The Evolving Role of Immune Checkpoint Inhibitors in the Treatment of Triple-Negative Breast Cancer

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Abstract: Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer for which chemotherapy had been the only active treatment option once metastatic disease developed. Immune checkpoint inhibitors (ICIs) are now available to treat patients with advanced TNBC who have programmed cell death ligand 1 (PD-L1)–positive tumors; these agents have been shown to improve clinical outcomes. Additionally, long-term disease control can be achieved in a subset of patients. Continued investigations of ICIs and optimal combinations with chemotherapy and targeted agents to enhance the immune response are ongoing, along with studies aimed at identifying the patients most likely to benefit. For early-stage TNBC, the data to date on administering ICI-based combination therapies in the neoadjuvant setting are compelling and suggest that the benefit from immunotherapy does not depend on PD-L1 expression. This review will discuss the clinical trial data on ICIs as monotherapy and in combination with chemotherapy in the treatment of patients with metastatic and early-stage TNBC.

Keywords
Checkpoint inhibitors, immunotherapy, triple-negative breast cancer

Introduction

Triple-negative breast cancer (TNBC) is an aggressive malignancy that accounts for approximately 12% to 17% of breast cancer cases in the United States annually, but for a disproportionate number of breast cancer–related deaths.[1] This breast cancer subtype disproportionately affects young women, as well as racial and ethnic minorities.[2] These facts increase the years of life lost to breast cancer, deepen the societal impact of the disease, and exacerbate racial disparities in breast cancer outcomes.

Because it lacks receptors for estrogen (ER), progesterone (PR), and human epidermal growth factor 2 (HER2), TNBC does not offer easy therapeutic targets. As a result, systemic treatment for TNBC centered almost exclusively on chemotherapy until very recently. Although immunotherapy, particularly with immune checkpoint inhibitors (ICIs), has revolutionized the treatment of many solid tumors over the last decade, breast cancers were initially thought to be relatively non-immunogenic.[3] However, recent studies

have revealed important biomarkers that may point to sensitivity to immunotherapy in certain breast cancers. Specifically, TNBC appears to be more immunogenic than hormonally driven breast cancers. TNBC is characterized by a higher level of expression of immune checkpoint receptors, such as programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1). Elevated expression of these receptors has been correlated with improved responses to ICIs in many malignancies.[4] Similarly, a subset of TNBCs have a microenvironment with high levels of tumor-infiltrating lymphocytes (TILs), which correlate with improved responses to neoadjuvant chemotherapy, a better overall prognosis, increased PD-L1 expression, and improved responses to immune checkpoint inhibition.[5-8] Clinical data also exist to show that TNBC with a high tumor mutational burden is more likely to respond to immunotherapy.[9] Taken together, these observations have made a strong case for a potential role of immune checkpoint inhibition in the treatment of TNBC.

Early trials of single-agent ICIs in metastatic TNBC yielded only modest response rates but revealed that among the patients who do respond, a potential exists for long-lasting control of this aggressive tumor type. This finding has aroused interest in research dedicated to identifying patients who might benefit the most from immunotherapy, as well as identifying strategies for combining ICIs with other agents to enhance the efficacy of immunotherapy.[10] With the approval of ICIs—specifically atezolizumab (Tecentriq, Genentech), a PD-L1 inhibitor, in combination with nab-paclitaxel (Abraxane, Bristol Myers Squibb) for the first-line treatment of PD-L1–positive metastatic TNBC, and pembrolizumab (Keytruda, Merck), a PD-1 inhibitor, in combination with different chemotherapy backbones for the first-line treatment of PD-L1–positive metastatic TNBC—immunotherapy is now an option for this specific breast cancer subtype.[11,12] These regimens are listed as category 1 recommendations in the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of PD-L1–positive metastatic TNBC as preferred first-line therapy. In addition, data published on combining ICIs with chemotherapy in the neoadjuvant setting show activity in patients with early-stage TNBC.[13-16] The following review summarizes the results of the most important clinical trials of immune checkpoint inhibition in the treatment of metastatic and early-stage TNBC.

Single-Agent Checkpoint Inhibition

Early clinical trials of ICIs as monotherapy in metastatic TNBC showed promising response rates, but these have not been consistently replicated in subsequent studies (Table 1). In the KEYNOTE-012 phase 1b trial, 32 heavily pretreated patients with metastatic PD-L1–positive TNBC received pembrolizumab monotherapy at 10 mg/kg intravenously (IV) every 2 weeks.[17] PD-L1 positivity was defined as expression in the stroma or in at least 1% of tumor cells and was determined with use of the 22C3 anti–PD-1 antibody.[18] In the 27 evaluable patients, the overall response rate (ORR) was 18.5% (95% CI, 6.3-38.1). An additional 25.9% of patients had stable disease (SD). Although median progression-free survival (PFS) was only 1.9 months, the disease control rate (DCR), defined as the sum of the percentages of patients with a complete response (CR), partial response (PR), or stable disease (SD) for at least 24 weeks, was 25.9%. Among the 5 patients (1 CR, 4 PRs) who responded to pembrolizumab monotherapy, the median duration of response (DOR) was not reached (15-47.3+ weeks). Of the 5 responders, 3 remained on therapy with continued clinical benefit at the time of publication. The patient with a CR had received 8 prior lines of therapy for metastatic disease, discontinued pembrolizumab 11 months after the CR, and remained in a CR for 15 months. Of the patients who had PRs, 2 stopped pembrolizumab after 2 years of therapy; 1 patient had a sustained response for 22.7 months and the second patient for 7.7 months. Median DOR had not been reached at the last update, presented at the 2016 San Antonio Breast Cancer Symposium (SABCS; range, 15 to >58 weeks). The median overall survival (OS) was 10.2 months (95% CI, 5.3-17.5).[19] This response rate and the durability of some of these responses were the first indications of the potential role for immunotherapy in metastatic TNBC, in which DOR to standard chemotherapy would be estimated at 4 to 12 weeks in a similar population.[20] Additionally, the treatment was relatively well tolerated, with 5 of the 32 total patients (15.6%) experiencing grade 3 or higher toxicity, including 1 treatment-related death. These high-grade toxicities included anemia, lymphopenia, headache, pyrexia, aseptic meningitis, and disseminated intravascular coagulation.

