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The progress of combination therapy with immune checkpoint inhibitors in breast cancer

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Key words: Breast cancer, Immune checkpoint inhibitors, Combination therapy

Abstract: Immunotherapy targets the dysfunctional immune system to induce cancer cell killing by CD8-positive T cells. Immune checkpoint inhibitors (ICIs), specifically anti-PD-1 antibodies, anti-PD-L1 antibodies, and anti-CTLA4 antibodies, have revolutionized the management of many malignancies due to their significant role in generating a durable clinical response. However, clinical data suggest that response rates to ICI monotherapy are low due to the immunologically silent characteristics of breast cancer (BC). Chemotherapy, surgery, radiotherapy, and targeted therapy were recently reported to alter the tumor microenvironment and enhance the ICI response. Some clinical studies supported that ICIs, in combination with other treatment strategies, show superior efficacy in BC control, especially triple-negative breast cancer. Therefore, seeking a reasonable combination therapy is a promising way to improve ICI response. The present review highlights the clinical efficacy of ICIs treatment options in combination with standard-of-care therapies, such as chemotherapy and targeted therapy.

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer (30% of new cancer cases in women each year) and was the second leading cause of death due to cancer (15% of female cancer-related deaths annually) in women worldwide in 2020 (Siegel *et al.*, 2022; Wilkinson and Gathani, 2022). Most patients with early-stage BC are effectively treated with surgical resection, and the average five-year overall survival rate for women with non-metastatic invasive BC is 90% (Kashyap *et al.*, 2022). However, there are only a few treatment strategies for patients with unresectable BC or who develop distant metastatic disease (Kashyap *et al.*, 2022; Loibl *et al.*, 2021). Chemotherapy and/or radiotherapy provide only modest clinical benefits for these patients, and their five-year overall survival rate is less than 30% (Kashyap *et al.*, 2022; Riggio *et al.*, 2021). Most patients with BC die due to BC progression (Emens, 2018). Increasing evidence shows that the immune system plays a crucial role in the progression of various cancers by facilitating immune escape and decreasing the responses to standard BC treatment (Savas *et al.*, 2016). Altering the immune system is effective for tumor control (Farkona *et al.*, 2016).

Immune checkpoints are essential for maintaining self-tolerance, which is necessary to prevent damage to normal tissue in the immune response to infection (Morad *et al.*, 2021). Tumors use a variety of mechanisms to evade immune detection and eradication, including activation of inhibitory pathways controlled by immune checkpoints (Bagchi *et al.*, 2021). Therefore, targeting these dysfunctional immune checkpoints is a promising therapeutic strategy for tumor control. The most successful immune checkpoints are cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and its ligand (PD-L1), which could improve the cytotoxicity and proliferative capacity of tumor-infiltrating lymphocytes (TILs). Inhibitors developed to target the above immune checkpoints have been reported to induce durable objective responses in multiple cancers by disrupting the interaction between immune checkpoints and their receptors, including BC (Doroshow *et al.*, 2021). However, clinical data show that response rates to immune checkpoint inhibitor (ICI) monotherapy are low due to the immunologically silent characteristics of BC (Thomas *et al.*, 2021). Increasing data show that systemic therapy, such as chemotherapy and radiotherapy, helps reshape the tumor microenvironment into an immune-favorable phenotype by altering the infiltration of TILs and Treg cells. More clinical studies support that combining ICIs and chemotherapy or

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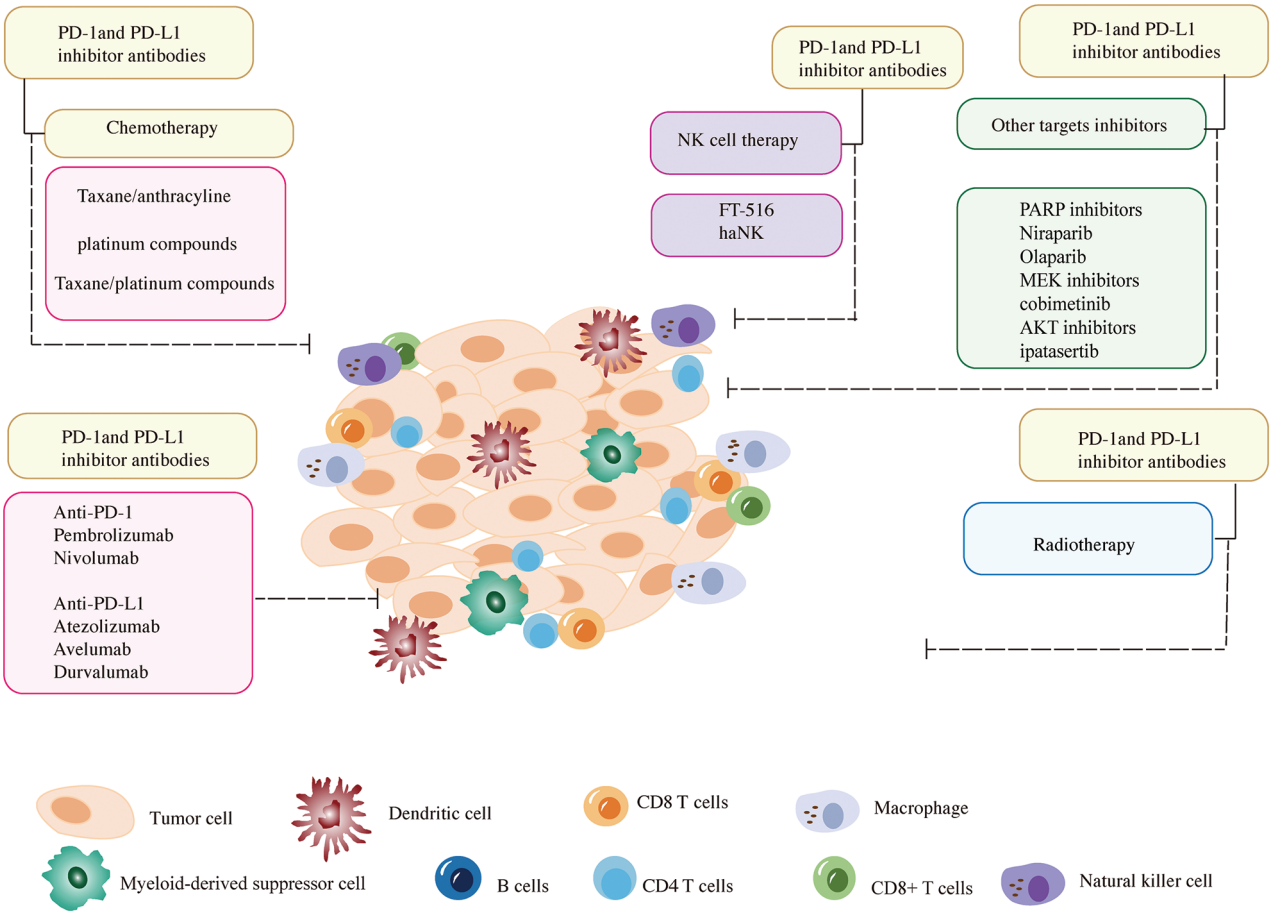

