Immunotherapy for Triple-Negative Breast Cancer: A Focus on Immune Checkpoint Inhibitors

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Abstract

Triple-negative breast cancer (TNBC) is a clinically heterogeneous and molecularly diverse disease. At present, chemotherapy is the standard treatment for early-stage and metastatic TNBC. The paucity of actionable targets, lack of targeted therapies, and relatively poor prognosis of patients with TNBC have created ample opportunity to evaluate novel treatment approaches. An improved understanding of the immunogenicity of TNBC has led to clinical studies of several immunotherapeutic agents. Early phase I trials with immune checkpoint inhibitors in TNBC report an overall response rate of up to 19% with durable clinical responses and a tolerable safety profile. The hope is that immunotherapy strategies will provide new therapeutic options for TNBC. This review focuses on the emerging data about immune checkpoint inhibitors in the treatment of TNBC.

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Introduction

Triple-negative breast cancer (TNBC) is clinically defined as breast tumors lacking expression of estrogen receptor (ER) and progesterone receptor, with normal human epidermal growth factor receptor type 2 *(HER2)* gene copy number and expression.[1] It accounts for approximately 15% to 20% of all breast cancers and is more prevalent in younger women and in African-American women.[2] TNBC has an aggressive natural history, with an increased mortality rate during the first 5 years with most deaths occurring in the first 5 years.[3] Typically, there is a high risk of early recurrence and this tends to occur within the first 4 years after diagnosis. Compared with other subtypes, visceral metastasis is more likely, involving the brain and lungs.[4]

TNBC is also characterized by molecular heterogeneity. There is diversity in the histologic patterns and transcriptional subtypes. The majority of TNBCs are high-grade invasive ductal carcinomas, but there is a small subset with distinct pathology and indolent biologic behavior, such as adenoid cystic carcinoma.[5] Lehmann and colleagues proposed a classification that defined several molecular subtypes of TNBC; these include 2 basal-like (BL1 and BL2), an immunomodulatory, a mesenchymal, a mesenchymal stem-like, and a luminal androgen receptor subtype.[6] Similarly, another gene expression analysis suggested the following subgroups: luminal/androgen receptor, mesenchymal, BL/immune-suppressed, and BL/immune-activated.[7] These classifications help to increase our understanding of the biology of TNBC and identify rational therapeutic strategies for TNBC subtypes.

Chemotherapy is the current standard-of-care treatment of TNBC in the adjuvant, neoadjuvant, and metastatic settings. TNBCs are highly sensitive to chemotherapy, as evidenced by pathologic complete response (pCR) rates in the 30% to 40% range after neoadjuvant chemotherapy, compared with complete response (CR) rates for ER-positive breast cancer, which range from 10% to 25%. However, TNBC has higher rates of relapse, which has been referred to as the triple-negative paradox.[8-10] The need to improve the outcomes of patients with TNBC drives large-scale clinical investigational efforts to evaluate novel therapeutic approaches. Immunotherapy, such as checkpoint inhibitors, represents a modality that has changed the treatment landscape for other solid tumors, especially melanoma and non–small cell lung cancer (NSCLC). The potential role of immune checkpoint blockade therapy in TNBC is the focus of this review.

