

The clinical promise of immunotherapy in triple-negative breast cancer

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Abstract: Triple-negative breast cancer (TNBC) is a heterogeneous disease with poorer outcomes compared to other breast cancer subtypes. Contributing to the worse prognosis in TNBC is the higher rates of relapse and rapid progression after relapse. Advances in targeted therapeutics and conventional chemotherapy for TNBC have been stymied due to the lack of specific targets. Moreover, the responses to chemotherapy in TNBC lack durability, partially accounting for the higher rates of relapse. Immunotherapy, notably immune-checkpoint blockade, has shown to improve survival and maintain robust antitumor responses in both hematologic and solid malignancies. Unlike lung cancer, melanoma, and bladder cancer, most breast cancers are not inherently immunogenic and typically have low T cell infiltration. However, among breast cancer subtypes, TNBC is characterized by greater tumor immune infiltrate and higher degree of stromal and intratumoral tumor-infiltrating lymphocytes (TILs), a predictive marker for responses to immunotherapy. Moreover, in TNBC, the high number of stromal TILs is predictive of more favorable survival outcomes and response to chemotherapy. Immunotherapy is being extensively explored in TNBC and clinical trials are showing some promising results. This article focuses on the rationale for immunotherapy in TNBC, to explore and discuss preclinical data, results from early clinical trials, and to summarize some ongoing trials. We will also discuss the potential application of immunotherapy in TNBC from a clinician's perspective.

Keywords: triple-negative breast cancer, immunotherapy, PD-1/PDL-1 antibody, CTLA-4 antibody, checkpoint inhibitors, cancer vaccines

Introduction

Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by absence of estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2) and represents about 15%–20% of all breast cancer.¹ TNBC patients often present with visceral involvement and typically show rapid progression and thus providing limited window of treatment opportunity. Tremendous advances have occurred in other subtypes of breast cancer such as HER2+ tumors with the development of targeted agents against the HER2 receptor. Monoclonal antibodies, such as trastuzumab and pertuzumab and drug–antibody conjugates, like T-DM1, have changed the management of HER2+ breast cancer.² ER+ breast cancers have agents that block estrogen signaling through either aromatase inhibition or selective ER modulation. Coupling the anti-estrogen therapy with newly approved cyclin-dependent kinase inhibitors, like palbociclib, ribociclib, and abemaciclib, has shown improvements in progression-free survival.^{3,4} In an effort to discover actionable targets and drug

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development, TNBC has been further stratified into molecular subtypes.⁵ Gene expression profiling has revealed six distinct molecular subtypes, including two basal-like, an immunomodulatory, a mesenchymal, a mesenchymal stem-like, and a luminal androgen receptor.⁵ These molecular subtypes could be utilized in identifying personalized treatment strategies as they appear to have both predictive and prognostic value.⁵

Tumor-infiltrating lymphocytes (TILs), present both intratumorally and in adjacent stromal tissues, have predictive and prognostic roles in breast cancer. Within breast cancer, increased TILs at diagnosis have been significantly associated with pathologic complete responses with neoadjuvant chemotherapy.^{6,7} Interestingly, the improved overall survival in the context of neoadjuvant therapy was only seen in TNBC and HER2+ breast cancer and this improved prognosis was inversely associated with disease stage.^{6,7} This subtype-specific disparity in overall survival may be due to elevated TILs in TNBC compared to other breast cancer subtypes.⁸ In the context of HER2+ breast cancer, increased levels of TILs have been associated with improved response to the anti-HER2 antibody, trastuzumab.⁹ In subsequent work, a high degree of TILs found in majority of TNBC have been correlated with higher likelihood of benefit from adjuvant and neoadjuvant chemotherapy, with lower risk of disease relapse.⁹⁻¹³ This association of TILs in TNBC with therapeutic response and both overall and disease-free survival underscores the prognostic value of antitumor immunity in treating patients with TNBC. The presence of TILs also serves as a predictive marker of immunotherapy response, making the examination of immunotherapy in TNBC particularly intriguing.¹⁴ However, important consideration should be made for TNBC subtypes, with IM and basal-like subtypes possessing elevated infiltration of immune cells, antigen-presenting cells, and activation of immune pathways.¹⁵ Additionally, basal-like TNBC subtypes are known to have high frequency of *BRCA1* and *BRCA2* mutations and hence unstable genetics, another predictive marker for immunotherapy response.^{5,14}

The immune system not only plays a role in tumor initiation and progression, but also participates in recognition and destruction of cancer cells. The antitumor immune response dampens development/progression through tumor-directed immune responses involving cytolytic T lymphocytes.^{16,17} For progression to occur, tumors must evade the cytotoxic antitumor response through a diverse array of mechanisms. The evasion of immune activation is recognized as a hallmark of cancer and can involve chronic activation of humoral immunity, infiltration by Th2 T cells, protumor-polarized innate inflammatory cells, downregulation of tumor-specific anti-

gens, expression of negative immune checkpoints by tumors, and the absence of major histocompatibility complexes (MHC) on the surface of tumors cells.^{14,16,17} Ultimately, these mechanisms act in concert to moderate antitumor response and promote tumor development and disease progression.¹⁸