FIGURE 1. A summary of the combinations of immune checkpoint inhibitors and other breast cancer treatment strategies discussed in this review. The represented inhibitors of anti-PD-1 and anti-PD-L1 are listed at the bottom of the left corner. The current common combination methods of anti-PD-1 and anti-PD-L1 with chemotherapy are shown in the upper left corner. The combination methods of anti-PD-1 and anti-PD-L1 inhibitors with NK cells or other targeted inhibitors are listed in the upper right corner. In addition, the combination of anti-PD-1 and anti-PD-L1 inhibitors with radiotherapy is exhibited at the bottom of the right corner.

radiotherapy is effective for BC control (Schmid *et al.*, 2018). Therefore, seeking a rational combination of ICIs with other treatments is a promising direction for BC control in the future (Ulas *et al.*, 2021). The present review highlights the clinical efficacy of ICIs in combination with standard therapies, such as chemotherapy and targeted therapy (Fig. 1).

Immune Checkpoint Inhibitor-Chemotherapy Combination Treatment

Chemotherapeutic agents, such as oxaliplatin and 5-fluorouracil, induce macrophages to release inflammatory cytokines, increase the expression of MHC class I molecules, enhance tumor-associated antigen expression, and promote dendritic cell activation, potentially augment the immune response following or during ICI treatment (Kgd *et al.*, 2022; Najmeh *et al.*, 2018). Therefore, the combination of ICIs and chemotherapy is a more promising treatment method for metastatic triple-negative breast cancer (mTNBC) control than ICI monotherapy (Table 1).

Programmed cell death-1 antibody-chemotherapy combination treatment

Taxanes and anthracyclines are the most common chemotherapy agents in the treatment of early and metastatic BC (Ghersi *et al.*, 2005). Anthracycline-based regimens decrease BC mortality by 20%–30% (Hatzis *et al.*, 2011; Jasra and Anampa, 2018). The I-SPY 2 (NCT01042379) study evaluated pathologic complete response (pCR) rates in erb-B2 receptor tyrosine kinase (ERBB2)-negative BC or TNBC patients who received neoadjuvant chemotherapy with pembrolizumab and taxanes or anthracyclines at an early stage. This combination treatment strategy increased the pCR rate from 17% to 44% (Schmid *et al.*, 2020b). The KEYNOTE-522 trial (NCT03036488) reported that the addition of pembrolizumab to paclitaxel plus carboplatin and an anthracycline plus cyclophosphamide as neoadjuvant therapy followed by surgery plus an additional nine cycles of adjuvant pembrolizumab improved pCR rates from 51.2% to 64.8% and 18-month event-free survival (EFS) rates from 85.3% to 91.3%. Patients in this trial with node-negative TNBC had a smaller benefit, which suggests that the risk of this five-drug regimen is greater than the benefit of early node-negative TNBC patients and TNBC patients with high TIL levels, who have a good prognosis under the current standard regimen. The pCR rate of early BC patients who received combination therapy before surgery was significantly higher than patients who received chemotherapy alone, regardless of PD-L1 expression

TABLE 1

Immune checkpoint inhibitors (ICIs)-chemotherapy combinations in triple-negative breast cancer (TNBC)