Rationale for Immunotherapy in Triple-Negative Breast Cancer

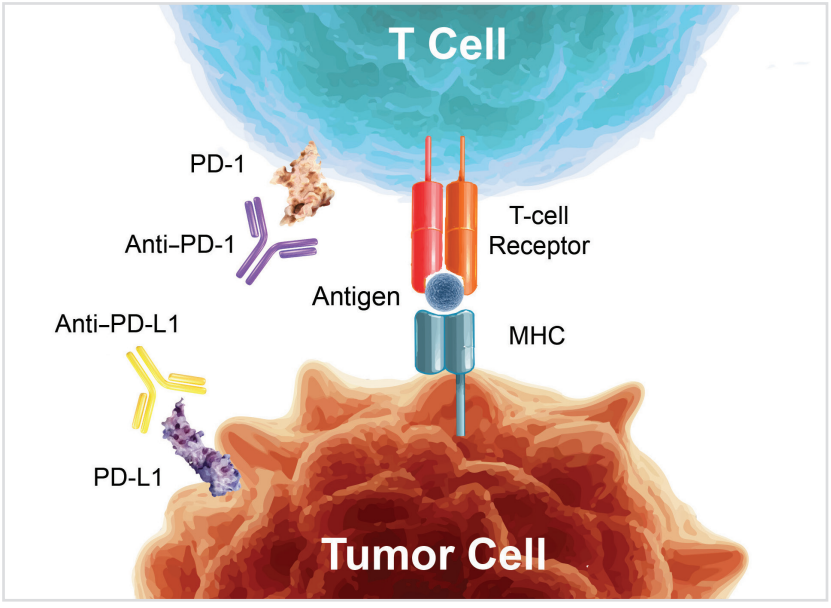
Breast cancer is not traditionally considered an immunogenic tumor. Available literature suggests that it is reasonable to investigate therapies that target programmed death-1/programmed death ligand-1 (PD-1/PD-L1) in TNBC. PD-1 is a checkpoint receptor expressed primarily by activated T cells, and it limits T-cell effector functions. PD-L1, a T-cell inhibitory molecule, is expressed on cancer cells, tumor-infiltrating inflammatory cells, and immune cells. The binding of PD-L1 to PD-1 on T cells is a major mechanism of tumor immune evasion (**Figure**). Mittendorf and colleagues reported higher expression of PD-L1 in TNBC than in hormone receptor (HR)-positive breast cancers.[11] The analysis on tissue microarrays showed that 19% of 105 primary TNBC specimens were PD-L1 positive.

In addition, Tung and colleagues found that 26% of primary TNBCs (51 of 193) expressed PD-L1 on the surface of the cancer

cells,[12] although the role of PD-L1 as a biomarker is unclear. Based on the current clinical studies described later, it may not be completely predictive of treatment response. Additionally, there is variability in the methodologies to assess PD-L1 expression, in the different numerical cut-off values for positivity, and in the analysis being performed on different types of tissue, which include archived, fresh, primary, and metastatic specimens.

The presence of tumor-infiltrating lymphocytes (TILs) suggests an immune response to tumor-associated antigens. Several studies have evaluated TILs in breast cancer specimens and a higher level of TILs has been reported in TNBCs compared with HR-positive breast cancers.[13] Also, available data indicate that TILs have prognostic significance in TNBC.[14,15] Furthermore, TNBC is characterized by genomic instability and high rates of genetic mutations, which implicate production of more neoantigens and increased immunogenicity.[16,17] The tumor mutational load is higher in TNBC compared with other subtypes.[18] Taken together, there is strong rationale to therapeutically target TNBC with monoclonal antibodies that block the PD-1/PD-L1 axis. Findings from some of the early phase I clinical trials with checkpoint inhibitors that enrolled patients with metastatic TNBC will be discussed (**Table**).

FIGURE. Immune Checkpoint Blockade



MHC indicates major histocompatability complex. A major checkpoint, mediated by the interaction between PD-1 on T cells and its ligand, PD-L1, on tumor cells, has been the focus of many clinical trials. Immune checkpoint blockade has changed the treatment landscape of several solid tumors. Source: Drake CG, Lipson EJ, Brahmer JR. Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer.
Source: *Nat Rev Clin Oncol.* 2014 Jan;11(1):24-37.

TABLE. Select Clinical Trial Results of Checkpoint Inhibitors in Metastatic Triple-Negative Breast Cancer

Trial	Phase	Agents	Evaluable Subjects for Response	PD-L1 Status	Endpoints
KEYNOTE-012, NCT01848834	Ib	Pembrolizumab	27 TNBC	PD-L1 expression in stroma or in ≥ 1% of tumor cells	ORR: 18.5% 1 CR, 4 PRs, and 7 SD 6-month PFS: 24.4%
GO27831, NCT01375842	I	Atezolizumab	21 TNBC	PD-L1 ≥ 5% on tumor-infiltrating immune cells	ORR: 19% 2 CRs, 2 PRs 6-month PFS: 27%
JAVELIN, NCT01772004	Ib	Avelumab	168 58 TNBC	Unselected	In the overall group: ORR: 4.8% 1 CR, 7 PRs, and 39 SD In TNBC: ORR: 8.6% 5 PR and 13 SD
GP28328, NCT01633970	Ib	Atezolizumab and nab-paclitaxel	32 TNBC	Unselected	ORR: 38% 3% CR, 34% PR, 44% SD

CR indicates complete response; ORR, overall response rate; PD-L1, programmed cell death ligand; PFS, progression-free survival; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

