International Journal of Cancer Medicine

Review Article | Vol 6 Issue S8

Targeted and Immunotherapeutic Approaches in Breast Cancers

Rasit Dinc

Universidad Empresarial de Costa Rica, San Jose, San José, CR

Correspondence should be addressed to Rasit Dinc, Mutlukent Mah. 1961 Cd. No.27 06810 Cankaya/Ankara/Turkey

Received: September 10, 2023; Accepted: September 25, 2023; Published: September 30, 2023

ABSTRACT

Breast cancer is the one of leading causes of death and the most prevalent cancer worldwide. Currently, standard treatment options in breast cancers rely on surgery, chemotherapy, hormone therapy, and radiotherapy. Surgery, radiotherapy, chemotherapy have serious side effects. The most common subtype of breast cancer is hormone-receptor-positive, where hormone therapy is very effective. HER2+ breast cancers are another subtype, and anti-HER2 agents are also efficacious on that group. However, these agents are not effective in triple negative breast cancers in which hormone and HER2 receptors are negative. Again, resistance, which can be seen even in hormone and HER2 receptor positivity, is a common problem. Complex mechanisms play role in the resistance, such as epi(genetic) changes in signaling pathways that are important for the cancer cells survival and progression. Different treatment strategies, alone or combinations with each other, have been evaluated to overcome these problems. Recently, several agents blocking these targets have contributed significant clinical outcomes. In addition, although breast cancers are usually immunologically cold tumors, immunotherapeutic strategies have played an important role in the treatment of breast cancer. Several monoclonal antibodies, adoptive cell strategies, bioengineered immunotherapy and different vaccine applications have been explored for these purposes.

For selection of the most appropriate therapy options, molecular or immunological mechanisms should be considered. This review discusses major targeted therapies and immunotherapies based on ongoing therapy trials on breast cancers.

KEYWORDS

Targeted therapy; Immunotherapy; Vaccines; Breast Cancers; Pathways

INTRODUCTION

Globally, in 2020, 2.3 million women were diagnosed with breast cancer (BC) and 685,000 women died from BC. By the end of 2020, this disease is the most prevalent cancer worldwide, with 7.8 million women diagnosed in the last 5 years [1].

Common therapeutic applications are surgery, radiotherapy (RT), chemotherapy (CT), hormone therapy, targeted therapy, and immunotherapy in BCs [2-4]. The last two have received a lot of attention in recent years. Surgery, RT, CT have serious side effects, resulting in long hospital stays and huge costs. In addition, hormonal treatments are ineffective in triple negative BC and problems with treatment resistance may occur during

Citation: Rasit Dinc, Targeted and Immunotherapeutic Approaches in Breast Cancers. Int J Can Med 6(S8): 65-80.

treatment [5,6]. Again, there are no effective treatment options for metastatic BC [7]. In addition to surgery, it is generally given neoadjuvant (pre-operative) therapy to shrink a large tumor and/or adjuvant (post-operative) therapy to reduce the risk of recurrence [8]. The decision to go for neoadjuvant therapy is highly determined by the type of carcinoma and the tumor, node, metastasis (TNM) stage of the disease [5]. Due to still incurable, the treatment options are mostly palliative for metastatic BCs [3,5].

As shown in Table 1, the most common molecular subtype of BCs is the hormone receptor positive (HR+) group [9]. In the luminal B subtype, a small proportion of tumors could be HER2-positive. Thus, HER2-positive expression is not necessarily a universal finding in luminal B tumors. Rather, these tumors could be HER2-negative while expressing high Ki67 levels and more aggressive phenotypes compared to luminal A [9]. These subtypes are characterized by the expression of the estrogen receptor (ER+) and/or progesterone receptor (PR+) and generally respond to hormone therapy. The other subtype of BCs is human epidermal growth factor receptor 2+ (HER2+), which is higher proliferation marker [10,11]. The expression of hormone receptors is not a very robust prognostic factor, rather predictive for potential use of endocrine therapies. Not all HER2-targeted therapies available are monoclonal antibodies, small molecule tyrosine kinase inhibitors are also available [9,12].

	Luminal A-Like	Luminal B-Like	HER2-Overexpressing	Triple-Negative
ER	+	+	-	-
PR	≥20%	<20%	-	-
HER2	-	+	+	-
Frequency	30%-40%	20%-30%	12%-20%	15%-20%
Prognosis	Favorable	Intermediate	Unfavorable	Unfavorable/Poor

Table 1: The molecular subtypes and their features in BCs.

Fortunately, most BCs are sporadic which means they don't pass to the children from parents with BC. Hereditary BCs are only making up 5% to 10%. One of the most important causes for BCs is mutations that occurred in tumor suppressor genes such as BRCA1, BRCA2, and PALB2. The family history of the disease is also a very strong risk factor even in the absence of high prevalence gene mutations [13].

ER and HER2 are the best-determined targets for treatment of BCs. The hormone therapies and HER2-targeted agents have shown effective results for HR+ and HER2+ BCs, respectively [11,14]. Nonetheless, these agents aren't effective in triple-negative breast cancers (TNBC). In addition to that problem, acquired resistance to these agents is frequent even the presence of ER and HER2 [11]. Complex molecular mechanisms including several aberrations and signaling pathways are involved in endocrine resistance. Of them, activation of PI3K/Akt/mTOR pathway and cyclin D/CDK/pRb pathway, ESR1 gene mutations, cross talk between ER and growth factors receptors signaling, and epigenetic alterations are well-defined mechanisms [15-18]. The molecular mechanisms of resistance to monoclonal antibodies are also multifactorial, including downregulation or loss of HER2 expression, high p95HER2 expression, loss of PTEN and so on [19].

To overcome the increasing drug resistance or side effects, new therapeutic strategies are urgently needed. By selecting the most appropriate molecular mechanisms/pathways, targeted therapeutics should be considered as viable therapeutic options with fewer side effects against TNBC and resistant ER and HER2+ BCs [5,19].

In this review, it was discussed major targeted therapies and immunotherapies based on ongoing therapy trials on BCs. It also highlights clinical significance of the combination therapy options, including targeted or immune therapy.

TARGETED THERAPY IN BREAST CANCERS

Targeted therapy in cancer therapy is the inhibition of the growth of cancer cells through its use in certain ways [19]. Compared to CT, hormone therapy is newer, more effective treatments that can attack certain breast cancer cells with less harm on healthy cells [20].