Trial/Clinical trial	Regimen	Stage	Prior line	Biomarker	N	ORR, %	Median PFS months	Median OS months	Trial status
NCT02819518	Pembrolizumab + nab-paclitaxel or paclitaxel or Gemcitabine/carboplatin	Metastatic TNBC	0–1	PD-L1+ or –	847	NR	9.7	23.0	Active, not recruiting
NCT02755272	Pembrolizumab + gemcitabine/ carboplatin	Metastatic TNBC	1	PD-L1+ or –	87	NR	NR	NR	Recruiting
NCT02513472	Pembrolizumab + eribulin mesylate	Metastatic TNBC	0–2	PD-L1+ or –	212	25.6	4.2	17.7	Completed
NCT02499367	Nivolumab + cyclophosphamide, cisplatin, or doxorubicin	Metastatic TNBC	0, 1, 2 +	PD-L1+ or –	84	35	NR	NR	Active, not recruiting
NCT01042379	Neoadjuvant pembrolizumab + paclitaxel, followed by AC	Locally advanced and metastatic TNBC	1	PD-L1+ or –	5000	NR	NR	NR	Recruiting
NCT02622074	Neoadjuvant pembrolizumab + chemotherapy combination (nab-paclitaxel, paclitaxel, doxorubicin, cyclophosphamide, carboplatin)	Locally advanced and metastatic TNBC	1	PD-L1+ or –	60	60	12	NR	Completed
NCT03036488	Neoadjuvant pembrolizumab + paclitaxel-carboplatin followed by adjuvant pembrolizumab	Locally advanced and metastatic TNBC	1	PD-L1+ or –	1174	64.8	NR	NR	Active, not recruiting
NCT01633970	Atezolizumab + nab-paclitaxel	Locally advanced and metastatic TNBC	0–2	PD-L1+ or –	240	39.4	5.5	14.7	Completed
NCT02425891	Atezolizumab ± nab-paclitaxel	Metastatic TNBC	0–1	PD-L1+ or –	902	53	21	25	Completed
NCT03125902	Atezolizumab ± paclitaxel	Locally advanced and metastatic TNBC	0–1	PD-L1+ or –	651	63	6	22.1	Active, not recruiting
NCT03371017	Atezolizumab + gemcitabine/ carboplatin or capecitabine	Locally advanced and metastatic TNBC	0	PD-L1+ or –	572	NR	NR	NR	Recruiting
NCT02685059	Neoadjuvant durvalumab + nab paclitaxel + EC	Early stage TNBC	1	PD-L1+ or –	174	53	NR	NR	Completed
NCT02620280	Neoadjuvant atezolizumab + nab paclitaxel + carboplatin, followed by AC or EC or FEC	Early high-risk, locally advanced TNBC	0	PD-L1+ or –	278	NR	NR	NR	Active, not recruiting
NCT03197935	Neoadjuvant atezolizumab + nab paclitaxel, followed by AC	Early stage TNBC	0	PD-L1+ or –	333	57.6	NR	NR	Completed
NCT01375842	Atezolizumab + nab-paclitaxel	Locally advanced and	0–2	PD-L1+ or –	661	39.4	9.1	14.7	Completed

(Continued)

Table 1 (continued)

Trial/Clinical trial	Regimen	Stage	Prior line	Biomarker	N	ORR, %	Median PFS months	Median OS months	Trial status
		metastatic TNBC							
NCT03281954	Neoadjuvant atezolizumab + paclitaxel + carboplatin, followed by adjuvant atezolizumab + AC or EC	Early stage TNBC	1	PD-L1+ or –	1150	NR	NR	NR	Active, not recruiting
NCT03498716	Atezolizumab + paclitaxel, followed by atezolizumab + AC or EC	Locally advanced and metastatic TNBC	1	PD-L1+ or –	2300	NR	NR	NR	Active, not recruiting

Abbreviations: AC, doxorubicin + cyclophosphamide; EC, epirubicin + cyclophosphamide; FEC, fluorouracil + epirubicin + cyclophosphamide; ORR, overall response rate; PFS, progression-free survival; OS, overall survival.

(Schmid *et al.*, 2020a). Several ongoing trials will further elucidate the role of chemotherapy in combination with ICIs in early BC, and detailed information is provided in Table 1.

KEYNOTE-173 (NCT02622074) trial was an international phase Ib, open-label, multicohort study which evaluated six chemotherapy (nab-paclitaxel or paclitaxel, anthracycline, cyclophosphamide, carboplatin, and doxorubicin) plus pembrolizumab regimens as neoadjuvant treatment for patients with high-risk, early-stage TNBC. This study confirmed that the toxicity profile of this combination treatment strategy was similar to that of pembrolizumab and chemotherapy individually, including neutropenia, nausea, anemia, and febrile neutropenia, with a pCR rate of 60% across all treatment cohorts. This study also revealed that patients with higher pre-treatment PD-L1 expression were associated with better outcomes (Schmid *et al.*, 2020b). The KEYNOTE-355 (NCT02819518) was a randomized, placebo-controlled, double-blind, phase 3 clinical trial that recently reported that first-line chemotherapy (paclitaxel, gemcitabine + carboplatin, or nab-paclitaxel) with pembrolizumab significantly improved progression-free survival (PFS) compared to chemotherapy alone in patients with mTNBC expressing PD-L1 with a combined positive score ≥10, which was defined as the ratio of all PD-L1-expressing cells (including tumor cells, lymphocytes, and macrophages) to the number of all tumor cells (Cortes *et al.*, 2020). Eribulin is a halicassicin class of antineoplastic non-taxane inhibitors of microtubule dynamics that inhibit transforming growth factor β, and it exerts a powerful function in BC control. The clinical activity of the combination of eribulin and pembrolizumab was first evaluated in the KEYNOTE-150 (NCT02513472) study, and this study revealed a significant improvement in ORR (26.4%) and median PFS (4.1 months) in these patients (Tolaney *et al.*, 2021). The subsequent randomized IMpassion130 phase III trial (NCT00388726) also revealed that overall survival (OS) was significantly improved in patients who underwent eribulin treatment (Cortes *et al.*, 2011). BR-076 (NCT02755272) is a phase 2 clinical trial on pembrolizumab in combination with gemcitabine/carboplatin in mTNBC that is ongoing.

Nivolumab is a human IgG4 monoclonal antibody that blocks PD-1 to inhibit signals that prevent the activation of T cells from attacking the cancer (Fong and Cunningham, 2021). Nivolumab has been used to treat various solid tumors, such as melanoma, lung cancer, renal cell carcinoma, and colon cancer (Carlino *et al.*, 2021). Some clinical trials evaluated the safety and clinical efficiency of nivolumab monotherapy in BC treatment (Brahmer *et al.*, 2012). The most common drug-related adverse events were fatigue, infusion reactions, diarrhea, arthralgia, rash, nausea, pruritus, and headache, but these side effects were endurable (Brahmer *et al.*, 2012). A single-center phase 2 clinical trial TONIC (NCT02499367) evaluated the efficacy of nivolumab in pretreated mTNBC (cyclophosphamide, cisplatin, and doxorubicin). Notably, the objective response rate (ORR) of nivolumab plus doxorubicin was 35%, compared to 23% for cisplatin and 17% for patients who did not receive chemotherapy. This trial also detected an upregulation of immune-related genes involved in PD-1/PD-L1 (programmed death ligand 1) and T-cell cytotoxicity pathways after doxorubicin and cisplatin induction. The results demonstrated that JAK-STAT and TNF-α signaling were enriched. Taken together, the clinical and translational data of this study indicate that short-term doxorubicin and cisplatin treatment may induce a more favorable tumor microenvironment and increase the likelihood of response to PD-1 blockade in TNBC, which also suggests that chemotherapy preconditioning induces inflammatory tumor microenvironments (Voorwerk *et al.*, 2019). Several ongoing trials will elucidate the efficacy of the combination of ICIs and nivolumab for BC, but the results have not been determined.