The phase 1b JAVELIN study enrolled 168 heavily pretreated patients with metastatic breast cancer, including 58 patients with TNBC.[21] Patients received the PD-L1 inhibitor avelumab (Bavencio, EMD Serono/Pfizer) at 10 mg/kg IV every 2 weeks. PD-L1 positivity was determined by immunohistochemistry (Dako) and defined as expression in at least 1% of tumor cells or at least 10% of tumor-associated immune cells. The ORR was 3% in the trial overall and 5.2% in the TNBC subgroup. Despite the low ORR, a potential for long-term benefit was noted among the few patients who did respond. Of 5 objective responders (3 with TNBC and 2 with hormone receptor–positive/HER2-negative disease), 4 remained on treatment with an ongoing clinical response at the time of publication. Of the 58 patients with TNBC, 3 had PRs

Table 1. Selected Trials of Immune Checkpoint Inhibitor Monotherapy in Metastatic Triple-Negative Breast Cancer

Trial	Phase	Evaluable Patients, No.	First Line?	PD-L1 Status Required?	Regimen	ORR, %	mPFS, mo (95% CI)	mOS, mo (95% CI)
KEYNOTE-012[17,19] (NCT01848834)	1b	27	No	Yes	Pembrolizumab	18.5	1.9 (1.3-4.3)	10.2 (5.3-17.5)
JAVELIN[21] (NCT01772004)	1b	58	No	No	Avelumab	5.2; PD-L1+, 22.2	5.9 (wk) (5.7-6.9)	9.2 (4.3-NR)
GO27831[22] (NCT01375842)	1	115	No	No	Atezolizumab	10; PD-L1+, 12; first line, 24	1.4 (1.3-1.6)	8.9 (7-12.6)
KEYNOTE-086A[23] (NCT02447003)	2	170	No	No	Pembrolizumab	5.3; PD-L1+, 5.7	2.0 (1.9-2.0)	9.0 (7.6-11.2)
KEYNOTE-086B[24] (NCT02447003)	2	84	Yes	Yes	Pembrolizumab	21.4	2.1 (2.0-2.2)	18.0 (12.9-23.0)
KEYNOTE-119[25,26] (NCT02555657)	3	622	No	No	Pembrolizumab vs single-agent chemotherapy*	9.6 vs 10.6; CPS ≥10, 17.7 vs 9.2	2.1 vs 3.3; HR, 1.60 (1.33-1.92) CPS ≥10, 2.1 vs 3.4; HR, 1.14 (0.82-1.59)	9.9 vs 10.8; HR, 0.97 (0.82-1.15) CPS ≥10, 12.7 vs 11.6; HR, 0.78 (0.57-1.06)

CPS, combined positive score; HR, hazard ratio; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NR, not reported; ORR, overall response rate; PD-L1+, programmed death ligand 1–positive; wk, weeks.

*Physician's choice of single-agent chemotherapy: capecitabine, eribulin, gemcitabine, or vinorelbine.

and 15 had SD as best response, for a DCR of 31%. It is important to point out, though, that SD in this calculation was defined as SD on the first post-baseline tumor assessment, 6 weeks after treatment initiation. This differs from other study definitions, including that of the KEYNOTE-012 trial, which required SD for 24 weeks to contribute to the DCR. Treatment-related adverse events (TRAEs) of any grade occurred in 68.5% of patients, and 13.7% of patients experienced a grade 3 or higher event. Of the 17 patients (10.1%) who experienced an immune-related adverse event (irAE), 5(3%) had grade 3 or higher toxicity. This included 3 patients with autoimmune hepatitis, 1 patient with grade 3 pneumonitis, and 1 patient with grade 4 thrombocytopenia. One patient with autoimmune hepatitis, who also had progressive liver metastasis, died of acute liver failure. Another died of respiratory failure in the setting of pre-existing pulmonary disease, extensive lung metastases, health care–associated pneumonia, and possible immunotherapy-related pneumonitis.

In GO27831, a phase 1 trial of atezolizumab monotherapy in 115 evaluable patients with metastatic TNBC, the ORR was 10% in the overall population.[22] TRAEs occurred in 63% of patients, with 11% of patients experiencing grade 3 or higher events. Of note in this trial, although the ORR in the overall population was 10%, of the 21 patients receiving atezolizumab as first-line therapy for metastatic TNBC, the ORR was 24%. PD-L1 positivity, defined as expression in at least 1% of immune cells on the VENTANA PD-L1 (SP142) assay, was also correlated with an improved response rate, with an ORR of 12% in patients with PD-L1–positive tumors vs 0% in those with PD-L1–negative tumors. The median PFS was 1.4 months (95% CI, 1.3-1.6), and median OS was 8.9 months (95% CI, 7.0-12.6). Again, despite modest response rates and short PFS, the durability of benefit in some of those who did respond was promising. Of the 11 responders, 3 had CRs, and the median DOR was 21 months (range, 3 to ≥38 months). This trial supported the increasingly likely hypothesis that the immunogenicity of TNBC may correlate not only with PD-L1 status but also with line of therapy.