PD-1 Inhibitors

Nivolumab and pembrolizumab are PD-1–targeting antibodies that are approved by the FDA. Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody directed against PD-1, and it is indicated in the treatment of several cancers, including wild-type *BRAF* and mutant *BRAF* metastatic melanoma; previously treated metastatic NSCLC; advanced renal cell cancer after prior antiangiogenic therapy; recurrent or metastatic squamous cell carcinoma of the head and neck on or after platinum-based therapy; previously treated locally advanced or metastatic urothelial carcinoma progressed during or following platinum-based chemotherapy; and relapsed or progressed classical Hodgkin lymphoma after auto-hematopoietic stem cell transplant and posttransplantation brentuximab vedotin.[19-28]

Several phase I and II trials are being conducted with nivolumab in TNBC. Nivolumab is currently being studied in an adaptive phase II trial of metastatic TNBC in which it is being given as monotherapy after induction treatment with various agents, including radiation, low-dose doxorubicin, metronomic

cyclophosphamide, and cisplatin (NCT02499367). Nivolumab is also being evaluated in combination with TAK-659, an inhibitor of spleen tyrosine kinase, in a phase Ib study of solid tumors with a dose expansion in metastatic TNBC (NCT02834247).

Pembrolizumab is a humanized monoclonal antibody of the IgG4 isotype that binds to PD-1 and blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab was approved by the FDA in several solid tumors including metastatic melanoma; in combination with pemetrexed plus carboplatin as a frontline treatment for patients with metastatic or advanced nonsquamous non–small cell lung cancer (NSCLC); untreated metastatic NSCLC whose tumors have high PD-L1 expression and no EGFR or anaplastic lymphoma kinase aberrations; metastatic NSCLC whose tumors express PD-L1 after disease progression on or after platinum-containing chemotherapy; and recurrent or metastatic head and neck squamous cell cancer with disease progression on or after platinum-containing chemotherapy.[29-32] Pembrolizumab was also granted accelerated approval for refractory classical Hodgkin lymphoma in adult and pediatric patients who have relapsed after 3 or more lines of therapy.[33]

KEYNOTE-012 (NCT01848834) was a multicohort, nonrandomized phase 1b basket trial that enrolled multiple subpopulations of tumors including metastatic TNBC, advanced head and neck cancer, advanced urothelial cancer, and advanced gastric cancer. Nanda and colleagues reported the results of the first single-agent anti-PD-1 therapy in the metastatic TNBC cohort within KEYNOTE-012.[34] This trial screened 111 metastatic TNBC patients for PD-L1 positivity, defined as staining in the stroma or in ≥1% of tumor cells assessed immunohistochemically using a 22C3 antihuman PD-1 antibody. Of of the 65 patients (58.6%) with tumors that were PD-L1–positive, 32 patients were treated with pembrolizumab 10 mg/kg intravenously (IV) every 2 weeks. About 50% of patients had at least 3 prior regimens for metastatic disease; 25% of patients received 5 or more previous lines. The median number of prior therapies for metastatic disease was 2 (range, 0-9). Most patients (87.5%) had previous neoadjuvant or adjuvant therapy. All patients had prior taxane exposure and 72% had prior anthracyclines.

The overall response rate (ORR) based on central review assessed by RECIST v1.1 in 27 evaluable patients was 18.5% (95% CI, 6.3-38.1); 1 (3.7%) patient had a CR; 4 (14.8%) partial responses (PRs) were observed; and 7 (25.9%) patients had stable disease. Median time to response was 17.9 weeks (range, 7.3-32.4 weeks). Median duration of stable disease was 17.0 weeks (range, 7.1 weeks-32.1 weeks). Additionally, the 6-month progression-free survival (PFS) rate was 24.4%. At the time of the publication, the median duration of response had not been reached (range, 15.0 to ≥47.3 weeks), and 3 responders had received treatment for ≥1 year. An updated status of the responders in this metastatic TNBC cohort was presented at the 2016 San Antonio Breast Cancer Symposium.[35] Median PFS was 1.9 months (95% CI, 1.3 months-4.3 months) and median overall survival (OS) was 10.2 months (95% CI, 5.3-17.5). Of the 5 responses, 3 have been described as long-lasting. The TNBC patient who experienced a CR, who had previously been treated with 8 lines of chemotherapy for metastatic disease, discontinued pembrolizumab 11 months after achieving a CR and was in a CR for an additional 15 months after treatment was stopped. Two of the patients with a PR discontinued pembrolizumab after 2 years of treatment; 1 patient has maintained response for 22.7 months and the other patient experienced disease progression after 7.7 months and restarted the pembrolizumab per protocol, which led to stable disease.