Programmed cell death-ligand 1 antibody-chemotherapy combination treatment

Atezolizumab, avelumab, and durvalumab selectively target PD-L1 to prevent the interaction between PD-1 (CD279)

and B7-1, which reverses T-cell suppression (Schmid *et al.*, 2018). The safety and clinical efficacy of these three anti-PD-L1 antibodies have been reported in BC (Emens *et al.*, 2021). NCT01375842 is a multicohort phase I study involving 116 patients with mTNBC that evaluated the efficacy of atezolizumab monotherapy in BC. Atezolizumab treatment prolonged the ORR (5 of 21 [24%]), with a median OS of 17.6 months. This clinical trial also demonstrated that patients with PD-L1 overexpression and more tumor-infiltrating immune cells had higher ORRs and longer OS (12% [11 of 91]; 10.1 [95% CI, 7.0–13.8] months, respectively) than patients with fewer immune cells (0 of 21; 6.0 [95% CI, 2.6–12.6] months, respectively) (Emens *et al.*, 2019). GP28328 (NCT01633970) was a multicenter and multicohort phase 1b study of atezolizumab plus chemotherapy in the treatment of advanced solid tumors, which showed that the atezolizumab plus nanoparticle albumin-bound (nab) paclitaxel group had a better ORR (53.8% *vs.* 30.0%) and PFS (8.6 *vs.* 5.1 months). OS also increased significantly in the atezolizumab plus nab-paclitaxel group compared to nab-paclitaxel monotherapy (24.2 *vs.* 12.4 months) (Adams *et al.*, 2019). The IMpassion130 (NCT02425891) trial showed that the combination of atezolizumab with first-line nab-paclitaxel for metastatic TNBC significantly improved PFS and showed a clinically meaningful effect on OS in patients with PD-L1-positive tumors. The intention-to-treat analysis showed that the median PFS was 7.2 months with atezolizumab plus nab-paclitaxel compared to 5.5 months with placebo plus nab-paclitaxel. For patients with PD-L1–positive tumors, the median PFS was 7.5 and 5.0 months, respectively. The intention-to-treat analysis revealed that the median OS increased to 21.3 months, and the median OS was 25.0 and 15.5 months, respectively, in patients with PD-L1–positive tumors (Emens *et al.*, 2021). Based on these results, the Food and Drug Administration (FDA) granted accelerated approval to atezolizumab on March 8, 2019 (TECENTRIQ, Genentech Inc., South San Francisco, CA, USA) plus nab-paclitaxel adult patients with unresectable locally advanced or mTNBC whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells of any intensity covering ≥1% of the tumor area), as determined by an FDA-approved test. The subsequent IMpassion131 study (NCT03125902) evaluated the safety and efficacy of atezolizumab plus paclitaxel as a first-line therapy in patients with locally advanced or mTNBC. However, this trial showed that this combination treatment strategy did not improve PFS or OS *vs.* paclitaxel alone (Miles *et al.*, 2021). IMpassion132 (NCT03371017) is a multinational, double-blind placebo-controlled two-arm randomized phase III trial comparing atezolizumab plus chemotherapy (capecitabine [mandatory in platinum-pretreated patients] or gemcitabine/carboplatin) *vs.* placebo plus chemotherapy in early relapsing TNBC (Cortés *et al.*, 2019). The primary endpoint of IMpassion132 is OS in the intent-to-treat population. Median OS will be estimated in the atezolizumab and placebo groups using Kaplan–Meier methodology, but the result is pending. Compared to atezolizumab, there is limited information on the effect of durvalumab combined with chemotherapy in early TNBC treatment. A randomized phase II study, the GeparNuevo trial (NCT02685059), investigated the safety and efficacy of the combination of durvalumab and anthracycline taxane-based neoadjuvant therapy in early TNBC. The results indicated that durvalumab plus anthracycline taxane-based neoadjuvant therapy provided significantly improved survival (95.2% *vs.* 83.5%) despite a modest pCR (53.4% *vs.* 44.2%) (Loibl *et al.*, 2022b). The NeoTRIPaPDL1 (NCT02620280) clinical trial is a phase III study that also revealed that neoadjuvant atezolizumab plus carboplatin and nab-paclitaxel followed by adjuvant chemotherapy in early-stage high-risk or locally advanced TNBC did not significantly increase the rate of pCR in women with TNBC (48.6% *vs.* 44.4%; $p = 0.48$) (Gianni *et al.*, 2022). Additional studies are needed to clarify the optimal duration and sequence of ICIs in early TNBC treatment.

