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Systematic Review

Positive progress: current and evolving role of immune checkpoint inhibitors in metastatic triple-negative breast cancer

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Abstract

Background: Triple-negative breast cancer (TNBC) represents an aggressive breast cancer subtype with historically poor overall outcomes, due primarily to a lack of effective targeted agents. Chemotherapy has been the primary treatment approach, although immune checkpoint inhibitors (ICIs) are currently being investigated to improve patient outcomes. This review examines the clinical implications of current evidence on the use of ICIs for the treatment of metastatic TNBC.

Methods: Our systematic search identified two phase III and five phase I/II trials reporting on the efficacy of ICIs used as monotherapy or combined with chemotherapy for the treatment of metastatic TNBC.

Results: The phase III IMpassion 130 trial showed a significant improvement in median progression-free survival in the intent-to-treat (net 1.7 months, $p = 0.002$) and PD-L1-positive populations (net 2.5 months, $p < 0.001$) for the addition of first-line atezolizumab versus placebo to nab-paclitaxel in metastatic TNBC. Although median overall survival was not significantly improved in patients receiving atezolizumab overall [net 2.3 months, hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.72–1.02, $p = 0.078$], numerical improvements in the PD-L1-positive population were compelling (net 7.0 months, HR 0.71; 95% CI 0.54–0.93). Toxicity profiles were as expected, and no new safety signals were observed. Pembrolizumab monotherapy did not significantly improve overall survival in similar patients that had received prior treatment in KEYNOTE-119.

Conclusions: Atezolizumab plus nab-paclitaxel represents a potential new first-line standard of care for patients with metastatic PD-L1-positive TNBC. Other ICIs used as monotherapy, or combined with chemotherapy for advanced TNBC, as well as their use for earlier stage disease, are areas of ongoing investigation.

Keywords: Anti-PD-1, Anti-PD-L1, atezolizumab, checkpoint inhibitors, immunotherapy, TNBC, triple-negative breast cancer

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Introduction

Breast cancer is the most common cancer diagnosis, and the leading cause of cancer related death in females, with nearly 2.1 million new cases resulting in over 620,000 deaths worldwide in 2018, and approximately 6% of patients presenting with metastatic disease.[1,2] Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by the lack of expression of the human epidermal growth factor receptor 2, estrogen receptor, and progesterone receptor.[3] TNBC accounts for 13–20% of all breast cancers and represents an aggressive breast cancer subtype.[2–4] Outcomes for patients who develop metastatic TNBC are poor, owing in part due to a lack of effective targeted therapeutic agents, and the

mainstay of treatment has therefore been traditional chemotherapy.[4–7]

Although the classification of TNBC is useful from a clinical standpoint, it does not provide much insight into the heterogeneity of the disease.[3,4] There are multiple approaches to further characterize TNBC, including classic clinical pathology techniques, gene expression profiling, and the assessment of genomic alterations.[3,8] Immunohistochemistry studies indicate a range of TNBC tumors, which can be androgen receptor positive or negative, show varying degrees of proliferation estimated by the expression of Ki-67, and contain tumor-infiltrating lymphocytes (TILs).[3,9–11] Gene expression profiling shows a broad spectrum of TNBC subtypes, ranging from basal-like to luminal, with most, but not all, of TNBCs expressing basal-like attributes.[3,12] Other subtypes of interest include immunomodulatory TNBC, which is enriched for gene signatures involved in immune cell processes;[3,8] and basal-like immune activated TNBC, which have basal-like features characterized by STAT transcription factors and high cytokine levels.[3,13] Many genomic alterations have been identified in TNBC, including *TP53, PIK3CA*, and germline *BRCA1* or *BRCA2* mutations.[3,14] germline *BRCA1/2* mutations occur in approximately 11% of unselected TNBC cases,[15] and TNBC has the highest frequency of mutations among breast cancer subtypes.[3,16] It has become evident that TNBC is indeed highly heterogeneous, adding to the challenge of identifying a consistent therapeutic target for this disease.

The standard of care for metastatic TNBC consists of treatment with multiple lines of chemotherapy, preferably given sequentially without treatment breaks based on progression free survival (PFS) and overall survival (OS) benefit.[17,18] International guidelines support the use of single-agent anthracyclines and taxanes for first-line treatment, followed by sequential single agent chemotherapy including eribulin,[19–24] until either a rapid decline in performance status or the approach of end of life.[25] TNBC patients with germline *BRCA*1/2 mutations can receive poly ADP ribose polymerase (PARP)-inhibitors based on results from the phase III OlympiAD and EMBRACA trials,[21,26,27] or platinum therapy based on results of the phase III TNT study.[28] Guidelines also suggest that chemotherapy combinations may play a role in those with high tumor burden, visceral crisis, or rapidly progressing disease.[19,21,22] The overall lack of targeted therapy options and targetable mutations for TNBC means that new therapeutic approaches are needed for these aggressive and heterogeneous tumors.