Manipulation of the immune system represents an attractive strategy for TNBC, a breast cancer subtype that has not seen substantial advances in clinical management. Immune-checkpoint inhibitors have yielded promising results in both advanced and early-stage disease of TNBC patients and are expected to substantially improve the overall prognosis of TNBC. A focus of the field in translating immunotherapies from immunogenic tumors, like melanoma or renal cancers, to the majority of solid tumors is the identification of patients who would benefit most from immunotherapy and identification of agents to prime the tumor microenvironment.¹⁴ Of particular interest in the clinical management of TNBC would be the use of radiation or chemotherapy to augment responses to immunotherapy. Radiation increases mutational load of tumors, optimizes antigen presentation, and may act to decrease immune suppressors in the tumor microenvironment, priming the tumor for immunotherapy.¹⁹⁻²³ In addition to radiation, recent investigation into the use of platinum-based chemotherapy before the induction of immunotherapy in lung cancer has shown superior response and progression-free survival compared to the standard of care.^{24,25} In this review, we will comprehensively summarize early and ongoing clinical trials of immunotherapy in TNBC. Our goal is to offer a clinical perspective on the potential promise and perils of translating immunotherapies into TNBC and likely some other nonimmunogenic solid cancers.

Immunotherapy

Immunotherapy works through stimulation of the immune system by active immunization with cancer vaccines, or passive immunization through tumor-specific antibodies and immune modulators, like immune-checkpoint inhibitors.

Immune-checkpoint inhibitors

Immune checkpoints are a diverse set of regulatory points for the adaptive immune system, with roles in self-tolerance and antitumor immunity (Figure 1A). Physiologically, these checkpoints function in either the negative or positive regulation of the immune response, coordinating the magnitude and type of response.²⁶ The majority of published clinical trials using immune-checkpoint blockade have focused on antibodies that target cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death protein

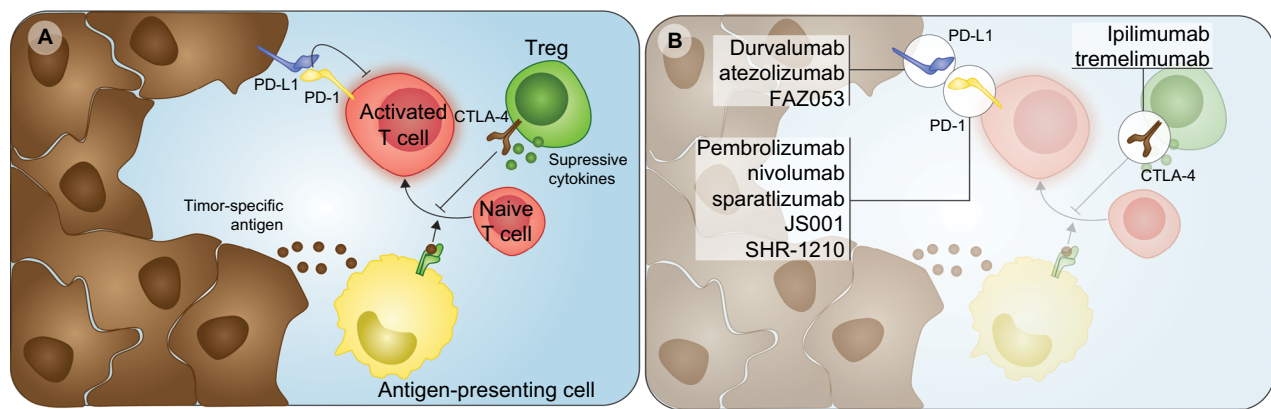


Figure 1 General mechanisms and agents targeting immune checkpoints in TNBC.

Notes: (A) Major immune cell players and interactions in the tumor microenvironment regulated by immune checkpoints. (B) Current therapies targeting PD-L1, PD-1, and CTLA-4 immune checkpoints under investigation in triple-negative breast cancer.

Abbreviations: CTLA-4, cytotoxic T lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TNBC, triple-negative breast cancer; Treg, regulatory T cell.

1 pathway (PD-1/PD-L1). As negative regulators of immune activation, the presence of CTLA-4 and PD-1 in the tumor microenvironment prevents a comprehensive antitumor immune response.²⁶ Monoclonal antibodies targeting PD-1/PD-L1 or CTLA-4 are thought to function by removing the inhibition of the antitumor immune response.²⁶ A visual summary of agents targeting these two immune checkpoints that are currently being investigated in TNBC is available in Figure 1B.