The placebo-controlled NSABP B-59 trial (NCT03281954) and the IMpassion030 (NCT03498716) trial evaluated the efficacy, safety, and pharmacokinetics of adjuvant atezolizumab in combination with chemotherapy, such as paclitaxel, doxorubicin, epirubicin, and cyclophosphamide, in patients with stage II–III TNBC (Pérez-García *et al.*, 2020; Adams *et al.*, 2019). Another small trial is examining whether the combination of atezolizumab and neoadjuvant chemotherapy provides clinical benefits for advanced TNBC patients. The IMpassion031 trial (NCT03197935) evaluated whether the addition of atezolizumab to the novel adjuvant nab-paclitaxel, doxorubicin, and cyclophosphamide resulted in a higher pCR rate compared to placebo. Interim analysis showed that atezolizumab combined with the sequence nab-paclitaxel and anthracycline chemotherapy prolonged OS and PFS in patients with early TNBC. Patients receiving atezolizumab in combination with chemotherapy had a pCR rate of 57.6% compared to 41.1% in patients who did not receive atezolizumab. Among PD-L1-positive patients, the pCR rate reached 69% in patients who received atezolizumab plus chemotherapy and 49% in patients receiving placebo plus chemotherapy (Mittendorf *et al.*, 2020). Two other locally advanced TNBC studies are ongoing to evaluate the effect of PD-L1 blocking chemotherapy in adjuvant therapy. The phase III randomized trial A-Brave (NCT02926196) is examining whether 1 year of adjuvant therapy improves disease-free survival (DFS) compared with high-risk primary TNBC patients who have completed treatment, including surgery following neoadjuvant chemotherapy. The study focused on avelumab in patients with high-risk or residual disease, but the results are pending (Table 1).

Immune Checkpoint Inhibitor-Surgery Combination Treatment

Surgery has been the primary modality for the treatment of BC for centuries since it was first performed by Halsted in 1882 (Matsen and Neumayer, 2013). Surgery was recently reported to alter immune function by switching to a Th2 immune response, activating Treg cells, recruiting MDSCs, and inhibiting natural killer cells (NK) and T-cell function

(Loibl *et al*., 2021; Miles *et al*., 2021; Popa and Georgescu, 2017). Therefore, the perioperative phase is considered the best time to improve immunity and reduce tumor recurrence and metastasis (Forde *et al*., 2018). However, no trial has directly evaluated the safety and clinical efficacy of ICIs in combination with surgery. We conclude from the above five clinical trials, I-SPY 2, GeparNuevo, KEYNOTE-173, KEYNOTE-522, and NeoTRIPaPDL1, that surgery after the combination of ICIs and chemotherapy prolonged the pCR and OS regardless of PD-L1 expression. However, the combination of the treatment plan, operation time, and postoperative treatment must be further discussed (Loibl *et al*., 2022a, 2022b). Four ongoing clinical studies are examining the efficacy of the combination of ICIs and surgery for patients with early BC (Table 2).

Immune Checkpoint Inhibitor-Radiotherapy Combination Treatment

Radiotherapy is the standard treatment for BC, and it reduces local recurrence and improves OS in early to locally advanced BC (Dandawate *et al*., 2016). The role of radiotherapy in BC management continues to evolve. For patients with early-stage breast cancer, low-grade whole breast irradiation after breast-conserving surgery is the standard of care (Zi *et al*., 2017). Radiotherapy is associated with tumor DNA damage, which leads to the release of antigens and danger signals that promote antigen presentation and tumor-specific T-cell activation, and RT enhances the anti-tumor activity of ICIs (Bradley and Mendenhall, 2018; Lhuillier *et al*., 2021; Zi *et al*., 2017).

TABLE 2

Immune checkpoint inhibitors combination chemotherapy and surgery in early-stage breast cancer

Trial/Clinical trial	Regimen	Stage	Biomarker	N	pCR %	Trial status
NCT01042379	Paclitaxel ± pembrolizumab × 4 → AC × 4 surgery	II–III	PD-L1+ or –	29 *vs*. 85	60 *vs*. 22	Active, not recruiting
	Paclitaxel ± pembrolizumab × 4 → pembrolizumab *vs*. AC × 4 → surgery	Tumor size ≥2.5 cm	PD-L1+ or –	68 *vs*. 295	27 *vs*. 27	
NCT02685059	Nab-paclitaxel ± durvalumab × 4 → EC × 4 → surgery	cT1b to cT4a-d	PD-L1+ or –	174	53.4 *vs*. 44.2	Completed
	Durvalumab/placebo 2 weeks before nab-paclitaxel	cT1b to cT4a-d	PD-L1+ or –	117	61.0 *vs*. 41.4	
NCT02622074	Nab-/paclitaxel ± carboplatin + pembrolizumab → AC + pembrolizumab → surgery	T2/T3	PD-L1+ or –	60	60	Completed
NCT03036488	Paclitaxel + carboplatin × 4 ± pembrolizumab × 4 → AC/EC ± pembrolizumab × 4 → surgery ± pembrolizumab × 9 cycle	T1cN1-2 or T2-4N0-N2	PD-L1+ or –	1174	64.8 *vs*. 51.2 13.6	Active, not recruiting
NCT02620280	Carboplatin + nab-paclitaxel ± atezolizumab × 8 → surgery → AC/EC/FEC × 4 cycles	T1cN1, T2N1, T3N0, or locally advanced	PD-L1+ or –	280	43.5 *vs*. 40.8	Active, not recruiting
NCT03197935	Nab-paclitaxel ± atezolizumab × 12 wk → AC ± atezolizumab × 4 → surgery	cT2-cT4, cN0-cN3, cM0	PD-L1+ or –	324	57.6 *vs*. 44.1	Completed
Trial/Clinical trial	Regimen	Stage		N	Primary Endpoint	Trial status
NCT02954874	Adjuvant pembrolizumab *vs*. observation × 1 y	ypT ≥1 cm or ypN1-3		1000	iDFS, PROs	Active, not recruiting
NCT02926196	Adjuvant avelumab *vs*. observation × 1 y	ypT > 1 mm or ypN1-3 or IIB-III		335	DFS	Active, not recruiting
NCT03281954	Paclitaxel + carboplatin ± atezolizumab × 4 → AC/EC ± atezolizumab × 4 → surgery ± atezolizumab × 1 y	≥T2N0 or T1cN1		1520	pCR, EFS	Active, not recruiting
NCT03498716	Paclitaxel ± atezolizumab × 12 wk → AC ± atezolizumab × 4 → surgery ± atezolizumab × 1 y	II–III		2300	iDFS	Active, not recruiting