Although breast cancer has historically been considered nonimmunogenic,[29] there are a number of biological rationales for the use of immune checkpoint inhibitors (ICIs) in TNBC.[30,31] TNBC is often associated with increased numbers of TILs,[13,30–32] which are associated with high expression of the programmed cell death ligand-1 (PD-L1),[33] indicating an immunogenic environment. PD-L1 expression can decrease T-cell proliferation and increase apoptosis in the tumor microenvironment,[31] providing additional rationale for targeting the PD-1 (programmed cell death protein-1)/PD-L1 axis to improve tumor control. Most TNBC patients will receive chemotherapy, either in the adjuvant or metastatic settings. These tumors therefore may be more primed to respond to ICIs, as cytotoxic chemotherapy can also increase the production of tumor cell (TC) antigens,[34,35] decrease production of T-cell inhibitory molecules,[34,35] and possibly increase PD-L1 expression.[36] Furthermore, combining ICIs with standard chemotherapeutic agents has the potential to increase the magnitude and duration of response in patients with TNBC. ICIs, including the PD-1 inhibitor nivolumab and pembrolizumab, and the PD-L1 inhibitors atezolizumab, durvalumab, and avelumab, are currently under investigation, either as monotherapy or in combination with chemotherapy, for the treatment of patients with advanced TNBC.[37]

The rapidly evolving role of ICIs in TNBC is currently being investigated and early clinical indicators suggest that PD-1/PD-L1 ICIs are active in the treatment of TNBC.[30,31] The objective of this clinical review is to discuss phase I-III efficacy and safety data on the use of ICIs alone, or in combination with chemotherapy, for the treatment of patients with advanced TNBC, and to consider future clinical applications.

Methods

A search of published and presented literature was conducted to identify clinical trials (phase I–III) reporting outcomes on the use of ICIs as monotherapy or in combination with chemotherapy for the treatment of metastatic TNBC. PubMed (all time to 9 June 2019), the proceedings of the American Society of Clinical Oncology (ASCO