PD-1 is expressed on the surface of lymphocytes and antigen-presenting cells. In the context of antitumor immunity, the binding of PD-1 on T cells with the ligands, PD-L1 or PD-L2, functions to suppress signals downstream of T-cell-receptor activation.^{27,28} With a lower side effect profile compared to anti-CTLA-4 and a wider range of approvals by the Food and Drug Administration (FDA), agents targeting PD-1 or PD-L1 have become a focus of moving immune-checkpoint blockade into many tumors. Several agents, such as pembrolizumab (anti-PD-1), nivolumab (anti-PD-1), atezolizumab (anti-PD-L1), avelumab (anti-PD-L1), and durvalumab (anti-PD-L1), have shown to be effective in various malignancies and are approved for treatment in melanoma, non-small-cell lung cancer, Hodgkin's lymphoma, bladder cancer, gastroesophageal cancer, primary mediastinal large B-cell lymphoma, cervical cancer, renal cancer, and head and neck cancer.²⁹ Recent unprecedented approval of pembrolizumab in metastatic cancers with microsatellite instability or deficiency in DNA mismatch repair irrespective of the tissue of origin emphasizes the importance of mutational burden in response to immune-checkpoint blockade.^{30,31}

PD-L1 expression has been found in 20%–50% of all breast cancer subtypes and its expression has been associated

with higher histologic grades, larger tumors, and absence of hormone receptors.³² Higher PD-L1 expression has been observed in TNBCs as compared to non-TNBCs.^{33–35} This increased expression may be a result of genomic amplification of 9p24.1, containing *CD274* (PD-L1) and *PDCD1LG2* (PD-L2) in a subset of TNBC, but not ER+ tumors.³⁶ Across a number of malignancies, the expression of PD-L1 has been associated with increased TILs and response to anti-PD-L1 immune-checkpoint blockade.^{37–44} In the context of the latter, PD-L1 staining in melanoma and lung cancer has been used to identify patients that would likely benefit from anti-PD-1/PD-L1 therapies.⁴⁵ Interestingly, the presence of PD-1+ lymphocytes and PD-L1 expression in breast cancer has been linked to poor prognosis in several reports.^{33,34} However, the immunohistochemical (IHC) staining of PD-1/PD-L1 was also tied to increased tumor stage, nodal involvement, triple-negative status, and Ki-67 proliferative marker staining, all independent poor prognostic indicators.^{33,34} More recently, the expression of PD-L1 in breast cancer, and specifically in basal-like TNBC, has been associated with longer overall and disease-free survival.^{46,47} The use of PD-L1 staining to segregate TNBC patients may be useful with increasing single-agent response rates from 5%–8.8%^{48,49} to 18.5%–26%^{50–52} with the use of PD-L1 IHC staining as inclusion criteria.

Pembrolizumab

Receiving the initial FDA approval for unresectable or metastatic melanoma in 2014, pembrolizumab is one of the most studied of the immune-checkpoint therapies. Highlighting this fact was the presentation of clinical trial results in 25 tumor types at the 2018 annual meeting of the American Society of Clinical Oncology (ASCO). In 2016,

the KEYNOTE-012 trial, Phase Ib study reported efficacy with acceptable safety profile when pembrolizumab was given 10 mg/kg every 2 weeks to patients with heavily pretreated, advanced TNBC.⁵⁰ Among the 27 patients who were evaluated for antitumor activity, the overall response rate was 18.5%, with median response time of 17.9 weeks.⁵⁰ A single-agent Phase II study examining a 200 mg dose given once every 3 weeks is ongoing. The KEYNOTE-086 trial is currently investigating the use of pembrolizumab in metastatic TNBC (NCT02447003) at 200 mg every 3 weeks. In the oral session at the 2017 ASCO meeting, cohort A and B were presented.^{48,52} Cohort A consisted of TNBC patients that progressed on at least one systemic therapy. In this 170-patient cohort, 8 (4.7%) responded and 13 (7.6%) achieved disease control, to include stable disease, partial response, and complete response, for 24 weeks or longer.⁴⁷ Additionally, one patient (0.6%) had a complete response to pembrolizumab monotherapy, and 27% had an initial reduction in target lesion.⁴⁷ Cohort B of the KEYNOTE-086 trial consisted of metastatic TNBC with PD-L1+ tumors, as defined by an IHC-based composite score, with no prior systemic therapy. In this cohort, objective responses were seen in 23% of 52 patients.⁵² The increased response in cohort B may be a result of the use of pembrolizumab as a first-line therapy and the use of PD-L1+ tumors as an inclusion criterion, with only 58% of the enrolled patients possessing a combined positive PD-L1 composite score of greater than 1.⁵²