The most common adverse events (AEs) of any grade related to pembrolizumab were arthralgia (18.8%), fatigue (18.8%), myalgia (18.8%), nausea (15.6%), and diarrhea (12.5%). There was 1 grade 5 disseminated intravascular coagulation felt to be treatment-related. Immune-related AEs included grade 2 hypothyroidism, grade 3 colitis, and grade 3 hepatitis (1 of each).

To test the efficacy of pembrolizumab as monotherapy in a trial appropriately powered to assess response, a phase II, 2-part, multisite, open-label trial (KEYNOTE-086; NCT02447003) in metastatic TNBC was designed. Part 1 included 2 cohorts for enrollment. Cohort A enrolled patients with centrally confirmed metastatic TNBC who had received at least 1 systemic treatment for metastatic disease and documented disease progression on the most recent therapy. Participants must have been previously treated with an anthracycline and a taxane in the neoadjuvant, adjuvant or metastatic setting. Cohort B enrolled subjects with centrally confirmed PD-L1–positive metastatic TNBC who had not received any prior systemic treatment for metastases. Part 2 is an expansion of cohort A that will enroll patients with tumors strongly positive for PD-L1 expression; part 2 will be initiated only if ≥1 response is observed in the cohort A PD-L1–strong-positive population. In all cohorts, patients will receive pembrolizumab 200 mg IV every 3 weeks until disease progression, intolerable toxicity, or patient or investigator decision. The primary outcome measure is ORR. This trial has completed accrual.

Several phase III trials are currently underway or planned which will further evaluate the role of pembrolizumab monotherapy in the treatment of TNBC. A phase III study (KEYNOTE-119; NCT02555657) is testing the activity of single-agent pembrolizumab versus chemotherapy of physician's choice as second- or third-line treatment for metastatic TNBC. Eligible subjects must have centrally confirmed TNBC, have received 1 or 2 prior chemotherapy treatments for metastatic disease, have documented progression on most recent therapy, and have been previously treated with an anthracycline and/or a taxane. Randomization is 1:1 to pembrolizumab or single-agent chemotherapy chosen by the investigator, which includes capecitabine, eribulin, gemcitabine, or vinorelbine. The primary outcome measures are OS and PFS, and the accrual goal is 600 patients.

It is observed that patients with TNBC who achieve a pCR after neoadjuvant chemotherapy have excellent survival, and those who

have residual disease are at high risk for recurrence.[9] Several clinical trials have been designed to evaluate the role of further adjuvant therapy in patients with TNBC who have residual disease, since the presence of residual disease after neoadjuvant treatment predicts a poor prognosis. One example is a large randomized trial evaluating adjuvant pembrolizumab in early-stage TNBC. This phase III trial (SWOG-S1418, BR006; NCT02954874) will evaluate the effect of adjuvant treatment with pembrolizumab in 1000 patients with TNBC who have completed definitive local treatment. This is a collaborative effort led by Southwest Oncology Group and NRG Oncology, sponsored by the National Cancer Institute. Randomization is 1:1 to either 12 months of treatment with pembrolizumab or observation. Eligible patients are those who did not achieve a pCR following at least 16 to 24 weeks of neoadjuvant chemotherapy followed by surgery, with residual tumor ≥1 cm and/or axillary-node–positive disease. The primary endpoint is invasive disease-free survival (DFS). This is a very large trial with the potential to change the current adjuvant standard of care for TNBC patients with residual disease after neoadjuvant chemotherapy.

PD-L1 Inhibitors

Several PD-L1 inhibitors are in clinical development and include atezolizumab, avelumab, and durvalumab. Atezolizumab is an engineered monoclonal antibody of the IgG1 isotype that binds selectively to PD-L1 on immune cells or tumor cells to prevent interactions with the PD-1 receptor or B7-1 (CD80). Both interactions provide inhibitory signals to T cells. Atezolizumab is approved by the FDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy; or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; or in patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy, regardless of PD-L1 status.[36-38]