Like many other malignancies, BC is also a very heterogeneous cancer. For optimal treatment selection, the BC subtype must be determined [21]. Not only their efficacy, but also the safety, dosage, and route of administration of the targeted agents must be thoroughly evaluated. For these reasons, the decision to go for alternative agents targeting different pathways, which are important for the survival and spread of BCs, can overcome resistance and improve the clinical situation in the optimum situation [5,19].

Targeted Therapy in Hormone Receptor (HR)+ BCs

HER2-targeted agents in HR+HER+ BCs

ER takes an important place in proliferation, survival, and invasion of BC cells. For treatment of HR+ BCs, endocrine therapy targeting estrogen/ER pathway has been most successful. But resistance to endocrine therapy is an important problem, in which complex mechanisms play role. Activation of certain estrogen-independent growth and survival signaling pathways based on genomic or epigenetic variations has been associated with endocrine resistance. These pathways have been considered as therapeutic targets [22].

About 10% of ER+BCs express HER2 (ERBB2) gene, which is the one of four subunits (HER1, HER2, HER3, HER4) of HER [23]. This patient population with ER+HER+ BC (Table 1, Luminal B) is associated with a higher risk of relapse group than the ones don't express HER2 (ER+HER-) (Table 1, Luminal A). This may be due to incomplete cell cycle arrest, which is perhaps stopped under treatment with endocrine agents alone. The various studies indicated that adding HER2-targeted agents to the hormonal therapy is more effective in the ER+HER+ patient population [24].

In a study compared the efficacies of trastuzumab (an anti-HER2 monoclonal antibody) combined with anastrozole and anastrozole alone, the combined group demonstrated a longer progression-free survival (PFS) (4.8 versus 2.4 months) in the metastatic ER+HER+ patient population. This combination also displayed a higher clinical benefit rate (CBR) (42.7% vs 20.3) [25]. In another study evaluated the combination of letrozole and lapatinib (a HER1/HER2 kinase inhibitor) and letrozole alone, it demonstrated a significant difference in PFS (8.2 vs 3 months) and overall response rate (ORR) (28% *vs*. 15%) [26].

Adding trastuzumab to standard hormonal therapy resulted in reduction of relapse in treatment ER+HER+ BCs [27,28]. Thus, the addition of HER2-targeted agents to the hormonal therapy must be a standard application for these population.

PI3K/Akt/mTOR pathway in HR+ BCs

The phosphoinositide 3 kinase (PI3K)/Akt/target of rapamycin (mTOR) pathway is a cardinal pathway in the transduction of cell growth and proliferation in BCs. This pathway also plays a significant role in endocrine resistance [29,30]. The PI3K heterodimer, with the regulatory subunit (p85) regulating the activation of the catalytic subunit (p110), has the central role in this pathway. Gain-of- function mutation in PIK3CA-subunit gene occurs at approximately one-third of ER+BCs. This mutation increases cell survival in HR+ BCs [31]. Akt can activate the ER pathway in an estrogen-independent condition [32]. mTOR, which is a serine/threonine protein kinase, takes place downstream of PI3K and Akt. Of its subunits, mTORC1 is the target of rapamycin/rapamycin

analogs. The other subunit mTORC2 plays role in AKT activation [32].

Suppressing or downregulating the PI3K/Akt/mTOR pathway could be considered as one of the potential strategies to prevent BC [7]. Everolimus treatment modulates PI3K/AKT/mTOR signaling pathways, leading to suppress growth and aggression of breast cancer cells [33]. Inhibition of PI3K or AKT signaling reduced cancer cell growth and survival [31,33]. As a part of this pathway, combination of mTOR inhibitors with endocrine therapy is also able to overcome endocrine resistance [32]. It has also been found that the PI3K/Akt/mTOR pathway is associated with trastuzumab resistance in HER2+ BC. The studies implied that inhibitors of the pathway can synergistically act with trastuzumab in resistant BCs [29]. Numerous inhibitors against PI3K/Akt/mTOR pathway are in different phases (Phase I, II or III) of clinical trial [Table 2]. They can be used as pan - (like pan-PI3K), dual (PI3K and mTOR inhibitors), or isoform-specific (like mTORC1 isoform inhibitors). These agents are generally well tolerated and are being evaluated in clinical trials for suitability and can be used in combination with other targeted agents, endocrine therapy or cytotoxic agents [19,32].

There are several other factors affecting the PI3K/Akt/mTOR pathway. These may also be considered for targeted therapy. For example, phosphatidylinositol 3,4-bisphosphate (PIP2) and 3,4,5-triphosphate (PIP3) play role in activation of this pathway. In contrast to these, phosphoinositide-dependent protein kinase (PTEN) has a tumor suppressor role by blocking PI3K/AKT/mTOR pathway via inhibition of the transition from PIP2 to PIP3. Because in regular way, the stimulating factors such as growth factors and cytokines activate PI3K leads to transition from PIP2 to PIP3. PIP3 generation results in a conformational change of AKT [7,34].

Inhibitors	Target	Agent
PI3K inhibitor	PI3Kα	Alpelisib*
		GDC-0077
		Serabelisib
	PI3Kβ	AZD-8186
	pan-PI3K	Pictilisib
AKT inhibitor	AKT	Uprosertib
	ATP binding pocket	Ipatasertib
		Capivasertib
mTOR inhibitor	mTORC1	Everolimus*
		WYE-687
PI3K/mTOR dual inhibitor	PI3K/mTOR	Apitolisib
		Bimiralisib
		Dactolisib
		XL765

Table 2: Example for inhibitors targeting the PI3K-AKT-mTOR pathway.*FDA Approved.

CDK4/6 inhibitors in HR+ BCs

The G1-to-S phase transition is controlled by cyclin-dependent kinases 4/6 (CDK4/6). Thus, the action of CDK4/6 is vital for cell proliferation [35]. CDK4/6 are activated once binding to D-type cyclins. Then they phosphorylate the retinoblastoma-associated protein (pRb), which releases the E2F transcription factors and activates expression of genes required for G1-to-S phase transition [19].

CDK4/6-D1-type cyclin relation is associated with endocrine resistance and poor clinical outcome. The CDK4/6 inhibitors reduce the cell cycle through disturbing CDK4/6-D1-type cyclin relation [35].

Of several CDK inhibitors, palbociclib, ribociclib, and abemaciclib have demonstrated efficacy and tolerable toxicity profile in clinical trials of BCs treatment. They have recently been approved by the US Food and Drug Administration (FDA) and European Medicine Agency (EMA) for HR-positive advanced or metastatic BC

[15,36]. Especially in the treatment of HR+ HER2- BC patients, the CDK4/6 inhibitors ensured a major advancement [15].