These findings laid the groundwork for the KEYNOTE-086 trial, which assessed the role of PD-L1 as a biomarker in dedicated cohorts. This phase 2 trial aimed to assess the efficacy of pembrolizumab at 200 mg IV

every 3 weeks in patients with metastatic TNBC who either had received prior therapy for their metastatic cancer, regardless of PD-L1 status (cohort A), or had PD-L1–positive disease and had not yet received therapy in the metastatic setting (cohort B).[23,24] Of 170 patients in cohort A, 43.5% had received at least 3 prior lines of therapy for metastatic disease, and 61.8% had PD-L1–positive tumors on the basis of a combined positive score (CPS) of at least 1. This score is calculated as the combined number of PD-L1–positive tumor cells, lymphocytes, or macrophages divided by the total number of tumor cells, multiplied by 100. The ORR in cohort A was 5.3%, which included 2 CRs and 7 PRs. Of the patients who responded, 75% had a continued response at 6 months or longer, and 62.5% had a continued response at 12 months or longer. Although PD-L1 positivity did not confer a higher likelihood of response to ICI therapy in the overall analysis (ORR, 5.7% in PD-L1–positive vs 4.7% in PD-L1–negative tumors), it is worth noting that the 2 patients with a CR to pembrolizumab had PD-L1–positive tumors, and that 4 additional patients in the PD-L1–positive group had SD at 24 weeks or longer. At the time of data cutoff, 6 of the 9 responders had a continued response to pembrolizumab. Of these 6 durable responses, 5 were in patients with PD-L1–positive tumors. This finding reinforces PD-L1 expression as a valuable biomarker for benefit from ICI therapy in both the short and the long term. Safety was comparable with that in prior studies, with 22 (12.9%) of the 170 patients experiencing at least one grade 3/4 TRAE and 33 patients (19.4%) experiencing irAEs. The most common irAEs observed were hypothyroidism and hyperthyroidism (11.8% and 5.3%, respectively). No TRAEs led to death.

Cohort B of KEYNOTE-086 enrolled 84 patients with previously untreated, PD-L1–positive, metastatic TNBC.[24] In this context, 4 patients achieved CRs and 14 achieved PRs, for an ORR of 21.4%. An additional 13 patients (15.5%) had SD, with 2 of those remaining stable for 24 weeks or longer, for an overall DCR of 23.8%. The PFS rate at 6 months was estimated at 27%, and the median PFS was 2.1 months. Among responders, the median DOR was 10.4 months but ranged from 4.2 to 19.2+ months, with 8 of 18 responders remaining on treatment at the time of data cutoff. Safety in this trial was again similar to that in other trials of ICI monotherapy, with 9.5% of patients experiencing at least one grade 3 event. No grade 4 or 5 TRAEs occurred. One patient discontinued pembrolizumab owing to a TRAE, and 14 patients (16.7%) experienced irAEs, with the most common being hypothyroidism and hyperthyroidism (9.5% and 4.8%, respectively). The only grade 3 irAE reported was a rash.

These encouraging results led to the design of the phase 3 KEYNOTE-119 trial, which randomly assigned 622 previously treated patients with metastatic TNBC to pembrolizumab at 200 mg IV every 3 weeks (n=312) or physician's choice of chemotherapy (capecitabine, eribulin [Halaven, Eisai], gemcitabine, or vinorelbine; n=310) in a 1:1 ratio.[25,26] The primary endpoint of the study was OS. Patients were stratified by the PD-L1 CPS. At a median follow-up of 31.4 months for the pembrolizumab group and 31.5 months for the chemotherapy group, pembrolizumab monotherapy did not significantly improve OS compared with single-agent chemotherapy as a second- or third-line treatment for metastatic TNBC in the intention-to-treat (ITT) population and in prespecified subgroups. In a post hoc exploratory subset analysis, patients with a CPS of at least 20 had a median OS of 14.9 months with pembrolizumab vs 12.5 months with chemotherapy (hazard ratio [HR], 0.58 [95% CI, 0.38 -0.88]), possibly indicating a role for pembrolizumab monotherapy in selected patients with a higher CPS. The ORR was similar in the 2 groups in the ITT population. Among those treated with pembrolizumab, the ORR was 12% in patients with a CPS of at least 1, 18% in those with a CPS of at least 10, and 26% in those with a CPS of at least 20. Among those treated with chemotherapy, the ORR was 9% among those with a CPS of at least 1, 9% among those with a CPS of at least 10, and 12% among those with a CPS of at least 20. Median DOR was also similar in the 2 groups but did increase with higher levels of PD-L1 expression. The rate of grade 3 or higher TRAEs was 14% in the pembrolizumab arm vs 36% in the chemotherapy arm. Grade 3/4 immune-mediated AEs and infusion reactions occurred in 3.2% of patients in the pembrolizumab arm vs 1.0% of patients in the chemotherapy arm. The most common immune-mediated AE was hypothyroidism. Given these results, single-agent pembrolizumab is not recommended as second-line or later therapy for metastatic TNBC.

Immune Checkpoint Inhibition in Combination With Chemotherapy

These early data established the role of PD-L1 as a biomarker and suggested improved benefit from ICI therapy when given earlier in the metastatic setting. Most importantly, these trials demonstrated that if a response to an ICI is achieved, a small subset of patients may experience long-lasting benefit. This finding ignited interest in combination strategies aimed at altering the tumor microenvironment, increasing immunogenicity, and ultimately enhancing sensitivity to checkpoint inhibition. Preclinical studies have demonstrated varying effects of chemotherapy on tumor immunogenicity and have made chemotherapy, with its known single-agent activity against TNBC, an

Table 2. Selected Trials of Immune Checkpoint Inhibitors in Combination With Chemotherapy in Metastatic Triple-Negative Breast Cancer