The safety of atezolizumab was assessed in a phase I study that enrolled patients with metastatic solid tumors (NCT01375842).[39] Fifty-four patients with metastatic TNBC were enrolled in this multidisease basket trial. The initial cohort enrolled only PD-L1–positive tumors, and this was later changed to all patients. Atezolizumab was given IV at 15 mg/kg, 20 mg/kg, or fixed dose of 1200 mg every 3 weeks. PD-L1 expression was assessed on tumor-infiltrating immune cells (ICs) using a proprietary immunohistochemical (IHC) SP142 antibody assay. PD-L1 positivity was defined as IHC IC3 (≥10% ICs PD-L1–positive) or IHC IC 2 (≥5% to <10% of ICs PD-L1–positive). Most patients (89%) had received 4 or more previous systemic regimens, including adjuvant, neoadjuvant and metastatic treatments. Similar to the pembrolizumab phase I study, the ORR was 19% (4 of 21 evaluable; 95% CI, 5-42), including 2 CRs and 2 PRs, and all these patients' tumors met PD-L1 positivity of ≥5%. Of note, 3 patients experienced pseudoprogression, or the appearance of new lesions that subsequently resolve in the context of a continued decrease in tumor burden. Three patients experienced stable disease. At the time of the presentation, the median duration of response had not been reached (range 18 to >56 weeks).

The 6-month PFS was 27% (95% CI, 7-47). The most common all-grade AEs in ≥3 patients were fatigue (15%), fever (15%), and nausea (15%). There was 1 case of grade 4 pneumonitis.

Another PD-L1 inhibitor undergoing clinical development is avelumab, which is a fully human IgG1 monoclonal antibody that binds to PD-L1. In May 2017, the FDA granted an accelerated approval to the agent in patients with locally advanced or metastatic urothelial carcinoma. Prior to that, the agency granted accelerated approval to avelumab for the treatment of adult and pediatric patients 12 years and older with metastatic Merkel cell carcinoma.[40] In a phase Ib solid tumor trial (JAVELIN; NCT01772004), there was a metastatic breast cancer cohort expansion of 168 patients, unselected for PD-L1 status and breast cancer subtype, treated with avelumab at 10 mg/kg IV every 2 weeks until progression.[41] The median number of prior therapies for metastatic disease in the overall population was 3 (range, 0-10). The ORR in the overall population (n = 168) was 4.8% (95% CI, 2.1-9.2) with 1 CR and 7 PRs; 39 (23.3%) patients had stable disease. At the time of the presentation, the median duration of response was 28.7 weeks (95% CI, 6.1 to not estimable). The TNBC subtype composed about 34.5% (n = 58) of subjects. About 50% of the TNBC patients had ≤1 prior regimen for metastatic disease. The ORR in the TNBC cohort was 8.6% (95% CI, 2.9-19); 5 of 58 patients had a PR, and 13 had stable disease (22.4%). For the other subtypes, the ORR was 3.8% in HER2-positive (95% CI, 0.1-19.6), and 2.8% (95% CI, 0.3-9.7) in HR-positive/HER2-negative.

PD-L1 expression on tumor cells was assessed using cutoff criteria of ≥1%, ≥5%, and ≥25%. The ORR according to PD-L1 expression level in 48 evaluable TNBC tumors was 6.1% (2 of 33), 7.7% (1 of 13), and 0% (0 of 2), respectively, and this did not appear to impact efficacy. However, an interesting observation was that PD-L1 expression of ≥10% on immune cells within the tumor, so-called "hotspots," was associated with response to avelumab (44% vs 2.6%). Among the 5 TNBC responders, 4 (80%) had the immune-cell "hotspots." Further analysis of PD-L1 expression in the tumor, versus in immune cells within the tumor, as it relates to antitumor activity is warranted.

Notable immune-related and treatment-related AEs included hypothyroidism (grade 1-2, 4.8%), hepatitis (grade 3, 1.8%), and pneumonitis (grade 1-3, 1.8%). These results suggest that in unselected metastatic breast cancer, antitumor activity of a PD-L1 inhibitor is low, but specific subsets, such as TNBC with PD-L1 positivity, experienced clinical benefit. PD-L1 expression in tumor infiltrate in TNBC appeared to be related to clinical response to avelumab.