Similar to recent success of combinatorial platinum and anti-PD-1 therapy in lung cancer,^{24,25} the use of DNA damaging agents may improve response by inducing cancer cell death and releasing tumor-specific antigens. In locally advanced breast cancer, the addition of pembrolizumab to standard neoadjuvant chemotherapy (paclitaxel followed by doxorubicin and cyclophosphamide) increased the rate of pathologic complete response approximately threefold in the I-SPY 2 trial.⁵³ The addition of pembrolizumab to chemotherapy had a complete pathologic response of 60% vs 20% with chemotherapy-alone arm.⁵³ Initial data on a small cohort of patients in the KEYNOTE-173 presented at ASCO 2017 suggested improved objective response rate of 100% with combination of pembrolizumab and carboplatin vs 80% in another experimental group (nab-paclitaxel + pembrolizumab).⁵⁴ In spontaneous tumor models of *BRCA1*-mutated TNBC, the use of cisplatin inhibited tumor growth and functioned additively with anti-PD-L1 and anti-CTLA-4 combinatorial therapy.⁵⁵ A similar strategy of the use of poly-ADP ribose polymerase (PARP) inhibitors, selective single-strand DNA inhibitors, in *BRCA*-mutated TNBC and ovarian

cancer found a 45% objective response rate in combination with pembrolizumab,⁵⁶ compared to the single-agent Phase I trial of the same PARP inhibitor (niraparib) response rate of 16.7%, suggesting the combination of the two may function synergistically.⁵⁷

Anti-PD-L1 therapies

Initial phase I findings of the anti-PD-L1 monoclonal antibody (MPDL3280A, atezolizumab) in metastatic TNBC were also recently reported. Of the nine patients evaluable for efficacy, the overall response rate was 33% (one complete and two partial responders) among advanced TNBC patients, 90% of whom were previously treated with more than two prior regimens and one-third of whom enrolled had visceral metastases.⁵⁸ Similarly, a larger-scale Phase Ib study involving 168 patients, with 57 TNBC patients, who previously received taxane and anthracycline therapies, was used to evaluate the anti-PD-L1 agent (avelumab).⁴⁹ Across the entire cohort, the objective response rate was 5.4% with an additional 40 patients developing stable disease.⁴⁹ Importantly, TNBC patients with PD-L1 expression on immune cells had the clinical response as high as 44.4% vs 2.6% in those TNBC patients without the PD-L1-positive immune cells.⁴⁹ Similar response rate of 48.4% was seen using durvalumab in conjunction with neoadjuvant GeparNeuvo (NCT02685059).⁵⁹ The variable expression patterns of PD-L1 in a tumor led to investigations into antibody–drug conjugates (ADC) of anti-PD-L1 with monomethyl auristatin, an antimetabolic drug.⁶⁰ Using an anti-PD-L1 antibody with enhanced activity for glycosylated PD-L1, Li et al demonstrated that the use of the ADC enhances efficacy of immunotherapy and increases bystander-killing of adjacent tumor cells.⁶⁰

Combination of checkpoint blockade

CTLA-4 functions earlier in the T cell activation process and is a major suppressive mechanism of the regulatory T cell (Treg).^{26,61} Recent research has suggested that depletion of Tregs by anti-CTLA-4 therapy is one of the major reasons leading to therapeutic responses.^{62,63} The nonredundant function of PD-1 and CTLA-4 in eliciting and maintaining immune cell activation led to combinatory therapy blocking the two immune checkpoints. In both melanoma and lung cancer, the use of nivolumab and ipilimumab (anti-CTLA-4) antibody has demonstrated better responses compared to nivolumab or chemotherapy alone.^{64,65} Interestingly, the efficacy of such combination relies on cancer types. In lung cancer the combination of nivolumab and ipilimumab did not perform any better than nivolumab alone in progression-

free and overall survival regardless of PD-L1 staining.⁶⁵ This has not slowed down the exploration of combinatorial anti-CTLA-4/PD-1 trials, with an ongoing Phase I/II open-label trial of nivolumab plus ipilimumab vs nivolumab alone for patients with metastatic solid tumors, which include those with TNBC (NCT01928394). Additionally, a single-arm Phase II study of durvalumab in combination with the anti-CTLA-4, tremelimumab, is recruiting metastatic HER2–breast cancer patients (NCT02536794).

The combination of immune-checkpoint blockade with other drugs or targeting other immune checkpoints is moving forward in breast cancer (Figure 2). LAG-3 is another negative checkpoint that binds to MHC II receptors and modulates antigen-presenting cells; IMP321 (LAG-3Ig), a competitive inhibitor for LAG-3/MHC II receptor binding, when combined with paclitaxel had objective response rate of 50% as a first-line therapy.⁶⁶ Targeting LAG-3 is the basis of several clinical trials in breast cancer, being used as an adjuvant to paclitaxel (NCT02614833) and in conjunction with anti-PD-1 therapy in TNBC (NCT02460224 and NCT03250832). Preliminary results of anti-PD-1 with anti-LAG-3 therapy found an objective response of 40% in TNBC.⁶⁷ In contrast, OX-40 is a positive immune-checkpoint functioning in maintaining T cell proliferation after receptor activation and suppressing Treg function.^{68,69} A Phase I/II trial into the combination of agonistic monoclonal antibody combined with either