Histone deacetylase inhibitors in HR+ BCs

Multidrug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP) transporters are key efflux transporters that mediate the extrusion of drugs and toxicants in cancer cells and healthy tissues. This led to hormonal resistance and cell proliferation. The studies have demonstrated that inhibition of histone deacetylases (HDACs) modulates MDR1 and BCR transporters [37]. The exact rational HDAC inhibitors (known to be epigenetic modifiers) as potential targeted treatments in breast cancer is not clear [38]. Fortunately, this impact of HDAC inhibitors is less on normal tissues. HDAC inhibitors have also been shown to upregulate various tumor suppressor and proapoptotic genes to prevent cancer cell proliferation [37]. Consequently, HDAC inhibitors in some studies suggested that HDAC inhibition may be an important target to overcome resistance in ER+ BCs [19]. Even, several HDAC inhibitors such as romidepsin, suberoylanilide hydroxamic acid, belinostat, and panobinostat have been approved for some other malignancies [37].

Targeted Therapy in Human Epidermal Growth Factor Receptor (HER2)+ BCs

Approximately one-fifth of BC patients overexpress HER2 which is associated with the more aggressive phenotype [19]. Anti-HER2 antibody trastuzumab, FDA-approved for both metastatic and adjuvant therapy, has contributed to significant improvement in the outcome of this disease, by disrupting HER signaling and inducing antibody-dependent cell-mediated cytotoxicity (ADCC) [38]. Unfortunately, an important challenge is primary and acquired resistance to trastuzumab in HER2+ BC patients [39].

Different mechanisms are considerable as responsible for trastuzumab resistance. A crucial role in trastuzumab resistance is persistent activation of the PI3K/AKT signaling pathway because of several mechanisms such as activating mutations in the p110α subunit of PI3K, inactivating mutations in PTEN and up-regulation of Rac1 [40-42]. Hyperactivation of other tyrosine kinase receptors, such as insulin-like growth factor-I receptor (IGF-IR), is compensation pathway for the inhibition of HER2 signaling by trastuzumab [42]. These mechanistic pathways could be considered as therapeutic modalities to overcome trastuzumab resistance [39].

In addition to trastuzumab, several monoclonal antibodies against HER2 receptor and some inhibitor agents against various mechanisms which favor BC have been approved by FDA (Table 3). But their major clinical effects on clinical outcome occur when they are applied as combinational therapies. Combinational therapy attempts play a critical role to overcome the intrinsic or acquired resistance to trastuzumab. In this regard, trastuzumab monotherapy is not the current standard of care in BC therapy [43,44].

Agents	Proprietary Name	Agents	Proprietary Name
Monoclonal Antibodies		Antibody/drug conjugates	
Trastuzumab	Herceptin	Ado-trastuzumab emtansine	KADCYLA
Pertuzumab	PERJETA	Fam-trastuzumab deruxtecan	ENHERTU
Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf	PHESGO	Tyrosine kinase inhibitors	
Margetuximab-cmkb	MARGENZA	Lapatinib	TYKERB
		Neratinib	NERLYNX
		Tucatinib	TUKYSA

Table 3: Various FDA-approved HER2-directed mono- or combinational therapies.

Targeted Therapy in Triple-negative BCs (TNBCs)

TNBCs don't have receptor expressions for estrogen and progesterone, as well as there is little or no HER2 protein production. TNBC accounts for about 10-15% of all BCs and is frequently associated with an unfavorable prognosis [45].

Due to the molecular heterogeneity and complex biology, unlike ER+ and/or HER2+, development of the targeted agents in TNBC is problematic. There is also lack given specific target to threaten it. Even so, several promising pathways and agents are being investigated including anti-angiogenic agents and inhibitors against EGFR, PARP, PI3K, Src or CDKs [19].

Anti-angiogenetic agents in TNBCs

Angiogenesis is one of the fundamental steps for tumoral growth and metastasis [12]. Vascular endothelial growth factors/receptors (VEGFs/VEGFRs), particularly VEGF-A, are among the most prominent factors in angiogenesis process, meanwhile in inducing pathological angiogenesis. TNBC is associated with a higher level of intratumor VEGF-A expression than the other BC subtypes [12,46]. In this context, ligand blockade between VEGF and the VEGFR axis provides a rationale for evaluating potential anti-angiogenic agents. Bevacizumab, the most widely studied anti-angiogenic drug in BCs, is a recombinant humanized monoclonal antibody against all known isoforms of VEGF-A [47]. Ramucirumab is another the monoclonal antibody with anti-angiogenetic potential against the VEGFR2 external domain [48].

VEGFRs family is closely related to receptor tyrosine kinase (RTK). RTK inhibitors, such as axitinib, pazopanib, sorafenib, and sunitinib have anti-angiogenic effects. More than ten angiogenesis inhibitors have been approved by the US FDA. Some of them, such as cetuximab, vandetanib, and erlotinib show dual effect on both VEGF and EGF pathways [48].

The anti-angiogenetic agents have demonstrated good clinical effects in BC patients, particularly when used in combination standard chemotherapies [19,48].

PARP inhibitors in TNBCs

The poly (ADP-ribose) polymerases (PARPs) are a group of enzymes important in many cellular processes, including repairment of single-strand DNA breaks. PARP inhibition prevents repair of single stranded breaks and instead leads to double stranded breaks. This induces synthetic lethality in BRCA1- and BRCA2-related tumor cells. Because BRCA mutated cells cannot be repaired via the homologous recombination pathway [19,49].

PARP inhibitors have shown promising anti-cancer activity in several studies. Various PARP inhibitors are available FDA-approved as monotherapy including olaparib, rucaparib, niraparib, talazoparip [49].

On using PARP inhibitors, another treatment strategy is combination of the PARP inhibitors with cytotoxic CT, anti-angiogenesis agents, RT, immune therapy, or by inhibiting proteins in the DNA damage-response pathway. The combination promises to augment efficacy of PARP inhibition and overcome resistance mechanisms [49].

Other targets in TNBCs

Due to overexpression of EGFR in basal-like type of TNBCs and PI3K pathway activation as result of loss of negative regulators including PTEN, EGFR and PI3K pathway are attractive therapeutic targets [19].

SRC is broadly overexpressed in some BCs subtype and can crosstalk with HER2 when facilitated by other molecules. This mechanism plays a role in oncogenic process. Dasatinib is a SRC family kinase inhibitor, and its antitumor effect has been observed on some subtypes of TNBC. Like these, dinaciclib is a potent inhibitor of some CDK isoforms and was lethality in MYC-overexpressing TNBC [50].