The A-BRAVE-Trial (NCT02926196) is a phase III randomized trial to evaluate adjuvant treatment with avelumab in 335 patients with TNBC. Patients who complete definitive curative therapy, including surgery, adjuvant chemotherapy (if clinically indicated),

and radiotherapy are eligible if they have more than 4 involved axillary lymph nodes (>pN2) and their adjuvant chemotherapy included at least 3 courses of an anthracycline and 3 courses of a taxane. Patients who undergo neoadjuvant chemotherapy must have pathologic evidence of residual invasive carcinoma in the breast and/or axillary nodes in the definitive surgical specimen. This is a collaborative study between the Istituto Oncologico Veneto IRCCS and the University of Padova and is being conducted in Italy. The primary outcome measure is DFS. The results of this trial will help define the role of an immune-checkpoint–blocking antibody in the adjuvant therapy of TNBC to prevent recurrence.

Durvalumab is an IgG1 monoclonal antibody that binds to PD-L1, thereby blocking its binding to and activation of PD-1 expressed on activated T cells. The FDA has granted accelerated approval to durvalumab for treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy, or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Several studies are testing durvalumab in combination with other agents for early-stage TNBC. This includes a phase Ib study of durvalumab and the PVX-410 vaccine as adjuvant therapy for stage II/III TNBC (NCT02826434); a phase I/II neoadjuvant trial of weekly nab-paclitaxel followed by dose-dense doxorubicin and cyclophosphamide with concurrent durvalumab in stage I-III TNBC (NCT02489448); and a randomized phase II trial of neoadjuvant durvalumab/placebo followed by nab-paclitaxel plus/minus durvalumab followed by epirubicin and cyclophosphamide plus/minus durvalumab (NCT02685059).

For metastatic TNBC, durvalumab is being evaluated in combination with Vigil (autologous tumor cell immunotherapy; NCT02725489), and in combination with paclitaxel (NCT02628132), olaparib (NCT02484404), tremelimumab (NCT02527434), and epacadostat, an inhibitor of indoleamine 2,3-dioxygenase (NCT02318277). Data are not yet available, but forthcoming.

Combination Treatment

Although the sample sizes were small and the patients treated had mostly PD-L1–positive tumors, results from the aforementioned phase I studies are compelling; there were long-lasting clinical responses and a favorable safety profile in a highly pretreated group of metastatic patients with TNBC. In a breast cancer subtype in which response to chemotherapy is typically 4 to 12 weeks, immune-modulating therapy warrants further evaluation, given the observation of durable responses. Several larger-sized trials have been launched with PD-1 and PD-L1 inhibitors based on such encouraging results. However, it seems that the efficacy of single-agent immune checkpoint agents has thus far been limited to a subset of patients who expressed PD-L1. Both monotherapy trials with pembrolizumab and atezolizumab yielded response rates in a pretreated metastatic TNBC population of about 19%. Thus, combination immunotherapy approaches have been evaluated in the hopes of obtaining further improvement in antitumor activity.

Metastatic Setting

Several trials of combination immunotherapy are ongoing. A phase Ib study (NCT01633970) of atezolizumab in combination with nab-paclitaxel in metastatic TNBC was performed.[42] Combining nab-paclitaxel with immunotherapy is attractive, because nab-paclitaxel does not require premedication with steroids, which can cause immunosuppression. PD-L1 expression was assessed on tumor-infiltrating immune cells with the Ventana SP142 antibody, and the expression was scored as IC0, IC1, IC2, or IC3 (if <1%, between ≥1% and <5%, between ≥5% and <10%, or ≥10%, respectively).

In this multi-institution trial, 32 women with TNBC received atezolizumab 800 mg IV on days 1 and 15 with nab-paclitaxel 125 mg/m^2 IV on days 1, 8, and 15 on a 28-day cycle. Median number of previous systemic therapies, including adjuvant and neoadjuvant, was 5 (range, 1-10). Most had prior taxanes (88%). The confirmed ORR in 32 evaluable subjects was 38% (95% CI, 21-56), including 3% CRs and 34% PRs. Stable disease was observed in 44% of patients. In the first-line setting, the confirmed ORR in 13 patients was 46% (95% CI, 19-75). In the second-line setting, the confirmed ORR in 9 patients was 22% (95% CI, 3-60). In the third-line setting and beyond, the ORR in 10 patients was 40% (95% CI, 12-74). At the time of the updated ASCO 2016 presentation, 6 out of 12 responders remained on atezolizumab. ORRs by expression level of PD-L1 were 30% and 36%, respectively, in tumors that were IC0 and IC1, 2, or 3. An interesting observation is that responses were still observed in tumors lacking expression of PD-L1, although responses were slightly higher in tumors defined as PD-L1–positive. Another notable finding was that the responders tended to have higher baseline level of TILs. Though the trial was not powered to show a difference, the response rate was higher in patients who received the combination as first-line therapy compared with the group that had already received prior lines of therapy. Treatment-related grade 3-4 AEs were neutropenia (47%), thrombocytopenia (9%), anemia (6%), and diarrhea (6%).