Trial	Phase	Evaluable Patients, No.	Prior Lines of Therapy, No.	PD-L1+, %	Regimen	ORR, %	mPFS, mo (95% CI)	mOS, mo (95% CI)
ENHANCE-1[29,30] (NCT02513472)	1b/2	167	≤2	44	Pembrolizumab + eribulin	23.4; PD-L1+ (first line), 34.5	4.1 (3.5-4.2)	16.1 (13.3-18.5)
GP28328[31] (NCT01633970)	1b	33	≤2	50	Atezolizumab + nab-paclitaxel	39.4	5.5 (5.1-7.7)	14.7 (10.1-NE)
IMpassion130[11,32,33] (NCT02425891)	3	902	None	41	Atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel	56 vs 45.9	7.2 vs 5.5; HR, 0.80 (0.69-0.92); *P*=.002	21.3 vs 17.6; HR, 0.84 (0.69-1.02); *P*=.08
IMpassion131[34] (NCT03125902)	3	651	None	45	Atezolizumab + paclitaxel vs placebo + paclitaxel	54 vs 47	5.7 vs 5.6; HR, 0.86 (0.70-1.05)	19.2 vs 22.8; HR, 1.11 (0.87-1.42)
KEYNOTE-355[12,35] (NCT02819518)	3	847	None	75	Pembrolizumab + chemotherapy* vs placebo + chemotherapy*	41 vs 35.9	7.5 vs 5.6; HR, 0.82 (0.69-0.97) CPS ≥10: 9.7 vs 5.6; HR, 0.65 (0.49-0.86)	NR

HR, hazard ratio; ORR, overall response rate; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; NR, not reported; PD-L1+, programmed death ligand 1–positive.

*Chemotherapy choices: nab-paclitaxel, paclitaxel, or gemcitabine plus carboplatin.

attractive partner for ICI therapy. For example, building upon preclinical work that demonstrated an effect of the microtubule inhibitor eribulin on transforming growth factor beta (TGF-ß) expression and subsequent CD8+ T-cell exclusion, the phase 1b/2 ENHANCE 1 trial combined pembrolizumab at 200 mg IV on day 1 with eribulin at 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle.[27,28] Among 167 patients with metastatic TNBC who had received 2 or fewer prior lines of systemic therapy for metastatic disease, the ORR was 23.4%, with a trend toward improved outcomes in patients with PD-L1–positive tumors in the first-line setting.[29,30] Among 29 patients with PD-L1–positive tumors treated in the first-line setting, the ORR was 34.5% and the median PFS was 6.1 months, relative to 16.1% and 3.5 months in patients with PD-L1–negative tumors. This benefit was not sustained in the later-line setting, however, in which ORR and median PFS were 24.4% and 4.1 months in patients with PD-L1–positive tumors, vs 18.2% and 3.9 months in patients with PD-L1–negative tumors, respectively (Table 2).

In a phase 1b trial (GP28328) combining a taxane, nab-paclitaxel, at 125 mg/m^2 IV on days 1, 8, and 15 with atezolizumab at 800 mg IV on days 1 and 8 of a 28-day cycle, 33 patients with metastatic TNBC who had received 0 to 2 prior lines of therapy for metastatic disease had an ORR of 39.4%.[31] In addition to the 13 responders (1 CR and 12 PRs), 4 patients had SD for at least 12 weeks, for a DCR of 51.5%. Unlike in the ENHANCE 1 trial, however, exploratory subgroup analyses indicated that the clinical activity of this combination was independent of PD-L1 status or line of therapy. With such small patient numbers, though, it is difficult to establish these relationships. Of the 33 patients, 24 (73%) experienced grade 3/4 TRAEs that were at least partly attributable to atezolizumab, and 3 (9%) discontinued atezolizumab owing to side effects. One patient discontinued atezolizumab for prolonged, asymptomatic grade 2 aspartate aminotransferase elevation, 2 discontinued atezolizumab for grade 3 pneumonitis, and 5 (15%) discontinued nab-paclitaxel owing to TRAEs, all after having received the protocol-specified minimum of 4 cycles.

The results of this early-phase trial led to the conduct of

the IMpassion130 trial. In this randomized, double-blind, placebo-controlled phase 3 trial, 902 patients with previously untreated metastatic TNBC were randomized in a 1:1 ratio (451 in each arm) to nab-paclitaxel at 100 mg/m^2 IV on days 1, 8, and 15 with atezolizumab at 840 mg IV on days 1 and 15 of a 28-day cycle or to nab-paclitaxel with placebo.[11] Randomization was stratified by PD-L1 status, with positivity defined as PD-L1 expression in at least 1% of immune cells on the VENTANA SP142 assay. Primary endpoints were PFS in the ITT population and the PD-L1–positive subgroup, in addition to OS tested first in the ITT population and, if significant, then tested in the PD-L1–positive subgroup. Initial results, published in November 2018 after a median follow-up of 12.9 months, revealed a median PFS in the ITT population of 7.2 months with atezolizumab plus nab-paclitaxel vs 5.5 months with placebo plus nab-paclitaxel, with an HR for progression or death of 0.80 (95% CI, 0.69-0.92). In the subset of patients with PD-L1–positive tumors, median PFS was 7.5 months with atezolizumab plus nab-paclitaxel and 5.0 months with placebo plus nab-paclitaxel (HR for progression or death, 0.62; 95% CI, 0.49-0.78). The trial met its PFS endpoint in both the ITT and PD-L1–positive groups. Median OS in the ITT population was 21.3 months among patients who received atezolizumab with nab-paclitaxel vs 17.6 months in those who received placebo plus nab-paclitaxel, but this difference was not significant (HR for death, 0.84; 95% CI, 0.69-1.02; *P*=.08). ORR in the ITT population was 56% with nab-paclitaxel and atezolizumab vs 45.9% with nab-paclitaxel and placebo. In the PD-L1–positive subgroup, the response rate was 58.9% with nab-paclitaxel and atezolizumab vs 42.6% with nab-paclitaxel and placebo. In March 2019, initial results from the IMpassion130 trial led to US Food and Drug Administration (FDA) accelerated approval of atezolizumab and nab-paclitaxel for the treatment of metastatic TNBC in patients whose tumors express PD-L1, defined as PD-L1 staining in tumor-infiltrating immune cells of any intensity covering at least 1% of the tumor area.