IMMUNOTHERAPY IN BREAST CANCERS

In immunotherapy, it is used to protect the body's natural immune system against cancer by enhancing its ability to attack cancer cells [51]. Unlike some other cancers such as melanoma and renal cell carcinoma to immunotherapies responsive, BC has not traditionally been considered immunogenic. Hence, the drug development for immunotherapy purposes in BCs has been slower than in the other cancers. Even so, the immune system may be effective on primary tumor growth and prevention of metastases in BCs. In BCs, some studies showed that the standard therapies such as anthracyclines and trastuzumab modulate immunity as part of their mechanism of action [52]. Again, it has been reported a significant correlation between increased tumor-infiltrating lymphocytes (TILs), especially CD8+ T lymphocytes, and better clinical outcomes in early-stage BCs [52,53].

Besides, HR+ BCs are usually immunologically cold tumors with the TILs. HER2+ BCs respond well to HER2-targeted therapies, which because of partly mediated by immune effector mechanisms. TNBC is considered as the most immunogenic subtype of BCs. This promise for the development of immunotherapeutic agents [3].

Intratumoral CD8+ T cells infiltrates are generally associated with good prognosis in BCs. Unlike CD8+ T cells, CD4+ T cells associated with inconsistent result, but usually with poor prognosis. The poor prognosis is generally attributed to CD4+ FOXP3+ T regulatory cells (Tregs).

Macrophage infiltrates in BCs frequently associated with a poor clinical outcome. In contrast to M1-type macrophages inducing Th1 response, M2-type macrophages in tumoral microenvironment inhibit the Th1 response by secreting immunosuppressor molecules such as IL-10 and TGF-β. M2 macrophages are also associated with progression, invasion and metastasis of the tumor, as well as secreting angiogenic factors such as VEGF [54]. Like TAMs, myeloid-derived sup- pressor cells (MDSC) have also increased the growth and metastasis of BC [55].

Cancer-associated fibroblasts (CAFs) have an important role in reducing anti-tumor immunity. They contribute to proliferation and invasion of the tumor cells, tumoral angiogenesis, shaping the extracellular matrix (EMC) that facilitate tumor progression, and immunosuppression in tumor microenvironment [56-58].

The adaptive immune system is regulated by different immune checkpoints, mainly cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and PD-1/PD-L1. These checkpoints are important in self-tolerance and in regulation of the anti-tumoral immune response [54].

Cancer immunotherapy covers a broad spectrum, from an approach that focuses on attacking tumor cells to a strategy that targets the tumor microenvironment (TME) [59]. This article does not focus on approaches targeting TME.

Immunotherapy in Triple-Negative and HER2+ BCs

The characterization of the molecular portrait led to use the novel targeted therapy strategies. Like that, the immune profile of BCs has opened a door for immunotherapeutic strategies. Compared to standard CT, the immune-based approach has generally been demonstrated to improve progression-free survival (PFS) and overall survival (OS) and the pathological complete response rate (PCRR) in BCs [60-62]. TNBC is considered as the most immunogenic subtype of BCs, as well as lack of therapeutic targets in this group. Thus, the studies aiming immunotherapy mainly focused on TNBC [3,63].

There are some strategies for immunotherapeutic purpose [62]:

1. **Passive immunotherapy:** This strategy includes the infusion of monoclonal antibodies (moAbs) which targeting cancer-specific antigen. Consequently, it

yields death of the cancer cells by the lysis or ADCC way. Another option of this strategy is the systemic administration of recombinant cytokines.

2. **Active immunotherapy**: This strategy consists of the administration of immune check point inhibitors (ICIs) and vaccines.
3. **Adoptive immunotherapy:** In order to eliminate cancer cells, adoptive immunotherapy exploits immune system cells such as autologous T cells.

Immune Checkpoints Inhibitors (ICIs)

CTLA-4 acts as a suppressive molecule able to inhibit both the proliferation and the effector functions of T cells [64]. PD-1 is an inhibitory receptor acting as a suppressor of both adaptive and innate immune responses [65]. CTLA-4 overexpression is observed in about 50% of BC patients [66]. PD-L1 expression has been associated with positive lymph node metastasis, higher histological grade, larger tumor size, triple-negative subtype, and HER2 positivity [5]. Immune checkpoints inhibitors (ICIs) have been widely studied in BC treatments. PD-L1 has been widely used [63]. These inhibitors block CTLA-4 and/or PD-1/PD-L1, allowing effector T cells to attack the tumor [66,67].

The immune-based approach has generally demonstrated effective clinical outcomes. However, many patients do not benefit from immunotherapy. To increase immunogenicity in BC, several combination strategies have been recommended, including anti-PD-1/PD-L1 or other immune modulatory molecules [60,62]. Atezolizumab and pembrolizumab are the FDA- and the EMA-approved ICIs in combination with CT for TNBC patients. Pembrolizumab was also approved by the FDA as a single agent for nine cycles for patients with high-risk stage II or III TNBC after surgery [62,68].

While atezolizumab is an anti- PD-L1 moAb, pembrolizumab is an anti-PD-1 moAb. Thus, both block the interaction between PD-1 and PD-L1 [69,70].

Both atezolizumab and pembrolizumab provided successful clinical activity with an acceptable safety profile in single agent immunotherapy trials. Moreover, their combination with CT, RT or targeted agents or different ICIs enhanced the immune responses through synergistic effects. These observations have promoted the development of novel therapeutic strategies, particularly in combination [60,61,69-71].

Several other ICIs such as nivolumab (an anti-PD-1 moAb) as well as avelumab and durvalumab (anti-PD-L1 moAbs) are under investigation for efficacy and safety, alone or in a combination. Unlike the others, avelumab provokes ADCC more [72-74].

Most of the studies on the effects of anti-CTLA4 inhibitors in breast cancer combined CTLA4 inhibitors with other treatments such as aromatase inhibitors, RT, and CT [5,66].

Despite the encouraging results, many patients do not respond to immunotherapy in the initial or ongoing steps of the therapy. As a result of multifaceted escaping mechanisms driven by either intrinsic factors related with tumor cell or extrinsic factors that involve the TME, tumor resistance develops against immunotherapy [63]. Variations in the gene expressions (for ex., affect PD-1 or IFN-γ), reduction/ loss of tumor antigens expression, reduction/loss of MHC expression, release of immune suppressive cytokines (i.e., IL-10, TGF-β) are among the major intrinsic factors that play important role in resistance against immunotherapy [75-77]. The migration of Tregs, MDSCs or TAM (particularly M2 macrophages) to TME, the PD-L1/CTLA-4 upregulation, secretion of immunosuppressive factors (such as TGF-β and IL-10) [75-79] are extrinsic factors operating within the TME.