anti-PD-1 or anti-CTLA-4 therapies is recruiting advanced cancers including TNBC (NCT03241173). With a similar rationale, NKTR-214, a CD122 agonist, is being evaluated in TNBC with initial result of a 33% response rate when paired with anti-PD-1 therapy.⁷⁰ In contrast, the targeting of tumor-associated macrophages with anti-CSF1 and anti-PD-1 therapy had an objective response rate of 3.3% in a Phase Ib trial, underscoring the importance of selecting the right combinatorial agents for immune-checkpoint blockade.⁷¹ Comprehensive summaries of the diverse range of related Phase I and II trials are listed as in the neoadjuvant (Table 1) and adjuvant (Table 2) settings. Additionally, small-molecule inhibitors against growth factors, PARP inhibitors, other immune checkpoints, and/or radiotherapy are currently recruiting advanced-stage TNBC patients in combination with anti-PD-1/PD-L1 or anti-CTLA-4 antibodies (Table 3).

Combining radiotherapy/cryotherapy with immune-checkpoint blockade

Radiotherapy has potential to increase tumor mutation burden and increase tumor immunogenicity.^{21–23} The combination of radiotherapy with immune-checkpoint blockade has been studied in several tumor types like prostate cancer, lung cancer, sarcoma, and melanoma.^{21,23,72,73} The combination of local radiation to primary breast tumor with CTLA-4 blockade and PD-1/PD-L1 blockade has shown synergistic activity in

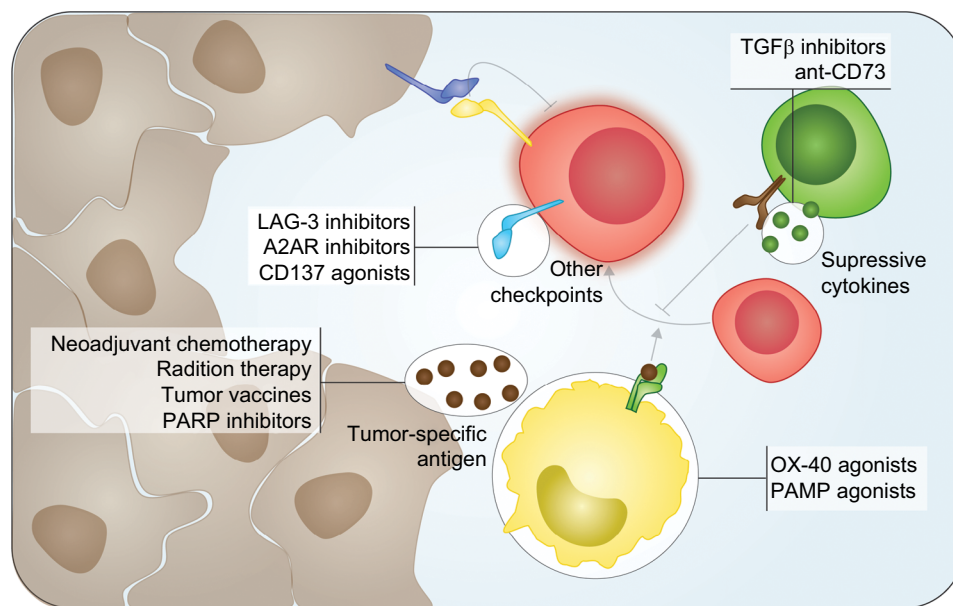


Figure 2 Emerging immunotherapy targets and combinatorial agents in TNBC.

Notes: Current trials focus on modulating the tumor microenvironment by increasing mutational burden in tumors, stimulating antigen-presenting cells, decreasing suppressive functions of Tregs, and targeting other negative immune checkpoints on effector T cells.

Abbreviations: PAMP, pathogen-associated molecular pattern; PARP, poly-ADP ribose polymerase; TGFβ, transforming growth factor beta; TNBC, triple-negative breast cancer; Treg, regulatory T cell.

Table 1 Clinical trials using immunotherapy with neoadjuvant chemotherapy

Clinical trial	Agent	Target	Combinatorial agent	Phase	Recruitment status
NCT02983045	Nivolumab	PD-1	NKTR-214 (CD122), ipilimumab (CTLA-4)	I/II	Recruiting
NCT02489448	Durvalumab	PD-L1	nab-Paclitaxel, doxorubicin, cyclophosphamide	I/II	Recruiting
NCT02685059	Durvalumab	PD-L1	nab-Paclitaxel, epirubicin, cyclophosphamide	II	Active, not recruiting
NCT03289819	Pembrolizumab	PD-1	nab-Paclitaxel, epirubicin, cyclophosphamide	II	Recruiting
NCT03036488	Pembrolizumab	PD-1	Carboplatin, paclitaxel, doxorubicin, epirubicin, cyclophosphamide	III	Recruiting
NCT03281954	Atezolizumab	PD-L1	Paclitaxel, doxorubicin, cyclophosphamide	III	Recruiting