Updated results published in January 2020 remained consistent with the first interim analysis. Again, no statistically significant improvement in median OS was observed in the ITT population. Although an ongoing improvement in median OS of 7 months was demonstrated in the atezolizumab arm of the PD-L1–positive subgroup (25 months with combination therapy vs 18 months with nab-paclitaxel and placebo [HR, 0.67; 95% CI, 0.53-0.86]), this positive result could not be formally tested.[32] Final OS results, presented at the European Society for Medical Oncology (ESMO) Virtual Congress in 2020, showed longer OS in the PD-L1–positive subgroup with atezolizumab plus nab-paclitaxel than with placebo plus nab-paclitaxel (25.4 months vs 17.9 months; final OS improvement of 7.5 months). Again, because the difference in OS was not statistically significant in the ITT population, significance was not formally tested in the PD-L1–positive subgroup, per the prespecified testing hierarchy.[33] Given that clinical benefit needs to be confirmed, the FDA Oncologic Drugs Advisory Committee (ODAC) will meet in 2021 to discuss the accelerated approval of atezolizumab and chemotherapy for the treatment of metastatic TNBC in patients whose tumors express PD-L1. Of the 890 patients evaluated for safety in IMpassion130, 51% in the atezolizumab arm and 43% in the placebo arm had grade 3/4 adverse events, with subsequent treatment discontinuation in 19% and 8%, respectively. The most common reason for treatment discontinuation was neuropathy.

Other recently presented phase 3 trials of ICIs in the metastatic setting include IMpassion131 and KEYNOTE-355. The phase 3 IMpassion131 trial, presented at the ESMO Virtual Congress in 2020, followed a design similar to that of the IMpassion130 study.[34] In IMpassion131, 651 patients with treatment-naive metastatic TNBC were randomly assigned to paclitaxel at 90 mg/m^2 IV on days 1, 8, and 15 with atezolizumab at 840 mg IV on days 1 and 15 of a 28-day cycle (n=439) or to paclitaxel with placebo (n=220). Paclitaxel is a chemotherapy agent very frequently used to treat metastatic TNBC. It is associated with less neuropathy than nab-paclitaxel but carries a risk for infusion reaction owing to the use of Cremophor as a vehicle, and therefore premedication with corticosteroids is required. The randomization ratio was 2:1, and patients were stratified according to PD-L1 status (<1% vs ≥1% by the VENTANA SP142 assay), prior taxane exposure, presence of liver metastases, and geographic region. The trial did not meet its primary endpoint of PFS in the PD-L1–positive population. PFS was not significantly improved by atezolizumab and paclitaxel vs placebo and paclitaxel in the ITT population (5.7 vs 5.6 months) and in the PD-L1–positive subgroup (6.0 vs 5.7 months). Secondary endpoints of OS and ORR also did not differ significantly between the 2 arms, although the response rate was numerically higher in the atezolizumab arm in each analysis. A total of 43% of patients in the placebo arm and 49% of patients in the atezolizumab arm experienced grade 3/4 toxicities. In September 2020, the FDA issued an alert to health care professionals that paclitaxel should not replace nab-paclitaxel in combination with atezolizumab for the treatment of metastatic TNBC in clinical practice.

The KEYNOTE-355 trial was a randomized phase 3 trial in which 566 patients with metastatic TNBC received pembrolizumab and chemotherapy and 281 received placebo and chemotherapy.[12] The backbone

Table 3. Selected Trials of Immune Checkpoint Inhibitors and Chemotherapy in the Neoadjuvant Treatment of Triple-Negative Breast Cancer

Trial	Phase	Patients, No.	Stage of Disease	Regimens	pCR, %
I-SPY2[37] (NCT01042379	2	29	II-III	Pembrolizumab + paclitaxel → AC vs paclitaxel → AC	60 vs 22
KEYNOTE-173[36] (NCT02622074)	1b	60	II-III	Pembrolizumab + different chemotherapy regimens	60 (overall)
KEYNOTE-522[13] (NCT03036488)	3	1174	II-III	Pembrolizumab + paclitaxel + carboplatin → pembrolizumab + AC/EC → surgery → pembrolizumab vs placebo + paclitaxel + carboplatin → placebo + AC/EC → surgery → placebo	64.8 vs 51.2
IMpassion031[14] (NCT03197935)	3	333	II-III	Atezolizumab + nab-paclitaxel → atezolizumab + AC → surgery → atezolizumab vs placebo + nab-paclitaxel → placebo + AC → surgery → observation	58 vs 41
NeoTRIPaPDL1[15] (NCT02620280)	3	280	II-IIIC	Atezolizumab + nab-paclitaxel + carboplatin → surgery → chemotherapy vs nab-paclitaxel + carboplatin → surgery → chemotherapy	43.5 vs 40.8
GeparNuevo[16] (NCT02685059)	2	174	I-III	Durvalumab + nab-paclitaxel → durvalumab + EC vs placebo + nab-paclitaxel → placebo + EC	53.4 vs 44.2

AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; pCR, pathologic complete response.