Abbreviations: AC, doxorubicin/cyclophosphamide; DFS, disease-free survival; EC, epirubicin/cyclophosphamide; EFS, event-free survival; FEC, fluorouracil/epirubicin/cyclophosphamide; HR, hazard ratio; IC, immune cells; iDFS, invasive disease-free survival; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

Rudqvist *et al.* (2018) demonstrated that the combination of anti-CTLA-4 antibodies and RT (12 Gy of irradiation) significantly inhibited BC growth. They also found that CTLA-4 blockade with one fraction of 12 Gy increased mouse survival time but did not lead to statistically significant tumor control compared with radiotherapy alone (Rudqvist *et al.*, 2018). Tremelimumab is a fully human monoclonal antibody against CTLA-4 (Santa-Maria *et al.*, 2017) that has been used for the control of various solid tumors, including melanoma, hepatocellular carcinoma, and non-small cell lung cancer (Ulas *et al.*, 2021). However, the role of tremelimumab in BC control has been poorly studied. The KCSG BR17-04 trial is a phase II trial that enrolled 119 patients with hormone receptor (HR)-positive metastatic BC to examine the efficacy and safety of combined durvalumab and tremelimumab in BC control. This combination showed modest activity and good tolerability in these patients (Moon *et al.*, 2022). The combination of radiotherapy and tremelimumab was first administered to six patients with advanced BC. The results of this trial showed that the best curative response was a stable disease, with one case of stable disease lasting more than six months. One patient lived for more than eight years, and the median OS increased to 50.8 months. Following 1 week of treatment, the proliferation of peripheral blood mononuclear cells increased in five patients, and the Treg number increased simultaneously (Jiang *et al.*, 2019). This study confirmed that patients with advanced BC benefited from the combination of tremelimumab and RT. A subsequent single-institution study (NCT02563925) confirmed the safety and efficacy of RT and concurrent tremelimumab ± HER2-directed therapy with trastuzumab for patients with BC brain metastases (Page *et al.*, 2022). A phase II clinical trial enrolled 17 patients with advanced TNBC with distant metastases to assess the clinical efficacy of pembrolizumab plus RT. The ORR reached 17.6% in this study, in which three patients achieved complete response (CR), and one patient achieved stable disease (SD) (Ho *et al.*, 2020). These clinical studies suggested that the combination of RT and ICIs provided benefits for patients with BC. However, the radiation doses, fractionation, and delivery schedules have not been validated. The Memorial Sloan Kettering Cancer Center and Cedars-Sinai Medical Center performed a trial to examine the efficacy of the combination of pembrolizumab and five fractions of 6 Gy in metastatic TNBC patients. A similar study is ongoing in different solid tumors, including metastatic melanoma, BC, and pancreatic cancer, comparing two irradiation schedules of three fractions of 8 Gy of irradiation or one fraction of 17 Gy in combination with tremelimumab and durvalumab (Craig *et al.*, 2021). NCT02303366 is a phase 1 study that examined the safety and biological effects of pembrolizumab and 1 fraction of 20 Gy in BC (Zi *et al.*, 2017). The Netherlands Cancer Institute is using 20 Gy one-part induction therapy in TNBC patients, low-dose doxorubicin, cyclophosphamide or cisplatin, or no nivolumab induction therapy (Table 3).

Immune Checkpoint Inhibitor-Targeted Therapy Combination Treatment

Immune checkpoint inhibitor-poly (ADP-ribose) polymerase inhibitor combination treatment

Poly (ADP-Ribose) polymerase inhibitors (PARPis) induce cell death by targeting the homologous recombination repair pathway in cells with BRCA1/2 mutation, and PARPis are approved for TNBC patients with germline mutations in BRCA1/2 (Shen *et al.*, 2019). Increasing evidence supports the potential for the combination of PARPis and ICIs to induce a stronger anti-tumor immune response in these TNBC patient subpopulations due to the activation of infiltrating T cells following PARPi induction of cell death

TABLE 3

Immune checkpoint inhibitors-radiotherapy combinations in breast cancer

Trial/Clinical trial	Regimen	Stage	N	Trial status
NCT02563925	Tremelimumab + trastuzumab + 30 Gy/10 fractions, 21 Gy single-dose (n = 1 patient), hypofractionated (30 Gy/5 doses, n = 1 patient), or combined (21 Gy/1 fraction with 30 Gy/5 fractions, n = 1 patient)	BC with brain metastases	26	Completed
NCT02730130	Pembrolizumab + 6 Gy × 5 fractions of irradiation	Metastatic TNBC	17	Completed
NCT02303990	Pembrolizumab and hypofractionated radiotherapy (8 Gy × 3 for the first half; 17 Gy × 1 for the second half in each stratum)	Metastatic BC	24	Completed
NCT02303366	Pembrolizumab and 20 Gy × 1 fraction stereotactic ablative radiation therapy	Oligometastatic BC	15	Completed
NCT02639026	Durvalumab with tremelimumab and 8 Gy × 3 fractions *vs.* 17 Gy × 1 fraction	Metastatic BC	30	Active, not recruiting
NCT02499367	Nivolumab was given after either 20 Gy × 1 fraction, low-dose doxorubicin, cyclophosphamide, cisplatin, or no induction treatment	TNBC	84	Active, not recruiting
NCT02608385	Pembrolizumab and stereotactic ablative radiation therapy	BC	117	Active, not recruiting

Abbreviations: TNBC, triple-negative breast cancer; BC, breast cancer.

and the release of tumor antigens (Li *et al.*, 2020). PARPis contributed to PD-L1 overexpression in cell lines and animal models, which supports the anti-tumor activity of the combination of PD1/PD-L1 inhibitors and PARPis in the treatment of BC (Jiao *et al.*, 2017). PARPi monotherapy prolonged the PFS and OS of TNBC patients with BRCA1/2 mutations (Tung *et al.*, 2020). However, whether PARPis combined with ICIs are safe and improve clinical efficacy remains to be discussed.