In order to overcome the resistance to ICIs, novel immunotherapeutic strategies are being explored.

Adoptive Cell Therapy (ACT)

Different strategies have been evaluated for ACT. As one of the important, autologous or allogenic TIL-based therapy has been tested for all BC subtypes. In this strategy, the isolated TILs from the TME are reinfused back into the patient after ex-vivo activation and expansion by using IL-2 [80].

But many patients don't respond to TIL-based therapy. In order to overcome these obstacles, chimeric antigen receptor-T cell (CAR-T) therapy strategy appears to be important among other alternative strategies [5,62]. CAR-T cell therapy relies on modifying T cell receptors (TCR) to give T cells the new ability to target a specific protein. Several CAR-T cells have been engineered to target different breast cancer antigens such as HER2, EGFR, HGFR/cMET, ROR1, AXL, MUC1, MSLN, CD70, CD133, CD44v6, EpCAM, CSGP4, ICAM1, TEM8, TROP2, FRα, GD2, NKG2D, CEA [81].

The results of CAR-T preclinical trials were promising in BCs; however, the therapy requires more optimization by testing their safety and activity.

Vaccines

Cancer vaccines represent a therapeutic approach to induce a durable immunologic response to eradicate tumor cells. In BCs, peptide/protein-based, cell-based and gene-based vaccination strategies have been evaluated in clinical trials. But none has led to significant benefits. Despite the disappointing results, various approaches have been explored to raise the efficacy of cancer vaccines such as combination with anti-HER2 monoclonal antibodies or immune checkpoint blockade [82]. In mice models, the combination of DC-based vaccines with PD-1/PD-L1 inhibitors has produced measurable antitumor activity and survival benefits [83].

Peptide-based vaccines focus on eliciting antigen-specific T-cell response against overexpressed antigens on tumor cells such as HER2 and MUC1 in breast cancer [84,85]. This group vaccines commonly use a cytokine adjuvant to increase the efficacy [86].

Gene-based vaccines can be either recombinant tumor-associated antigens expressed by viral vectors/bacterial plasmids or DNA vaccines. DNA vaccines are frequently combined with immunostimulatory molecules, such as toll-like receptors (TLR). Both the recombinant and DNA vaccines help to activate targeted cellular and humoral immunity [4,87].

In the cell-based vaccination, whole tumor lysates are used instead of a specific antigen for their immunogenicity. Whole-cell tumor vaccines may induce a broader immune response [88,89].

In another cell-based vaccination, the patient is given in vitro activated DCs against BC cell antigens. Activated DCs prime and activate CD8 T cells specifically for tumoral antigens [90].

Combination Therapy in BCs

Various strategies are under development to increase cancer targeting efficiency and disrupt metastasis [91-93].

BC therapy necessitates a multidisciplinary approach involving surgery, RT, CT, hormone therapy, targeted therapy, and immunotherapy. To ensure a good quality of life from BC treatments, it is aimed to maximize therapeutic efficacy and to minimize undesirable effects such as recurrence, resistance and toxic effects. The carefully chosen combination of therapeutic interventions appears to offer this potential opportunity [94].

Combination therapy attempts play a critical role in both eliminating undesirable effects and increasing the synergistic effect. The proper identification of the subtypes

and molecular pathways of BC would provide to select the best therapeutic strategy, alone or along with each other [29,43,87,95].

Numerous combination CT regimens have been evaluated in BC treatment so far such as CT plus immunotherapy, CT plus targeted therapy, targeted therapy plus immunotherapy, immunotherapy plus immunotherapy (Figure 1) [95,96].

Figure 1: A schematic representation of the major combination therapy options in BCs (Drawn using the information in references. Various dual or multiple combination options are available for breast cancer: for examples, TT+IT, TT/IT+ST, TT/IT+ST, ST+CT, ST+RT, ST+HT (dual) or ST+CT+RT (multiple), as well as targeted therapies directing to the different points on same pathway.
ST: Surgical Therapy; RT: Radiotherapy; CT: Chemotherapy; HT: Hormonal Therapy; TT: Targeted Therapy; IT: Immunotherapy

Abscopal Effect

Abscopal effect in oncology is a term used to describe systemic, non-target effect, antitumor effects triggered by local applications of radiation targeting local tumors. Its mechanism has not yet been fully resolved and in fact the term refers to any biological effect triggered by local therapy [97].

In the mechanisms of the abscopal effect, such studies suggest that the antitumor immune response induced by local RT is one of the key factors. The RT-induced local tissue destruction results in antigenic spreading. The antigenic spreading enhances the secretion of chemoattractant molecules, namely CXCL16, which activate CD8 effector T cells [98].

The combination ICIs with RT ensured a longer tumor growth delay, and a better long-term survival in mice [99]. This synergistic strategy may be an important treatment option for incurable metastatic BCs and for converting non-responders to immune therapy to responders.

CONCLUSION

Breast cancers are highly heterogeneous with several subtypes. They are generally immunologically cold tumors. Each subset of breast cancer has different prognostic features and differs from each other in terms of therapeutic approach. With associated complex mechanisms, such as epi(genetic) changes in signaling pathways important for cancer cell survival and progression, resistance to therapeutic agents is a common problem. However, significant advances have been made in the targeted and immunotherapy of BCs in recent years.

Knowledge of its molecular or immunological mechanisms plays a critical role in choosing the most appropriate treatment option. Several agents that block key pathways for breast cancer have contributed to significant clinical outcomes. Some of them, even immunotherapeutic, have recently been approved by the US FDA and EMA. Taken together, these developments in targeted therapies and immunotherapies hold promise for future clinical trials targeting breast cancers.

LIMITATION

This review is not a systematic review study and is vulnerable to selection bias. For the best treatment modality for BC patients, it is needed further trials. In the selection of the therapy strategy should be considered

subtypes, stages and molecular characteristic of BC, suffer from which the patient.

FUNDING

The authors received no extramural funding for the study.