chemotherapy agents were nab-paclitaxel (100 mg/m^2 on days 1, 8, and 15 of every 28 days), paclitaxel (90 mg/m^2 on days 1, 8, and 15 of every 28 days), or gemcitabine plus carboplatin (1000 mg/m^2 plus area under the curve 2 [AUC 2] on days 1 and 8 of every 21 days). Randomized patients (2:1) were stratified according to type of chemotherapy partner (taxane vs gemcitabine/carboplatin), PD-L1 status (CPS ≥1 vs <1), and prior (neo) adjuvant therapy with same-class chemotherapy. After a median follow-up of 25.9 months in the experimental arm and 26.3 months in the control arm, this trial met one of its dual primary endpoints of PFS in patients with PD-L1–positive tumors. The other primary endpoint, OS, has not yet been reported. In patients with a CPS of at least 10, median PFS in the pembrolizumab-containing arm was 9.7 months, compared with 5.6 months in the chemotherapy-and-placebo arm. The HR for PFS in this subgroup was 0.65 (95% CI, 0.49-0.86). In the subgroup with a CPS of at least 1, median PFS was 7.6 months with pembrolizumab vs 5.6 months with placebo, which did not meet the boundary for statistical significance (HR, 0.74; 95% CI, 0.61-0.89). Similarly, although not formally tested, the median PFS in the ITT population was higher for pembrolizumab (7.5 vs 5.6 months; HR, 0.82 (95% CI, 0.69-0.97). An exploratory analysis of patients with a CPS of 20 or higher showed a median PFS of 9.5 months in patients who received pembrolizumab plus chemotherapy vs 5.4 months in those who received chemotherapy alone (HR, 0.61; 95% CI, 0.43-0.87). Notably, this trial included the evaluation of a checkpoint inhibitor with non-taxane drugs and also included patients with more refractory metastatic TNBC, such as those with a disease-free interval as short as 6 months.

On the basis of the results of this trial, the FDA in November 2020 granted accelerated approval to pembrolizumab in combination with chemotherapy to treat locally recurrent and unresectable TNBC or metastatic TNBC in patients whose tumors express PD-L1 (CPS ≥10, as determined by an FDA-approved test). In December 2020 at the SABCS, PFS outcomes for each chemotherapy regimen and secondary efficacy endpoints were presented.[35] In the subgroup analysis, PFS with pembrolizumab plus chemotherapy vs placebo plus chemotherapy was improved regardless of the chemotherapy partner. In the ITT population, median PFS values in the pembrolizumab groups vs the placebo groups were as follows: 7.5 vs 5.4 months, respectively, when pembrolizumab was given with nab-paclitaxel; 8.0 vs 3.8 months, respectively, when it was given with paclitaxel; and 7.4 vs 7.4 months, respectively, when it was given with gemcitabine plus carboplatin. The HRs favored pembrolizumab over placebo, at 0.69 and 0.57 for nab-paclitaxel and paclitaxel (both values statistically significant), and at 0.93 for gemcitabine plus carboplatin (not statistically significant). Additional secondary endpoints of ORR, DCR, and DOR favored pembrolizumab plus chemotherapy, with treatment effect increasing as PD-L1 expression increased. Namely, in the pembrolizumab group, a PD-L1 CPS score of at least 10

resulted in a higher ORR compared with a PD-L1 CPS score of at least 1 and compared with the PD-L1–unselected ITT population. Notably, the median DOR in patients with a PD-L1 CPS score of at least 10 was 19.3 months in the pembrolizumab group vs 7.3 months in the placebo group. Although this updated analysis does not delineate which chemotherapy backbone is the optimal one, the data further support the role of immunotherapy in the first-line treatment of metastatic TNBC.

Early-Stage Triple-Negative Breast Cancer

The observation that responses to immunotherapy, particularly when it is combined with chemotherapy, are more robust in earlier-line therapy than in the metastatic setting has naturally led to the consideration of ICIs in early-stage disease. Although no ICIs are yet approved for the treatment of early-stage TNBC, several trials have demonstrated a potential role for immunotherapy in the neoadjuvant setting (Table 3). The KEYNOTE-173 trial established that pembrolizumab can be given safely and effectively with various standard neoadjuvant chemotherapy regimens.[36] In this phase 1b study, 60 patients were randomly assigned to 1 of 6 different chemotherapy regimen cohorts, with the chemotherapy to be given concomitantly with pembrolizumab following a run-in phase of pembrolizumab alone at 200 mg IV. All regimens included a taxane with or without carboplatin for 12 weeks, followed by doxorubicin and cyclophosphamide (AC) for 12 additional weeks. Initial results, reported at the ESMO Congress in 2019, revealed pathologic complete response (pCR) rates as high as 60% to 80%. The 12-month event-free survival (EFS) rate among those who achieved a pCR was 100%, and was 88% in those who did not achieve a pCR. Dose-limiting toxicities (DLTs) occurred in 22 patients, with neutropenia accounting for 73% of the DLTs. There were irAEs in 30% of patients, with events of grade 3 or higher in 10%. The pembrolizumab arm of the I-SPY2 trial, published in 2019, showed a similar improvement in the pCR rate with the addition of pembrolizumab.[37] Among 29 patients with TNBC who received pembrolizumab in addition to weekly paclitaxel, followed by standard anthracycline/cyclophosphamide, the pCR rate was 60%, compared with 22% in those who received standard neoadjuvant chemotherapy alone. Of note, benefit was also seen in the cohort that had hormone receptor–positive disease, with pCR rates of 30% vs 13% with and without pembrolizumab, respectively.