An open-label, multicenter, phase 1/2, basket study, the MEDIOLA trial (NCT02734004) was the first study to assess the safety and clinical activity of olaparib in combination with durvalumab in patients with germline BRCA1-mutated or BRCA2-mutated mBC (Domchek *et al.*, 2020). The results of this clinical trial showed that 11 (32%) patients experienced grade 3 or worse adverse events, of which the most common were anemia (four [12%]), neutropenia (three [9%]), and pancreatitis (two [6%]). Three (9%) patients were discontinued due to adverse events, and four (12%) patients experienced a total of six serious adverse events. There were no treatment-related deaths. Twenty-four of the 30 patients who were eligible for activity analysis had disease control at 12 weeks (Domchek *et al.*, 2020). The phase II TOPACIO trial (NCT02657889) revealed that the combination of niraparib plus pembrolizumab achieved an ORR of 21% and a disease control rate (DCR) of 49% in patients with advanced TNBC (Vinayak *et al.*, 2019). Within the limits of cross-trial comparisons, this ORR was slightly lower than the ORRs of 55% and 62% associated with single-agent PARP inhibitor therapy in patients with TNBC and germline BRCA mutations in the OlympiAD (NCT02000622) and EMBRACA (NCT01945775) trials, respectively. The MEDIOLA trial (NCT02734004) of the doublet or triplet combination of durvalumab, olaparib, and VEGFR inhibitors in mTNBC with germline BRCA mutations demonstrated an ORR of 58.8%, which was more similar to single-agent PARP therapy, with a median PFS of 4.9 months (Domchek *et al.*, 2020). Several clinical trials have evaluated the clinical efficacy of the combination of PD-L1 inhibition and PARPis in mTNBC. For example,

TABLE 4

Immune checkpoint inhibitors antibody-targeted therapy combinations in BC

Trial/Clinical trial	Regimen	Prior lines	Stage	Biomarker	N	ORR %	Median PFS (95% CI), mo	Median OS (95% CI), mo	Trial status
NCT02657889	Pembrolizumab + niraparib	01–Mar	Metastatic TNBC	PD-L1 + or –, *BRCA*m + or –	55	21	2.3	NR	Completed
			Metastatic TNBC	*BRCA*m +	15	47	8.3	NR	Completed
			Metastatic TNBC	*BRCA*m –	27	11	2.1	NR	Completed
NCT03167619	Durvalumab + olaparib + platinum	1 or 2	Metastatic TNBC	PD-L1 + or –	45	NR	NR	NR	Completed
NCT03801369	Durvalumab + olaparib	0–2	Metastatic TNBC	PD-L1 + or –	132	NR	NR	NR	Recruiting
NCT02849496	Atezolizumab + olaparib	0–2	Advanced BC	*BRCA*m	88	NR	NR	NR	Active, not recruiting
NCT02484404	Durvalumab + olaparib + cediranib	0–2	Advanced TNBC	PD-L1 + or –	384	NR	NR	NR	Recruiting
NCT02734004	Durvalumab + olaparib +/bevacizumab	0–1	Advanced TNBC	*BRCAm*	17	58.8	4.9	20.5	Active, not recruiting
NCT02322814	Atezolizumab + taxanes + cobimetinib	0	Metastatic TNBC	PD-L1 + or –	169	29-34.4	7	NR (10.2-NR)	Completed
NCT03106415	Pembrolizumab + binimetinib	0–2	Unresectable locally advanced or metastatic TNBC	PD-L1 + or –	23	NR	NR	NR	Active, not recruiting
NCT03971409	Avelumab + binimetinib + sacituzumab govitecan or liposomal doxorubicin	0–1	Stage IV or unresectable, recurrent TNBC	PD-L1 + or –	150	NR	NR	NR	Recruiting
NCT03800836	Atezolizumab + ipatasertib + paclitaxel or nab-paclitaxel	0	Locally advanced or metastatic TNBC	PD-L1 + or –	26	73	NR	NR	Completed

Abbreviations: TNBC, triple-negative breast cancer; BC, breast cancer; ORR, overall response rate; PFS, progression-free survival; OS, overall survival; NR, not reported.

ongoing larger trials of olaparib with atezolizumab (NCT02849496) or durvalumab (NCT03167619) are in progress. Cyclin-dependent kinase (CDK) inhibitors boosted effector T-cell activity and inhibited Treg proliferation, which led to fibroblast-derived proinflammatory cytokine secretion and enhanced cell surface antigen presentation (Roskoski, 2019). CDK inhibitors sensitize BC cells to PARPis, which may further augment the treatment response to ICIs (Johnson *et al.*, 2011). It would be interesting to examine the clinical benefits of combining PARPis, ICIs, and CDK inhibitors.

Immune checkpoint-inhibitor-anti-angiogenic therapy combination treatment

Low-dose anti-angiogenic therapy normalizes blood vessels, encourages $CD8^+$ T-cell and B-cell infiltration, increases PD-1 expression in tumor cells, and enhances anti-PD-1 therapeutic effectiveness. Previous trials showed that anti-angiogenesis or anti-PD-1/PD-L1 monotherapy only showed modest effects on TNBC. Preclinical studies demonstrated that anti-angiogenic therapy sensitized BC to PD-1/PD-L1 blockade by reshaping the tumor microenvironment (Wang *et al.*, 2020). Therefore, patients with TNBC may benefit from the combination of ICIs and anti-angiogenesis therapy. Camrelizumab, in combination with apatinib, has shown promising efficacy and a manageable safety profile in patients with advanced TNBC (Liu *et al.*, 2020). NCT04303741 also revealed the clinical efficacy of camrelizumab, famitinib, and eribulin in heavily pretreated patients with advanced TNBC. The ORR was 37.0% (17/46, 95% CI 23.2–52.5), the DCR was 87.0% (40/46, 95% CI 73.7–95.1), and the PFS was 8.1 (95% CI 4.6–10.3) months (Li *et al.*, 2022; Liu *et al.*, 2022; Wu *et al.*, 2022).