Abbreviations: CTLA-4, cytotoxic T lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

Table 2 Clinical trials using adjuvant immunotherapy

Clinical trial	Agent	Target	Combinatorial agent	Phase	Recruitment status
NCT03487666	Nivolumab	PD-1	Capecitabine	II	Recruiting
NCT02926196	Avelumab	PD-L1	None	III	Recruiting
NCT02954874	Pembrolizumab	PD-1	None	III	Recruiting

Abbreviations: PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

preclinical murine models.^{19,20} Current investigations into the use of combinatorial radiotherapy and immune-checkpoint blockade include a Phase II trial of pembrolizumab plus radiotherapy in metastatic TNBC (NCT02730130). This trial focuses on the benefit or harm of radiation concurrently with pembrolizumab. Similarly, a Phase II trial of nivolumab after radiotherapy induction or chemotherapy (low-dose doxorubicin, cyclophosphamide, or cisplatin) in patients with metastatic TNBC (NCT02499367) is being sponsored by the Netherlands Cancer Institute. Recent Phase II findings by the group have called into question of pairing these therapies with immune-checkpoint blockade, with an initial report that irradiation and/or cyclophosphamide halved the response rate compared to nivolumab alone.⁷⁴ Other combinatory pilot studies have started, including the combination of stereotactic radiosurgery for oligometastatic breast cancer with pembrolizumab (NCT02303366) and the combination of hypofractionated radiotherapy with pembrolizumab in patients with advanced cancers, including breast cancer (NCT02303990).

Cancer vaccine

Cancer vaccines constitute another novel strategy in cancer immunotherapy. Therapeutic cancer vaccines have potential to elicit immune response against tumor-specific and tumor-associated antigens. Cancer vaccines include monovalent vaccines that provide a single tumor-associated antigen (TAA) target for the immune system and polyvalent peptide vaccines that provide multiple TAA targets. Cellular vaccines are mod-

ified tumor cells or antigen-presenting cells. A current list of clinical trials in TNBC using tumor vaccines or oncolytic viruses with checkpoint blockade is summarized in Table 4. The use of polyvalent and antigen-specific vaccines offers the potential of truly precision therapy by using the mutations or drivers of a tumor to elicit an immune response. In high-risk breast cancers that include TNBC, cancer vaccines could play a role in preventing relapse; however, to date, multiple cancer vaccine trials have failed to show improvement in clinical outcome. Notably in a phase III trial of metastatic breast cancer, the targeting of sialyl-Tn, a carbohydrate antigen found on glycoproteins, demonstrated no improvements in progression-free interval or overall survival.⁷⁵ In a follow-up analysis of results from the same trial, the authors did identify improvement in progression-free interval, overall survival, and antibody titer response in a subset of the patients receiving concomitant endocrine therapy.⁷⁶

The use of antigen-specific vaccine strategies provides a selection pressure for tumors to evolve mechanisms to evade the narrow epitope targeting.⁷⁷ One way of possibly overcoming this evasion is the use of personalized vaccines based on neoantigen fitness, or the likelihood of the antigen to be presented by the MHC and activate T cells. Although a number of barriers exist to prevent personalized vaccine usage for broad spectrum of patients in real time, the selection of multiple antigens based on the predicted ability to activate the antitumor immune system has shown promise in melanoma.^{78–82} When paired with anti-PD-1 therapy, the vaccines work synergistically with immune-checkpoint blockade.^{79,81}

Table 3 Immunotherapy in combination with various agents under investigation in advanced triple-negative disease