CONFLICTS OF INTEREST

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Breast cancer (2021) The world health organization.
2. Alshareeda AT, Khatijah MN, Al-Sowayan BS (2023) Nanotechnology: A revolutionary approach to prevent breast cancer recurrence. Asian Journal of Surgery 46(1): 13-17.
3. Esteva FJ, Hubbard-Lucey VM, Tang J, et al. (2019) Immunotherapy and targeted therapy combinations in metastatic breast cancer. The Lancet Oncology 20(3): e175-e186.
4. Allahverdiyev A, Tari G, Bagirova M, et al. (2018) Current approaches in development of immunotherapeutic vaccines for breast cancer. Journal of Breast Cancer 21(4): 343-353.
5. Shimada H, Fukagawa T, Haga Y, et al. (2021) Clinical TNM staging for esophageal, gastric, and colorectal cancers in the era of neoadjuvant therapy: A systematic review of the literature. Annals of Gastroenterological Surgery 5(4): 404-418.
6. Bui TBV, Burgering BM, Goga A, et al. (2022) Biomarkers for cyclin-dependent kinase 4/6 inhibitors in the treatment of hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced/metastatic breast cancer: Translation to clinical practice. JCO Precision Oncology 6(1): e2100473.
7. Naeem M, Iqbal MO, Khan H, et al. (2022) A review of twenty years of research on the regulation of signaling pathways by natural products in breast cancer. Molecules 27(11): 3412.
8. Agostinetto E, Nader-Marta G, Paesmans M, et al. (2022) ROSALINE: A phase II, neoadjuvant study targeting ROS1 in combination with endocrine therapy in invasive lobular carcinoma of the breast. Future Oncology 18(22): 2383-2392.
9. Cheang MC, Chia SK, Voduc D, et al. (2009) Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. JNCI: Journal of the National Cancer Institute 101(10): 736-750.
10. Tsang J, Tse GM (2020) Molecular classification of breast cancer. Advances in Anatomic Pathology 27(1): 27-35.
11. Prat A, Cheang MCU, Martín M, et al. (2013) Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal A breast cancer. Journal of Clinical Oncology 31(2): 203-209.
12. Zarychta E, Ruszkowska-Ciastek B (2022) Cooperation between angiogenesis, vasculogenesis, chemotaxis, and coagulation in breast cancer metastases development: Pathophysiological point of view. Biomedicines 10(2): 300.
13. Apostolou P, Fostira F (2013) Hereditary breast cancer: The era of new susceptibility genes. BioMed Research International: 747318.
14. Park IH, Ro J, Lee KS, et al. (2010) Phase II parallel group study showing comparable efficacy between premenopausal metastatic breast cancer patients treated with letrozole plus goserelin and postmenopausal patients treated with letrozole alone as first-line hormone therapy. Journal of Clinical Oncology 28(16): 2705-2711.
15. Piezzo M, Cocco S, Caputo R, et al. (2020) Targeting cell cycle in breast cancer: CDK4/6 inhibitors. International Journal of Molecular Sciences 21(18): 6479.
16. Maurer C, Martel S, Zardavas D, et al. (2017) New agents for endocrine resistance in breast cancer. The Breast 34: 1-11.

17. Matikas A, Foukakis T, Bergh J (2017) Tackling endocrine resistance in ER-positive HER2-negative advanced breast cancer: A tale of imprecision medicine. Critical Reviews in Oncology/Hematology 114: 91-101.
18. Wang ZH, Zheng ZQ, Jia S, et al. (2022) Trastuzumab resistance in HER2-positive breast cancer: Mechanisms, emerging biomarkers and targeting agents. Frontiers in Oncology 12: 1006429.
19. Wu X, Yang H, Yu X, et al. (2022) Drug-resistant HER2-positive breast cancer: Molecular mechanisms and overcoming strategies. Frontiers in Pharmacology 13: 1012552.
20. Parati MC, Pedersini R, Perego G, et al. (2022) Ribociclib in the treatment of hormone-receptor positive/her2-negative advanced and early breast cancer: Overview of clinical data and patients selection. Breast Cancer: Targets and Therapy: 101-111.
21. Ruddy KJ, Ganz PA (2019) Treatment of nonmetastatic breast cancer. JAMA 321(17): 1716-1717.
22. Saatci O, Huynh-Dam KT, Sahin O (2021) Endocrine resistance in breast cancer: From molecular mechanisms to therapeutic strategies. Journal of Molecular Medicine 99(12): 1-20.
23. Ellis MJ, Tao Y, Young O, et al. (2006) Estrogen-independent proliferation is present in estrogen-receptor HER2-positive primary breast cancer after neoadjuvant letrozole. Journal of Clinical Oncology 24(19): 3019-3025.
24. Kim SR, Paik S (2011) Genomics of adjuvant therapy for breast cancer. The Cancer Journal 17(6): 500-504.
25. Kaufman B, Mackey JR, Clemens MR, et al. (2009) Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2–positive, hormone receptor–positive metastatic breast cancer: Results from the randomized phase III TAnDEM study. Journal of Clinical Oncology 27(33): 5529-5537.
26. Marcom PK, Isaacs C, Harris L, et al. (2007) The combination of letrozole and trastuzumab as first or second-line biological therapy produces durable responses in a subset of HER2 positive and ER positive advanced breast cancers. Breast Cancer Research and Treatment 102: 43-49.
27. Balic M, Rinnerthaler G, Bartsch R (2021) Position paper on the value of extended adjuvant therapy with neratinib for early HER2+/HR+ breast cancer. Breast Care 16(6): 664-676.
28. Lebert J, Lilly EJ (2022) Developments in the management of metastatic HER2-positive breast cancer: A review. Current Oncology 29(4): 2539-2549.
29. Nahta R (2012) Pharmacological strategies to overcome HER2 cross-talk and Trastuzumab resistance. Current Medicinal Chemistry 19(7): 1065-1075.
30. O'Regan R, Ozguroglu M, Andre F, et al. (2013) Phase III, randomized, double-blind, placebo-controlled multicenter trial of daily everolimus plus weekly trastuzumab and vinorelbine in trastuzumab-resistant, advanced breast cancer (BOLERO-3). Journal of Clinical Oncology 31: 15_suppl: 505.
31. Crowder RJ, Phommaly C, Tao Y, et al. (2009) PIK3CA and PIK3CB inhibition produce synthetic lethality when combined with estrogen deprivation in estrogen receptor–positive breast cancer. Cancer Research 69(9): 3955-3962.
32. Paplomata E, O'Regan R (2014) The PI3K/AKT/mTOR pathway in breast cancer: Targets, trials and biomarkers. Therapeutic Advances in Medical Oncology 6(4): 154-166.
33. Du L, Li X, Zhen L, et al. (2018) Everolimus inhibits breast cancer cell growth through PI3K/AKT/mTOR signaling pathway. Molecular Medicine Reports 17(5): 7163-7169.
34. Xu Z, Chu M (2022) Advances in immunosuppressive agents based on signal pathway. Frontiers in Pharmacology 13: 917162.