Taken together, these data formed the foundation for designing the phase 3 KEYNOTE-522 trial.[13] In this randomized, double-blind, placebo-controlled trial, 1174 patients with stage II or III TNBC were randomly assigned in a 2:1 ratio to receive pembrolizumab at 200 mg IV every 3 weeks or placebo for 4 cycles concurrently with paclitaxel at 80 mg/m^2 weekly × 12 and carboplatin at AUC 5 once every 3 weeks or carboplatin at AUC 1.5 weekly in the first 12 weeks, followed by pembrolizumab or placebo with an anthracycline (doxorubicin at 60 mg/m^2 or epirubicin at 90 mg/m^2)/cyclophosphamide (at 600 mg/m^2) once every 3 weeks for 4 cycles before surgery. Treatment with pembrolizumab or placebo continued postoperatively for up to 9 cycles (or 27 weeks). The coprimary endpoints were pCR and EFS, and a key secondary endpoint was OS. At the primary analysis of 602 evaluable patients, the pCR rate in 401 patients receiving neoadjuvant pembrolizumab was 64.8%, which was 13.6 percentage points higher than the pCR rate in the 201 patients in the control arm (95% CI, 5.4-21.8; P<.0001). Of note, this difference in the pCR rate was consistent across subgroups, including the PD-L1–positive and PD-L1–negative subgroups. In the PD-L1–positive subgroup, the pCR rate was 68.9% for patients receiving pembrolizumab vs 54.9% for patients receiving placebo. In the PD-L1–negative subgroup, the pCR rate was 45.3% in the pembrolizumab arm vs 30.3% in the placebo arm. The 18-month EFS was 91.3% among patients who received pembrolizumab and 85.3% in those who received placebo (HR, 0.63; 0.43-0.93). The absolute difference in pCR rates was relatively small across subgroups, however, and did not reach statistical significance. Similarly, the difference in EFS was small, and the data are quite immature. Owing to this lack of mature survival data and the unclear clinical meaningfulness of the pCR differences, the ODAC voted in February 2021 against approval of pembrolizumab in combination with chemotherapy as neoadjuvant therapy for early TNBC. Grade 3 or higher TRAEs occurred in 76.8% of the patients receiving pembrolizumab and 72.2% of those receiving placebo. A total of 23.3% of patients in the pembrolizumab/chemotherapy arm discontinued any trial drug owing to TRAEs, and 12.3% of patients in the placebo/chemotherapy discontinued any trial drug owing to TRAEs. There were 3 treatment-related deaths in the pembrolizumab-containing arm and 1 in the placebo arm.

Results of the IMpassion031 trial of neoadjuvant atezolizumab in combination with chemotherapy were similar.[14] In this randomized, double-blind, phase 3 trial, 333 patients with stage II or III TNBC were randomly assigned in a 1:1 ratio to receive atezolizumab at 840 mg IV every 2 weeks plus neoadjuvant chemotherapy (n=165) or placebo plus neoadjuvant chemotherapy (n=168). The chemotherapy regimen consisted of weekly nab-paclitaxel at 125 mg/m^2 for 12 weeks followed by AC (60/600 mg/m^2) every 2 weeks for 8 weeks. After surgery and subsequent unblinding, patients in the atezolizumab group continued treatment with atezolizumab at 1200 mg every

3 weeks for 11 cycles, and the placebo group underwent observation.

The trial met its coprimary endpoints of pCR rate in the ITT population as well as in the PD-L1–positive subgroup, with positivity defined as PD-L1 expression in at least 1% of tumor-infiltrating immune cells. In the ITT population, the pCR rate was 58% among patients who received atezolizumab and 41% among those who received placebo. In the PD-L1–positive subgroup, the pCR rate was 69% in those who received atezolizumab vs 49% in those who received placebo. The rate of TRAEs was 23% in the atezolizumab arm and 16% in the placebo arm. At SABCS 2020, Mittendorf and colleagues presented data on patient-reported outcomes, which showed that even though patients in both groups reported a mean decrease in physical function and role function, no differences were found between the reports of patients who received atezolizumab plus chemotherapy and the reports of those who received chemotherapy alone.[38] As the side effects lessened over time, patients in both groups rebounded equally well.

Data from other trials conducted in the neoadjuvant setting have not had similar results. In the open-label NeoTRIPaPDL1 trial, which examined neoadjuvant carboplatin at AUC 2 plus nab-paclitaxel at 125 mg/m^2 IV on days 1 and 8, with or without atezolizumab at 1200 mg IV on day 1, of every 3 weeks for 8 cycles, followed by surgery and then 4 cycles of an anthracycline regimen, the pCR rates between the 2 treatment arms were nearly identical.[15] Among 280 patients, those randomly assigned to receive chemotherapy plus atezolizumab had a pCR rate of 43.5%, compared with 40.8% in those who received chemotherapy alone. Among the PD-L1–positive subgroup, 51.9% of the patients who received atezolizumab achieved a pCR, compared with 48% of those who did not. Of note, however, the primary endpoint of this trial was 5-year EFS, which has not yet been reported, whereas in the KEYNOTE-522 trial, pCR was included as a primary endpoint. Similarly, the I-SPY2 trial, designed with the goal of omitting anthracycline, included an arm in which patients received weekly paclitaxel for 12 weeks in addition to pembrolizumab, followed by pembrolizumab monotherapy in place of AC. The pCR rates in the experimental arm were approximately equal to those in the control arm, at 27% and 22%, respectively.[39-41] Trials designed like the I-SPY2 trial suggest potential avenues for de-escalation of therapy in selected cases.

Additionally, the phase 2 GeparNuevo trial randomized 174 patients with TNBC, including 35% with stage I disease, to durvalumab (Imfinzi, AstraZeneca), a PD-L1 inhibitor, or placebo leading up to and throughout neoadjuvant chemotherapy (0.75 g IV 2 weeks before chemotherapy and then 1.5 g IV every 4 weeks), with a standard regimen of nab-paclitaxel 125 mg/m^2 weekly for 12 weeks followed by epirubicin plus cyclophosphamide every 2 weeks for 4 cycles.[16] Overall, pCR rates in the 2 arms were not significantly different (53.4% with durvalumab vs 44.2% with placebo). Of note, though, the pCR rates were higher in the so-called "window" cohort, in which 117 patients received durvalumab or placebo for 2 weeks before the initiation of chemotherapy (pCR, 61.0% vs 41.4%, respectively). The window cohort was an interesting feature of this trial that raised the issue of how to sequence immunotherapy and chemotherapy optimally. Future questions to address with regard to the use of immunotherapy in early-stage TNBC include whether every patient needs chemotherapy and immunotherapy, whether increases in the pCR rates after neoadjuvant chemotherapy and immunotherapy will translate into improved survival, and what is the best chemotherapy backbone and schedule to combine with ICIs.