Clinical trial	Agent	Target	Combinatorial agent	Phase	Recruitment status
NCT02655822	CPI-444	A2AR	Atezolizumab (PD-L1)	I	Recruiting
NCT03454451	CPI-006	CD73	Pembrolizumab (PD-I), CPI-444 (A2AR)	I	Recruiting
NCT03251313	JS001	PD-I	Gemcitabine and cisplatin	I	Recruiting
NCT03012230	Pembrolizumab	PD-I	Ruxolitinib (JAK)	I	Recruiting
NCT02890069	Spartalizumab	PD-I	Everolimus (mTOR), panobinostat (HDAC), LCL161 (apoptosis), QBM076 (CXCR2)	I	Recruiting
NCT03250832	TSR-033	LAG-3	Anti-PD-I antibodies	I	Recruiting
NCT02646748	Pembrolizumab	PD-I	Itacitinib (JAK), INCB050465 (PI3K)	I	Recruiting
NCT02947165	NIS793	TGFβ	Spartalizumab (PD-I)	I	Recruiting
NCT03549000	NZV930	CD73	Spartalizumab (PD-I), NIR178 (A2AR)	I	Not yet recruiting
NCT02838823	JS001	PD-I		I	Active, not recruiting
NCT02622074	Pembrolizumab	PD-I	nab-Paclitaxel, doxorubicin, cyclophosphamide, carboplatin	I	Active, not recruiting
NCT03292172	Atezolizumab	PD-L1	RO6870810 (BET)	I	Recruiting
NCT02936102	FAZ053	PD-L1	Spartalizumab (PD-I)	I	Recruiting
NCT03579472	M7824	PD-L1/TGFβ	Eribulin	I	Recruiting
NCT0280744	MCS110	CSF-1	Spartalizumab (PD-I)	I	Recruiting
NCT02460224	LAG525	LAG-3	Spartalizumab (PD-I)	I/II	Recruiting
NCT03241173	INCAGN01949	OX-40	Nivolumab (anti-PD-I) and/or ipilimumab (anti-CTLA-4)	I/II	Recruiting
NCT03591276	Pembrolizumab	PD-I	Pegylated doxorubicin	I/II	Not yet recruiting
NCT02628132	Durvalumab	PD-L1	Paclitaxel	I/II	Recruiting
NCT02657889	Pembrolizumab	PD-I	Niraparib (PARP)	I/II	Active, not recruiting
NCT03356860	Durvalumab	PD-L1	Paclitaxel, epirubicin, cyclophosphamide	I/II	Recruiting
NCT02513472	Pembrolizumab	PD-I	Eribulin	I/II	Recruiting
NCT02484404	Durvalumab	PD-L1	Olaparib (PARP)	I/II	Recruiting
NCT02708680	Atezolizumab	PD-L1	Entinostat (HDAC)	I/II	Recruiting
NCT02734004	Durvalumab	PD-L1	Olaparib (PARP)	I/II	Recruiting
NCT02614833	IMP321	LAG-3	Paclitaxel	II	Recruiting
NCT03394287	SHR-1210	PD-I	Apatanib (VEGFR)	II	Recruiting
NCT03414684	Nivolumab	PD-I	Carboplatin	II	Recruiting
NCT02648477	Pembrolizumab	PD-I	Doxorubicin	II	Recruiting
NCT03004183	Pembrolizumab	PD-I	SBRT and ADV/HSV-tk	II	Recruiting
NCT02536794	Durvalumab	PD-L1	Tremelimumab (CTLA-4)	II	Recruiting
NCT02752685	Pembrolizumab	PD-I	nab-Paclitaxel	II	Recruiting
NCT03095352	Pembrolizumab	PD-I	Carboplatin	II	Recruiting
NCT03184558	Pembrolizumab	PD-I	Bemcentinib (AXL)	II	Recruiting
NCT02971761	Pembrolizumab	PD-I	Enobosarm (selective androgen receptor modulator)	II	Recruiting
NCT02554812	Avelumab	PD-L1	Utomilumab (CD137)	II	Recruiting
NCT02849496	Atezolizumab	PD-L1	Olaparib (PARP)	II	Recruiting
NCT03483012	Atezolizumab	PD-L1	Stereotactic radiosurgery	II	Recruiting
NCT03164993	Atezolizumab	PD-L1	Pegylated doxorubicin	II	Recruiting
NCT01898117	Atezolizumab	PD-L1	Carboplatin and cyclophosphamide or paclitaxel	II	Recruiting
NCT02883062	Atezolizumab	PD-L1	Carboplatin	II	Recruiting
NCT02981303	Pembrolizumab	PD-I	Imprime PGG (PAMP)	II	Recruiting
NCT02819518	Pembrolizumab	PD-I	nab-Paclitaxel, gemcitabine, carboplatin	III	Active, not recruiting
NCT03498716	Atezolizumab	PD-L1	Paclitaxel, epirubicin, cyclophosphamide	III	Recruiting
NCT03197935	Atezolizumab	PD-L1	nab-Paclitaxel, doxorubicin, cyclophosphamide	III	Recruiting
NCT02425891	Atezolizumab	PD-L1	nab-Paclitaxel	III	Active, not recruiting
NCT03125902	Atezolizumab	PD-L1	Paclitaxel	III	Recruiting

Abbreviations: CTLA-4, cytotoxic T lymphocyte-associated antigen 4; HDAC, histone deacetylase; mTOR, mammalian target of rapamycin; PAMP, pathogen-associated molecular pattern; PARP, poly-ADP ribose polymerase; PD-I, programmed cell death protein I; PD-L1, programmed death ligand I; TGFβ, transforming growth factor beta; VEGFR, vascular endothelial growth factor receptor.