35. Shah M, Nunes MR, Stearns V (2018) CDK4/6 inhibitors: Game changers in the management of hormone receptor–positive advanced breast cancer?. Oncology (Williston Park, NY) 32(5): 216.
36. Lynce F, Shajahan-Haq AN, Swain SM (2018) CDK4/6 inhibitors in breast cancer therapy: Current practice and future opportunities. Pharmacology & Therapeutics 191: 65-73.
37. You D, Richardson JR, Aleksunes LM (2020) Epigenetic regulation of multidrug resistance protein 1 and breast cancer resistance protein transporters by histone deacetylase inhibition. Drug Metabolism and Disposition 48(6): 459-480.
38. Ahuja N, Easwaran H, Baylin SB (2014) Harnessing the potential of epigenetic therapy to target solid tumors. The Journal of Clinical Investigation 124(1): 56-63.
39. Tong CW, Wu M, Cho W, et al. (2018) Recent advances in the treatment of breast cancer. Frontiers in Oncology 8: 381990.
40. Nagata Y, Lan KH, Zhou X, et al. (2004) PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. Cancer Cell 6(2): 117-127.
41. Berns K, Horlings HM, Hennessy BT, et al. (2007) A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer. Cancer Cell 12(4): 395-402.
42. Lu Y, Zi X, Zhao Y, et al. (2001) Insulin-like growth factor-I receptor signaling and resistance to trastuzumab (Herceptin). Journal of the National Cancer Institute 93(24): 1852-1857.
43. Maadi H, Soheilifar MH, Choi WS, et al. (2021) Trastuzumab mechanism of action; 20 years of research to unravel a dilemma. Cancers 13(14): 3540.
44. Salkeni MA, Rizvi W, Hein K, et al. (2021) Neu perspectives, therapies, and challenges for metastatic HER2-positive breast cancer. Breast Cancer: Targets and Therapy: 539-557.
45. Masoud V, Pagès G (2017) Targeted therapies in breast cancer: New challenges to fight against resistance. World Journal of Clinical Oncology 8(2): 120.
46. Al Kawas H, Saaid I, Jank P, et al. (2022) How VEGF-A and its splice variants affect breast cancer development–clinical implications. Cellular Oncology 45(2): 227-239.
47. Hawighorst T, Skobe M, Streit M, et al. (2002) Activation of the tie2 receptor by angiopoietin-1 enhances tumor vessel maturation and impairs squamous cell carcinoma growth. The American Journal of Pathology 160(4): 1381-1392.
48. Zhou Z, Yao H, Hu H (2017) Disrupting tumor angiogenesis and “the hunger games” for breast cancer. Translational Research in Breast Cancer: Biomarker Diagnosis, Targeted Therapies and Approaches to Precision Medicine: 171-195.
49. Sachdev E, Tabatabai R, Roy V, et al. (2019) PARP inhibition in cancer: An update on clinical development. Targeted Oncology 14: 657-679.
50. Loo SK, Yates ME, Yang S, et al. (2022) Fusion-associated carcinomas of the breast: Diagnostic, prognostic, and therapeutic significance. Genes, Chromosomes and Cancer 61(5): 261-273.
51. Decker WK, da Silva RF, Sanabria MH, et al. (2017) Cancer immunotherapy: Historical perspective of a clinical revolution and emerging preclinical animal models. Frontiers in Immunology 8: 829.
52. Stagg J, Loi S (2015) Immunology and Immunotherapy of breast cancer. Cancer Immunology: Cancer Immunotherapy for Organ-Specific Tumors: 457-470.
53. Bayraktar S (2019) Immunotherapy in breast cancer. Breast Disease: Management and Therapies 2: 541-552.
54. Fan Y, He S (2022) The characteristics of tumor microenvironment in triple negative breast cancer. Cancer Management and Research: 1-17.

55. DeNardo DG, Brennan DJ, Rexhepaj E, et al. (2011) Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. Cancer Discovery 1(1): 54-67.
56. Brahmer JR, Tykodi SS, Chow LQ, et al. (2012) Safety and activity of anti–PD-L1 antibody in patients with advanced cancer. New England Journal of Medicine 366(26): 2455-2465.
57. Hamid O, Robert C, Daud A, et al. (2013) Safety and tumor responses with lambrolizumab (anti–PD-1) in melanoma. New England Journal of Medicine 369(2): 134-144.
58. Curran MA, Montalvo W, Yagita H, et al. (2010) PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proceedings of the National Academy of Sciences 107(9): 4275-4280.
59. Reisfeld R.A (2013) The tumor microenvironment: A target for combination therapy of breast cancer. Critical Reviews™ in Oncogenesis 18(1-2): 115-133.
60. Schmid P, Cortes J, Dent R, et al. (2022) Event-free survival with pembrolizumab in early triple-negative breast cancer. New England Journal of Medicine 386(6): 556-567.
61. Schreiber AR, Kagihara JA, Weiss JA, et al. (2021) Clinical outcomes for patients with metastatic breast cancer treated with immunotherapy agents in phase I clinical trials. Frontiers in Oncology 11: 640690.
62. Carlino F, Diana A, Piccolo A, et al. (2022) Immune-based therapy in triple-negative breast cancer: From molecular biology to clinical practice. Cancers 14(9): 2102.
63. Henriques B, Mendes F, Martins D (2021) Immunotherapy in breast cancer: When, how, and what challenges?. Biomedicines 9(11): 1687.
64. Navarrete-Bernal MG, Cervantes-Badillo MG, Martínez-Herrera JF, et al. (2020) Biological landscape of triple negative breast cancers expressing CTLA-4. Frontiers in Oncology 10: 1206.
65. Ahmadzadeh M, Johnson LA, Heemskerk B, et al. (2009) Tumor antigen–specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. Blood, The Journal of the American Society of Hematology 114(8): 1537-1544.
66. Kassardjian A, Shintaku PI, Moatamed NA (2018) Expression of immune checkpoint regulators, cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death-ligand 1 (PD-L1), in female breast carcinomas. PloS One 13(4): e0195958.
67. Ribas A, Wolchok JD (2018) Cancer immunotherapy using checkpoint blockade. Science 359(6382): 1350-1355.
68. Decker WK, da Silva RF, Sanabria MH, et al. (2017) Cancer immunotherapy: Historical perspective of a clinical revolution and emerging preclinical animal models. Frontiers in Immunology 8: 829.
69. Mavratzas A, Seitz J, Smetanay K, et al. (2020) Atezolizumab for use in PD-L1-positive unresectable, locally advanced or metastatic triple-negative breast cancer. Future Oncology 16(3): 4439-4453.
70. Nanda R, Liu MC, Yau C, et al. (2020) Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: An analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. JAMA Oncology 6(5): 676-684.
71. Guo LM, Ding GF, Xu WC, et al. (2022) Anti-PD-L1 antibody enhances t cell immune responses and reduces resistance of breast cancer cells to radiotherapy. Oxidative Medicine and Cellular Longevity 2022: 5938688.
72. Adams E, Wildiers H, Neven P, et al. (2021) Sacituzumab govitecan and trastuzumab deruxtecan: Two new antibody–drug conjugates in the breast cancer treatment landscape. ESMO Open 6(4): 100204.