Several clinical trials are under way that are supportive of the strategy of adding immunotherapy to chemotherapy in early-stage TNBC. The NSABP B-59 (GBG 96-GeparDouze, NCT03281954) trial is a randomized, double-blind, placebo-controlled phase 3 trial evaluating the neoadjuvant administration of atezolizumab with chemotherapy (weekly paclitaxel plus carboplatin followed by AC or epirubicin plus cyclophosphamide) followed by adjuvant atezolizumab in patients with high-risk TNBC. The primary endpoint of this study is pCR in the breast and lymph nodes, which is being assessed in 1520 patients. Another phase 3 trial (SWOG S1418/BR006, NCT02954874) is evaluating the effect of adjuvant treatment with pembrolizumab in 1000 patients with TNBC who have completed definitive local treatment. Randomization is 1:1 to either treatment with pembrolizumab for 12 months or observation. Patients are eligible if they do not achieve a pCR following neoadjuvant chemotherapy and surgery, with residual tumor of at least 1 cm and/or axillary node–positive disease. The primary endpoint is invasive disease-free survival (DFS). This very large trial has the potential to change the standard of care for patients with TNBC who have residual disease after neoadjuvant chemotherapy. The A-BRAVE trial (NCT02926196) is a phase 3 randomized trial to evaluate adjuvant treatment with avelumab in 355 patients with TNBC. Patients who complete definitive curative therapy that includes surgery, adjuvant chemotherapy, and radiation are eligible if they have more than 4 involved axillary lymph nodes. 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. The primary endpoints are overall DFS and DFS in PD-L1–positive patients. The results of this trial will help define the role of an ICI in the adjuvant therapy

of TNBC to prevent recurrence.

Clinical Implications

The results of these trials have helped to generate a framework for understanding the role of immunotherapy in TNBC. First, in the metastatic setting, identification of the patients most likely to respond to immune checkpoint inhibition is of paramount importance. Although PD-L1 expression is an imperfect biomarker, and in some cases does not correlate with ICI response, it appears to provide important insights into a tumor's immune microenvironment. The currently approved atezolizumab and nab-paclitaxel regimen, based on the IMpassion130 trial, requires PD-L1 positivity on the VENTANA PD-L1 (SP142) assay. Pembrolizumab treatment requires PD-L1 positivity according to the CPS score. The FDA-approved PD-L1 IHC 22C3 pharmDx from Dako is a companion diagnostic for the selection of patients with TNBC for pembrolizumab therapy. Clinicians will need to partner closely with their pathology colleagues when ordering and interpreting these different PD-L1 immunohistochemistry assays. Ongoing research aims to characterize emerging complementary biomarkers, such as TILs, tumor mutational burden, and immune gene expression signature.[42,43] The importance of identifying these predictive factors cannot be overstated. As the trials previously discussed highlight, the risks of immunotherapy are real, with serious adverse events occurring in as many as 70% of patients when it is combined with chemotherapy, but when it is given to the right patients, the responses can be durable.

Unlike in the metastatic setting, PD-L1 status appears to be less important as a biomarker of immunotherapy response in early-stage disease, and more important as a biomarker of response to therapy in general. As demonstrated by the KEYNOTE-522 study, PD-L1 positivity, regardless of the chemotherapy partner, predicts a better response to neoadjuvant therapy whether it includes immunotherapy or not. Thus, an intact immune system may overcome any inherent ICI resistance suggested by PD-L1 negativity. Although PD-L1 status may be less important in the early-disease setting, the specific chemotherapy partner may be very important. The 3 trials that have demonstrated a benefit from adding immunotherapy to neoadjuvant chemotherapy—KEYNOTE-522, I-SPY2, and IMpassion031—all incorporated an anthracycline into the chemotherapy regimen. Conversely, in the anthracycline-free arm of the I-SPY2 trial, as well as in the NeoTRIPaPDL1 trial, anthracyclines were omitted from the neoadjuvant regimen, and no benefit was seen with immunotherapy. It is important to point out, though, that in the anthracycline-sparing regimens, pCR rates were still quite high. This finding points toward identifying a population that may benefit from a de-escalated neoadjuvant regimen.

In the metastatic setting, the chemotherapy partner may also be important. IMpassion130, which partnered atezolizumab with nab-paclitaxel, showed significantly improved responses and survival compared with nab-paclitaxel alone, but these results were not replicated when atezolizumab was added to paclitaxel in the IMpassion131 trial. Possible explanations for the discordance could be related to the chemotherapy partner itself, or to the fact that paclitaxel requires the co-administration of a corticosteroid, which may dampen the efficacy of immune checkpoint inhibition. Of note, however, this effect of paclitaxel was not seen in the KEYNOTE-355 trial, in which most patients who received a taxane as the chemotherapy partner of pembrolizumab received paclitaxel, and this cohort performed numerically (although not statistically) better than the cohorts in which a different chemotherapy partner was used. Other factors to consider among these trials are the differences in patient baseline characteristics, chemotherapy exposure, and disease-free interval before protocol entry (≥12 months vs ≥6 months).

Conclusions

Metastatic TNBC was once a disease in which survival was measured in months. In recent years, however, research has begun to elucidate a strategy for extending survival. Although the ORRs with single-agent ICI treatment are modest, in the minority of patients who do achieve a response, the benefit can be long-lasting. Combining an ICI with chemotherapy significantly expands the number of patients who derive such benefit, as does using immunotherapy in an earlier line of treatment. These findings have led to the testing of immunotherapy in the setting of early-stage disease, in patients who have never been exposed to chemotherapy and have relatively intact immune systems. Our hope is that the benefit in this setting will be even more robust, and with pCR rates above 60% in some studies, it appears that the addition of an ICI to neoadjuvant chemotherapy may delay or prevent the development of metastatic TNBC. Ongoing research will help to identify more clearly those patients with TNBC who may benefit the most from immunotherapy, as well as better define optimal partner regimens to enhance clinical benefit. In the meantime, immunotherapy has an established role in the treatment of metastatic TNBC.

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