Table 4 Cancer vaccine and immunotherapy clinical trials currently being conducted

Clinical trial	Agent	Combinatorial agent	Phase	Recruitment status
NCT03362060	PVX-410	Pembrolizumab (PD-1)	I	Recruiting
NCT02826434	PVX-410	Durvalumab (PD-L1)	I	Recruiting
NCT03256344	T-VEC	Atezolizumab (PD-L1)	I	Recruiting
NCT03289962	RO7198457	Atezolizumab (PD-L1)	I	Recruiting
NCT01986426	LTX-315	Pembrolizumab (PD-1), ipilimumab (CTLA-4)	I	Active, not recruiting
NCT02432963	p53MVA	Pembrolizumab (PD-1)	I	Active, not recruiting
NCT02779855	T-VEC	Paclitaxel	I/II	Recruiting
NCT03387085	NANT	Aldoxorubicin, avelumab (PD-L1), bevacizumab (VEGF), capecitabine, cisplatin, cyclophosphamide, fluorouracil, nab-paclitaxel	I/II	Recruiting
NCT03328026	SV-BR-1-GM	Pembrolizumab (PD-1), ipilimumab (CTLA-4)	I/II	Recruiting

Abbreviations: CTLA-4, cytotoxic T lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; VEGF, vascular endothelial growth factor.

Similarly, the use of polyvalent vaccines derived from multiple antigens of the tumor or cell line has shown positive results in colorectal cancer,⁸³ prostate cancer,⁸⁴ follicular lymphoma,⁸⁵ and lung cancer.⁸⁶ The high rates of genomic instability within TNBC make the neoantigen fitness-based and polyvalent vaccination strategies intriguing.

Another avenue is the immunization of tumors with virus, such as the use of vaccinia virus modified to express MUC1 and interleukin 2.⁸⁷ The viral-mediated expression of MUC1, a nonspecific tumor antigen, to elicit an antitumor immune response mirrors the sialyl-Tn vaccination strategy.⁷⁵ Although partial tumor regression occurred in only 2 of the 31 patients with metastatic breast cancer, 14 patients developed stable disease.⁸⁷ A similar strategy of creating a tumor-specific antigen using a virus is being investigated in using a Modified Vaccinia Ankara virus to re-express wild-type p53 in combination with pembrolizumab.⁸⁸ Additionally, several small pilot studies of the oncolytic herpes simplex virus, HF10, demonstrated significant histopathologic response and reduction in tumor size of 30%–100%.^{89,90} The use of HF10 is currently being investigated in combination with chemotherapy for treatment of patients with unresectable pancreatic cancer (NCT03252808). Like these cancer-specific viral inoculations, newer vaccine approaches are on the horizon that can simultaneously vaccinate and use immune-checkpoint blockers to therapeutically block immune-suppressive pathway, which may increase the objective response rates.

Conclusion

TNBC remains the breast cancer subtype with the worse outcomes. Despite the progress made across many other cancers and other subtypes of breast cancer, effective treatment for advanced TNBC remains elusive. Immunotherapy with checkpoint inhibitors has shown promise, but response

rates are very modest as single agent in advanced TNBCs. We have seen durable response in early-phase trials with anti-PD1 or anti-PD-L1, but response rates are up to 10% in unselected TNBC patients and improves only slightly to 20%–30% when patients are selected based on IHC-based PD-L1+ tumors.^{48–52}

TILs appear to be higher in TNBC and multiple series of investigations have shown that higher TILs are associated with improved overall survival and higher response rate.^{9–13} The immunogenic microenvironment is associated with a better prognosis as a result of a higher likelihood of benefit from chemotherapy and possibly from immunotherapy, whereas cold immune microenvironment carries greater risk of relapse and lower benefit from chemotherapy and possibly immunotherapy.^{6,7,14} Identifying the subset of TNBC who will benefit most from available means of immune modulation should remain the priority while new targets and drugs are being developed. Biomarker-based patient identification, such as *BRCA* mutation, mutations in homologous recombination, and PD-L1 IHC testing, may improve clinical responses, but effort needs to focus on improving the development and standardization of valuable biomarkers of response.^{49,55,56}

Akin to the identification of biomarkers for immunotherapy response in TNBC, investigations are currently underway for combinatorial agents used as short-term induction treatment to increase immunogenicity in TNBC. Careful consideration of combination strategies, like the use of PARP inhibitors or specific chemotherapies, could be a highly successful strategy for immunotherapy in TNBC.

The development and early-phase trials into new immune checkpoints and tumor vaccine strategies for TNBC are compounding the excitement in the field. For a cancer that has not seen substantial advances in clinical management in recent decades, immunotherapy gives us a hope for durable

clinical response for patients with TNBC. New agents and new combinations of immunotherapies may unlock the key to truly personalized cancer medicine. Belying the promise of immunotherapy in TNBC is a number of steps required to translate these therapies into meaningful outcomes and ultimately could turn out to be a hype. Specifically, efforts focused on understanding biology, biomarker selection, and strategies to enhance immunotherapy response are vital to the success of immunotherapy in TNBC and cancers in general.

Abbreviations

TNBC, triple-negative breast cancer; TILs, tumor-infiltrating lymphocytes; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; MHC, major histocompatibility complexes; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1; IHC, immunohistochemical; ASCO, American Society of Clinical Oncology; PARP, poly-ADP ribose polymerase; ADC, antibody–drug conjugates; Treg, regulatory T cell; TAA, tumor-associated antigen.

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Disclosure

The authors report no conflicts of interest in this work.

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