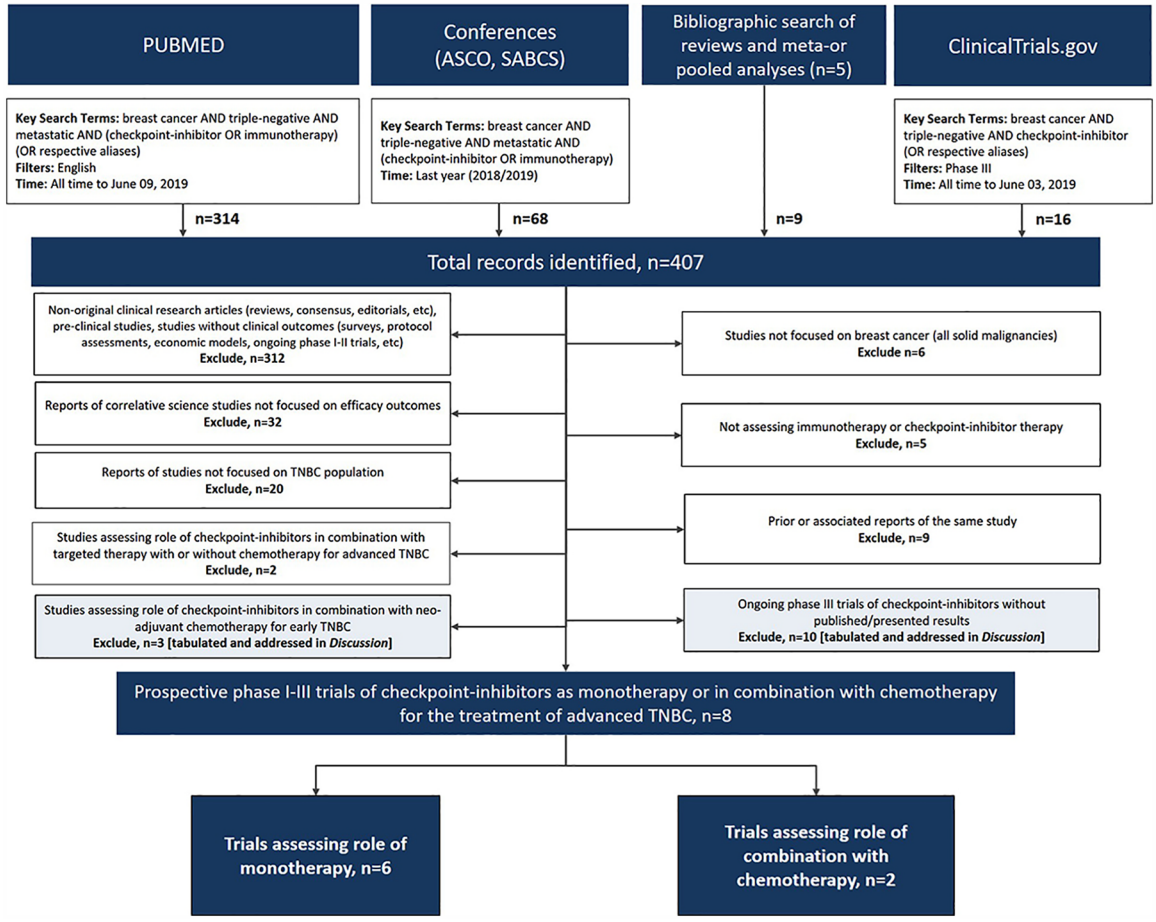

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.
ASCO, American Society of Clinical Oncology; SABCS, San Antonio Breast Cancer Symposium; TNBC, triple-negative breast cancer.

2019) annual meetings, and the proceedings of the San Antonio Breast Cancer Symposium (SABCS 2018) were searched for clinical trials assessing ICIs in the treatment of TNBC using the key search terms "checkpoint inhibitor" OR "immunotherapy" AND "triple-negative" AND "metastatic" AND "breast cancer" OR respective aliases. A supplemental bibliographic search of review articles and pooled/meta-analyses was also conducted.[3,31,37–39] In addition, ClinicalTrials.gov was searched on 3 June 2019 for ongoing phase III trials of ICIs in the treatment in TNBC using the key search terms "checkpoint inhibitor" AND "triple-negative" AND "breast cancer" OR respective aliases AND the "phase III" filter.

English language records were vetted at abstract level and confirmed at full text as needed. Studies were excluded if they were nonoriginal research, preclinical studies only, correlative science, not specific to breast cancer (phase I studies in all solid tumors), outside the metastatic setting, or addressed nonchemotherapy combinations; duplicate or prior reports or studies without reported outcomes were also excluded. Although not formally included in our search, phase I–III studies of combinations with neoadjuvant chemotherapy and ongoing phase III trials were summarized and addressed in the discussion.

Findings

The literature search identified a total of 407 records, which after vetting resulted in a total of eight clinical trials reporting efficacy outcomes on the use of ICIs as monotherapy ($n=6$) or in combination with chemotherapy ($n=2$) for the treatment of metastatic TNBC (Figure 1).[40–48] The phase II TONIC trial was excluded as this trial assessed ICI induction therapy and did not meet

Table 1. Efficacy of single agent immune checkpoint inhibitors in advanced TNBC. Efficacy outcomes of immune checkpoint inhibitor trials in metastatic TNBC ordered by line of therapy then size of trial.

Trial	Setting Line of treatment	Regimen(s)	*n*	Overall response rate, % (95% CI)	Median duration of response, months (95% CI) [range]	Median progression free survival, months (95% CI)	Median overall survival, months (95% CI)
JAVELIN Phase Ib Subgroup[45]	PD-L1 unselected 50.0% ⩽second-line	Avelumab	58	5.2 (1.1–14.4)	NE	1.4[a] (1.3–1.6)	9.2 (4.3–NE)
PCD4989g Phase I[46]	PD-L1 unselected[b] 18.3% first-line	Atezolizumab	115	10[c] (4.9–16.5)	21 [3–38+]	1.4 (1.3–1.6)	8.9[d] (7.0–12.6)
KEYNOTE-012 Phase Ib[47]	PD-L1-positive 15.6% first-line[e]	Pembrolizumab	27	18.5 (6.3–38.1)	NYR [3.4–10.9+]	1.9 (1.7–5.5)	11.2 (5.3–NYR)
KEYNOTE-086 Phase II Cohort B[43]	PD-L1-positive 100% first-line	Pembrolizumab	84	21.4 (13.9–31.4)	10.4 [4.2–19.2+]	2.1 (2.0–2.2)	18.0 (12.9–23.0)
KEYNOTE-086 Phase II Cohort A[44]	PD-L1 unselected second-line+ 31.2% second-line	Pembrolizumab	170	5.3 (2.7–9.9)	NYR [1.2+–21.5+]	2.0 (1.9–2.0)	9.0 (7.6–11.2)
KEYNOTE-119 Phase III[41,48]	PD-L1 Unselected second- or third-line	Pembrolizumab	312	9.6	12.2 [2.2–32.5+]	2.1 HR 1.60 (1.33–1.92)	9.9 HR 0.97 (0.82–1.15)
		Chemotherapy[f]	310	10.6	8.3 [2.1–33.0+]	3.3	10.8

