non-specific	Phase 2 trial	No conclusive results for breast cancer.	—	[70]

(Continues)

TABLE 2 (Continued)

Combined therapy	Target	Status	Results	Side effects	References
immunogen breast cancer vaccine plus aldesleukin					
Pelareorep plus paclitaxel	Non-specific	Phase 2 trial	Significant increase in the overall survival, but no significant difference in the progression-free survival of patients.	—	[74]
Pelareorep plus anti-PD-1	PD-1	Phase 2 trial	Improvement of the overall antitumor efficacy.	—	[74]

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HER-2, human epidermal growth factor receptor type 2 positive; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TNBC, triple-negative breast cancer.

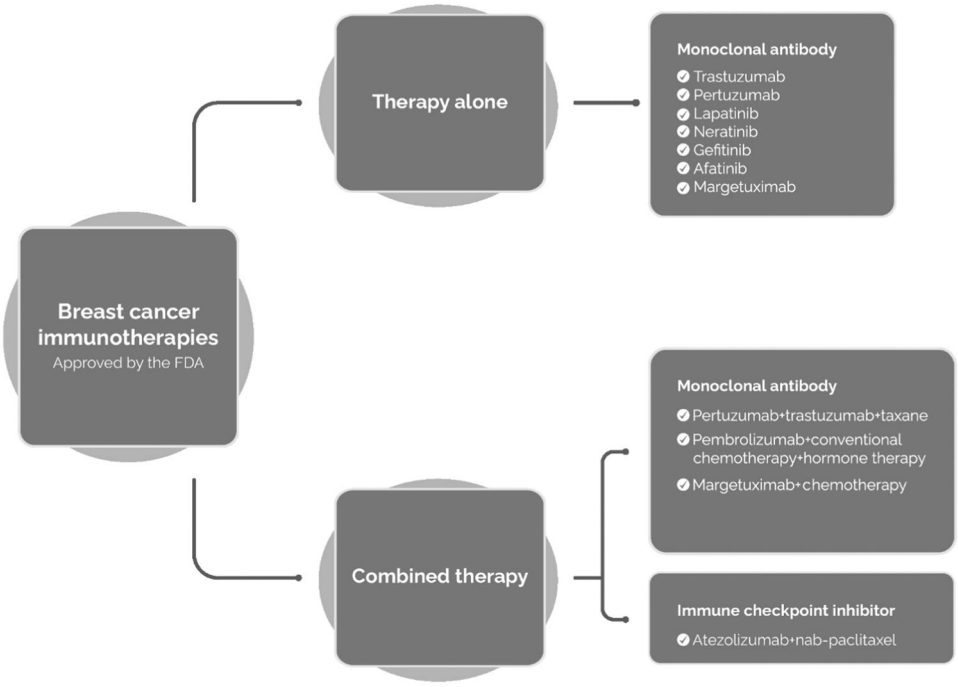

FIGURE 1 Summary of Food and Drug Administration (FDA)-approved immunotherapies for breast cancer.

4 | CONCLUSIONS

Over the last 10 years, the use of immunotherapies to treat primary tumors and prevent metastatic cancer has shown some success. Hence, several immunotherapy protocols have been approved for the treatment of different types of cancer such as metastatic kidney cancer, metastatic melanoma, nonsmall cell lung cancer, bladder cancer, Hodgkin's lymphoma, and other types of lymphoma, among others. However, the development of cancer immunotherapies is still a work in progress, and much more research is needed, particularly, for BC treatments, where the future of immunotherapy needs to be clarified [18, 19, 51].

mAbs were the first BC immunotherapy to be implemented, mainly toward the treatment of HER-2+ tumors. Nevertheless, the development of resistance and modest response rates remain the biggest barriers [34]. Likewise, the evaluation of CAR T-cell therapies, other than for HER-2+ tumors, needs to be better developed in BC [18, 19, 34] (Table 1). Moreover, cancer vaccines and OV therapies, either as monotherapy or in combination with other drugs, are being evaluated for the treatment of TNBC, but to date, there is no approved vaccine or OV therapy for BC [15, 63, 64, 66–68, 73, 76, 77].

Patients with TNBC have fewer therapeutic options compared to those with HER-2+ and HR+ BC

phenotypes. For this reason, much of the current scientific research in the field targets this specific condition. As a result, there are some promising outcomes using ICI therapies, and three different ICIs for the treatment of metastatic TNBC patients with PD-L1 overexpression have been approved by the FDA [18, 19, 39, 51, 53] (Tables 1 and 2) (Figure 1).

Currently, with plenty of studies on tumor escape mechanisms and advances in immunology, many new antitumor strategies aim to make immunotherapy a promising new treatment for BC. However, the appearance of severe adverse events is still the main limitation in the development of some immunotherapies. Thus, safer and more effective cancer immunotherapies still need to be conceptualized and developed or existing ones improved. In general, an urgent expansion in research into the complex interplay between the immune system and cancer cells is still required [18, 19, 23, 26].

AUTHOR CONTRIBUTIONS

Aixa Medina: Conceptualization (supporting); visualization (supporting); writing—original draft (lead). **Jeismar Carballo**: Conceptualization (lead); investigation (supporting); writing—original draft (supporting); review and editing (lead). **Eglys González-Marcano**: Review and editing (supporting). **Isaac Blanca**: Investigation (supporting); writing—review and editing (supporting). **Ana F. Convit**: Conceptualization (supporting); visualization (supporting), review and editing (supporting).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

Not applicable.

INFORMED CONSENT

Not applicable.

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