A large trial effort to evaluate chemoimmunotherapy as first-line treatment in metastatic TNBC was then designed. A phase III randomized (1:1) placebo-controlled trial (IMpassion130; NCT02425891) of atezolizumab in combination with nab-paclitaxel compared with placebo with nab-paclitaxel for patients with previously untreated metastatic TNBC is currently underway.[43] Atezolizumab 840 mg is given IV on days 1 and 15 and nab-paclitaxel 100 mg/m2 is given IV on days 1, 8, and 15 of a 28-day cycle. The co-primary endpoints are PFS and OS. The accrual goal is 900 patients.

A randomized, double-blind, phase III trial (KEYNOTE-355; NCT02819518) is evaluating pembrolizumab and chemotherapy versus placebo and chemotherapy as first-line treatment for metastatic TNBC. Eligible patients must have measurable disease, and those

who have relapsed must have been treated with anthracycline in the adjuvant or neoadjuvant setting unless anthracycline is contraindicated. The study consists of 2 parts. In Part 1, the safety of pembrolizumab in combination with 1 of 3 different cytotoxic regimens will be assessed in patients with metastatic TNBC who have not been previously treated. The chemotherapy agents include nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin. In Part 2, patients with metastatic TNBC who are treatment-naïve will be randomized to treatment with pembrolizumab 200 mg IV on day 1 of each 21-day cycle and chemotherapy or placebo IV (normal saline) and chemotherapy. The chemotherapy can be 1 of the following 3 regimens: 1) nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 of each 28-day cycle, 2) paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 of each 28-day cycle; or 3) gemcitabine/carboplatin 1000 mg/m^2 (gemcitabine) and an area under the curve 2 (carboplatin) on days 1 and 8 of each 21-day cycle. The primary endpoints are OS and PFS in all subjects and in those with PD-L1 positive tumors. The anticipated enrollment is 858 subjects.

Neoadjuvant

Based on the safety experience and potential clinical benefit shown in the metastatic studies, these agents have rapidly been moved for evaluation in the neoadjuvant setting for stage II and III TNBC. Another phase III clinical trial (KEYNOTE-522; NCT03036488) will evaluate the efficacy of pembrolizumab in combination with chemotherapy for neoadjuvant treatment of TNBC. This is a randomized, placebo-controlled trial enrolling women and men presenting with clinical stage IIa (T1cN1) to IIIB TNBC, who are candidates for potentially curative surgery. In this trial, they will first be randomized to pembrolizumab or placebo with weekly paclitaxel and carboplatin (weekly or every 3 weeks) for 4 cycles. This will be followed by treatment for 4 cycles with pembrolizumab or placebo, in combination with doxorubicin (epirubicin can be substituted) and cyclophosphamide, as neoadjuvant therapy prior to surgery. Then, that will be followed by 9 cycles of pembrolizumab or placebo every 3 weeks as adjuvant therapy post surgery. The primary endpoint is pCR, defined as no invasive residual disease in the breast and lymph nodes (ypT0/Tis ypN0). The trial seeks to accrue 855 subjects.

Another phase III neoadjuvant trial (NeoTRIPaPDL1, FM-14-B02; NCT02620280) is evaluating the efficacy of atezolizumab in combination with chemotherapy for TNBC. This is a trial randomizing women with locally advanced triple-negative tumors suitable for neoadjuvant therapy to the combination of nab-paclitaxel and carboplatin with or without atezolizumab. The primary endpoint is event-free survival. The accrual goal is 272 subjects in Europe. The results of these studies will help define the role of an immune checkpoint blocking antibody in the neoadjuvant setting for TNBC.

Conclusion

TNBC is a breast cancer subtype with only chemotherapy as the conventional treatment. Many clinical trials of immunotherapy agents are in progress for the treatment of TNBC. Emerging data in the phase I setting with checkpoint inhibitors demonstrate a tolerable safety profile. Ongoing and future trials will define the role of immune checkpoint blockade in the treatment of TNBC. The hope is that immune checkpoint blocking antibodies will change the standard of care for TNBC.

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