73. Juliá EP, Amante A, Pampena MB, et al. (2018) Avelumab, an IgG1 anti-PD-L1 immune checkpoint inhibitor, triggers NK cell-mediated cytotoxicity and cytokine production against triple negative breast cancer cells. Frontiers in Immunology 9: 2140.
74. Uchimiak K, Badowska-Kozakiewicz AM, Sobiborowicz-Sadowska A, et al. (2022) Current state of knowledge on the immune checkpoint inhibitors in triple-negative breast cancer treatment: Approaches, efficacy, and challenges. Clinical Medicine Insights: Oncology 16: 11795549221099869.
75. Sharma P, Hu-Lieskovan S, Wargo JA, et al. (2017) Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell 168(4): 707-723.
76. Bai R, Chen N, Li L, et al. (2020) Mechanisms of cancer resistance to immunotherapy. Frontiers in Oncology 10: 1290.
77. Rieth J, Subramanian S (2018) Mechanisms of intrinsic tumor resistance to immunotherapy. International Journal of Molecular Sciences 19(5): 1340.
78. Anderson AC, Joller N, Kuchroo VK (2016) Lag-3, Tim-3, and TIGIT: Co-inhibitory receptors with specialized functions in immune regulation. Immunity 44(5): 989-1004.
79. Petitprez F, Meylan M, de Reyniès A, et al. (2020) The tumor microenvironment in the response to immune checkpoint blockade therapies. Frontiers in Immunology 11: 784.
80. Salgado R, Denkert C, Demaria S, et al. (2015) The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: Recommendations by an International TILs Working Group 2014. Annals of Oncology 26(2): 259-271.
81. Yang YH, Liu JW, Lu C, et al. (20220 CAR-T cell therapy for breast cancer: From basic research to clinical application. International Journal of Biological Sciences 18(6): 2609.
82. Zhu SY, Yu KD (2022) Breast cancer vaccines: Disappointing or promising?. Frontiers in Immunology 13: 828386.
83. Ge Y, Xi H, Ju S, et al. (2013) Blockade of PD-1/PD-L1 immune checkpoint during DC vaccination induces potent protective immunity against breast cancer in hu-SCID mice. Cancer Letters 336(2): 253-259.
84. Weber J (2002) Peptide vaccines for cancer. Cancer Investigation 20(2): 208-221.
85. Kaumaya PT, Foy KC (2012) Peptide vaccines and peptidomimetics targeting HER and VEGF proteins may offer a potentially new paradigm in cancer immunotherapy. Future Oncology 8(8): 961-987.
86. Chung MA, Luo Y, O'Donnell M, et al. (2003) Development and preclinical evaluation of a Bacillus Calmette-Guérin-MUC1-based novel breast cancer vaccine. Cancer Research 63(6): 1280-1287.
87. Guo C, Manjili MH, Subjeck JR, et al. (2013) Therapeutic cancer vaccines: past, present, and future. Advances in Cancer Research 119: 421-475.
88. Srivatsan S, Patel JM, Bozeman EN, et al. (2014) Allogeneic tumor cell vaccines: The promise and limitations in clinical trials. Human Vaccines & Immunotherapeutics 10(1): 52-63.
89. Sharma A, Bode B, Wenger RH, et al. (2011) γ-Radiation promotes immunological recognition of cancer cells through increased expression of cancer-testis antigens in vitro and in vivo. PloS One 6(11): e28217.
90. Sakai Y, Morrison BJ, Burke JD, et al. (2004) Vaccination by genetically modified dendritic cells expressing a truncated neu oncogene prevents development of breast cancer in transgenic mice. Cancer Research 64(21): 8022-8028.
91. Ying K, Zhu Y, Wan J, et al. (2023) Macrophage membrane-biomimetic adhesive polycaprolactone nanocamptothecin for improving cancer-targeting efficiency and impairing metastasis. Bioactive Materials 20: 449-462.

92. Liu H, Wen Z, Chen H, et al. (2022) Nanoadjuvants actively targeting lymph node conduits and blocking tumor invasion in lymphatic vessels. Journal of Controlled Release 352: 497-506.
93. Guo J, Ma S, Mai Y, et al. (2022) Combination of a cationic complexes loaded with mRNA and α-Galactose ceramide enhances antitumor immunity and affects the tumor immune microenvironment. International Immunopharmacology 113: 109254.
94. Fisusi FA, Akala EO (2019) Drug combinations in breast cancer therapy. Pharmaceutical Nanotechnology 7(1): 3-23.
95. Wang M, Hou L, Chen M, et al. (2017) Neoadjuvant chemotherapy creates surgery opportunities for inoperable locally advanced breast cancer. Scientific Reports 7(1): 44673.
96. Ho AY, Tabrizi S, Dunn SA, et al. (2022) Current advances in immune checkpoint inhibitor combinations with radiation therapy or cryotherapy for breast cancer. Breast Cancer Research and Treatment 191(2): 1-13.
97. Kolberg HC, Hoffmann O, Baumann R (2020) The abscopal effect: Could a phenomenon described decades ago become key to enhancing the response to immune therapies in breast cancer?. Breast Care 15(5): 443-449.
98. Matsumura S, Wang B, Kawashima N, et al. (2008) Radiation-induced CXCL16 release by breast cancer cells attracts effector T cells. The Journal of Immunology 181(5): 3099-3107.
99. Wu CT, Chen WC, Chang YH, et al. (2016) The role of PD-L1 in the radiation response and clinical outcome for bladder cancer. Scientific Reports 6(1): 19740.