Immune checkpoint inhibitors-other target combination treatment

The COLET (NCT02322814) study assessed the combination of the MEK1/2 inhibitor cobimetinib, atezolizumab, and paclitaxel/nab-paclitaxel as first-line therapy for locally advanced TNB or mTNBC. Interim analysis revealed an ORR of 34% in combination with paclitaxel and 29% with nab-paclitaxel (Brufsky *et al.*, 2019). Two phase-II trials are underway to evaluate the safety and efficacy of pembrolizumab/avelumab in combination with binimetinib (NCT03106415 and NCT03971409) in patients with locally advanced TNBC or mTNBC (Chumsri *et al.*, 2020). Enobosarm (GTx-024) was used with pembrolizumab to treat luminal androgen receptor-positive TNBC. The adverse effects of combining enobosarm with pembrolizumab are well tolerated, with a 25% moderate response at 16 weeks regardless of PD-L1 expression (Yuan *et al.*, 2021). However, the trial ended early when the supply of the GTx-024 drug was interrupted. Clinical trials of AR+ TNBC combined with ICIs and AR-targeted therapy will be investigated in the future (Lehmann *et al.*, 2020; Yuan *et al.*, 2021). A nonrandomized, open-label, multicohort phase 1b study (NCT02779751) investigated the safety and efficacy of abemaciclib plus pembrolizumab with/without anastrozole in patients with hormone receptor-positive (HR+) human epidermal growth factor receptor 2-negative (HER2-) BC. The ORR and DCR were 23.1/28.6% and 84.6/82.1%, respectively, and the median PFS and OS were 8.9 and 26.3 months, respectively (Rugo *et al.*, 2022).

AKT inhibitors, in combination with ICIs, have also attracted considerable interest and are considered another important class of targeted therapies for BC control in combination with ICIs (Hua *et al.*, 2021). PTEN is a well-known tumor suppressor and a negative regulator of AKT (Álvarez-Garcia *et al.*, 2019). AKT inhibitors lead to immunotherapy resistance and promote tumor-specific lymphocyte amplification (de Bono *et al.*, 2019). This evidence supports the potential promising efficacy of the combination of ICIs and AKT inhibitors in BC treatment. A phase Ib trial (NCT03800836) evaluated the combination of ipatasertib (IPAT), atezolizumab, and taxane as first-line therapy for locally advanced TNBC or mTNBC. The results demonstrated an impressive ORR of 73%, with similar responses regardless of PIK3CA/AKT1/PTEN alteration status and PD-L1 expression (Heeke and Tan, 2021). These data also led to the addition of a paclitaxel, ipatasertib, and atezolizumab arm in the larger phase III IPATunity130 trial (NCT03337724), and the AKT inhibitor capivasertib in combination with paclitaxel and durvalumab is being investigated in the BEGONIA trial (NCT03742102) (Turner *et al.*, 2022).

Immune Checkpoint Inhibitor-Natural Killer Cell Combination Treatment

More than 40 years ago, it was discovered that NK are lymphocytes with the ability to dissolve tumor cells. Preclinical studies showed that NK cells modulated the immune response by secreting chemokines and cytokines and releasing cytotoxic particles containing granulocytes and perforins, which cause target cell death (Terrén *et al.*, 2019). The release of the stress-inducing ligands MHC class I polypeptide-related sequence A (MICA) and MICB by tumor cells leads to the downregulation of NKG2D receptors and decreased sensitivity of NK cells, which leads to immune escape (Liu *et al.*, 2021; Shimasaki *et al.*, 2020; Xie *et al.*, 2020). These results also provide a theoretical basis for the combined application of NK cells and ICIs. The ongoing QUILT-3.067 (NCT03387085) trial is evaluating the safety and efficacy of the combination of NK cells and ICIs in patients with refractory, metastatic, or unresectable TNBC tumors. The study is unique in design because it combines avelumab with high-affinity NK (haNK) cell therapy, IL-15 cytokine administration, cancer vaccines, and metronomic chemoradiation to stimulate the innate and adaptive immune systems. Interim results of nine patients demonstrated an overall response rate of 67%, with a disease control response rate of 78% and a CR rate of 22%. Notably, the duration of the treatment responses with a median PFS of 13.7 months is very promising compared to the historical PFS of 3 months (Nangia *et al.*, 2019). NCT04551885 is examining the efficacy of the combination of avelumab and FT-516 in patients with advanced TNBC, but the results of the data are not clear.

Conclusion

Accumulating evidence corroborates that ICI monotherapy, PD-1/PD-L1 antibodies, and CTLA-4 antibodies produce only modest or low response in BC control due to its immunological silencing characteristics. Finding appropriate ways to alter the BC immune microenvironment is critical to improving the efficacy of ICIs. Increasing evidence shows that chemotherapy, surgery, radiation, targeted therapy, and cellular immunotherapy reshape the tumor microenvironment. The safety and efficacy of the combination of ICIs and these treatment strategies are summarized in this review. These clinical trials show that many unanswered questions remain about the combination of ICIs and other treatment strategies. However, the identity of reliable biomarkers for predicting response, the most effective combination of ICIs and chemotherapy drugs, the combination of ICIs and other strategies that may be used as first-line therapy, and the dose of radiotherapy that will have the most benefit for patients are not known. Many ongoing clinical trials are being performed to help select the best treatment for BC patients.

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