[a]Weeks converted to months using 4.35 weeks/month as conversion factor.
[b]First 25 patients selected for PD-L1 ⩾5% ICs; enrollment subsequently extended all patients regardless of PD-L1 status.
[c]ORR for first-line: 24% (95% CI 8.2–47.2), second-line: 6% (95% CI 2.4–13.4).
[d]OS for first-line: 17.6 months (95% CI 10.2-NE), second-line: 7.3 months (95% CI 6.1–10.8).
[e]Of 32 enrolled patients.
[f]Physician's choice of single agent chemotherapy; capecitabine, eribulin, gemcitabine, or vinorelbine.
CI, confidence interval; HR, hazard ratio; NE, not estimable; NS, not significant; NYR, not yet reported; PD-L1, programmed cell death ligand-1; TNBC, triple-negative breast cancer.

the eligibility criteria of being used either as monotherapy or in combination with chemotherapy.[49]

ICIs as monotherapy

The activity of ICIs as monotherapy in metastatic TNBC was reported in four phase I/II studies,[43–47] and one phase III trial (Table 1).[48] Two recent phase I studies evaluated avelumab or atezolizumab in patients with PD-L1 unselected advanced TNBC.[45,46] JAVELIN included 58 patients with TNBC receiving avelumab, showing an objective response rate (ORR) of 5.2% [95% confidence interval (CI) 1.1–14.4], with a median duration of response (DOR) that was not estimable,[45] and the PCD4989g study evaluated atezolizumab in 115 TNBC patients showing an ORR of 10% (95% CI 4.9–16.5) with a median DOR of 21 months (95% CI 3–38+) (Table 1). Pembrolizumab was also assessed in phase I, II, and III trials in advanced TNBC.[43,44,47,48] The small Ib KEYNOTE-012 trial showed a promising ORR of 18.5% (95% CI 6.3–38.1) with a median DOR not yet reached (range 3.4–10.9+ months) among 27 PD-L1-positive patients.[47] The larger phase II KEYNOTE-086 study assessed pembrolizumab in two cohorts: the first-line PD-L1-positive cohort (B, $n=84$) showed an ORR of 21.4% (95% CI 13.9–31.4) with a median DOR of 10.4 months (range 4.2–19.2+),[43] and the second- or later-line PD-L1 unselected cohort (A, $n=170$) showed an ORR of 5.3% (95% CI 2.7–9.9) with the median DOR not yet reached (range 1.2+–21.5+).[44]

Table 2. Efficacy of immune checkpoint inhibitor plus chemotherapy combinations in advanced TNBC. Efficacy outcomes of immune checkpoint inhibitor trials in TNBC ordered by setting then size of trial.

Trial	Setting Line of treatment	Regimen(s)	*n*	Overall response rate, % (95% CI)	Median duration of response, months (95% CI)	Median progression free survival, months (95% CI)	Median overall survival, months (95% CI)
GP28328 Phase Ib[42]	PD-L1 unselected 39.4% first-line	Atezolizumab + nab-paclitaxel	33	39.4 (22.9–57.9)	9.1 (2.0–20.9)	5.5 (5.1–7.7)	14.7 (10.1-NE)
IMpassion 130 Phase III[40]	PD-L1 unselected first-line	Atezolizumab + nab-paclitaxel	451	56.0 (51.3–60.6)	7.4 (6.9–9.0)	7.2 HR 0.80 (0.69–0.92) $p=0.002$	21.3 HR 0.84 (0.69–1.02) $p=0.08$
		Placebo + nab-paclitaxel	451	45.9 (41.2–50.6)	5.6 (5.5–6.0)	5.5	17.6

CI, confidence interval; HR, hazard ratio; NE, not estimable; PD-L1, programmed cell death ligand-1; TNBC, triple-negative breast cancer.

Pembrolizumab was also assessed in the phase III KEYNOTE-119 trial, which randomized 622 second- or third-line PD-L1 unselected advanced TNBC patients to receive either pembrolizumab or physicians choice of single agent chemotherapy. The coprimary endpoints of this study were OS in the intent-to-treat (ITT) population and also in patients with PD-L1-positive tumors with a combined positive score {CPS; [total TCs + immune cells (ICs)]/total TCs × 100 ⩾1 and ⩾10}. At a median follow up of 9.9–10.9 months, no significant improvement in median PFS [2.1 *versus* 3.3 months, hazard ratio (HR) 1.60, 95% CI 1.33–1.92] or OS (9.9 *versus* 10.8 months, HR 0.97, 95% CI 0.82–1.15) was observed for pembrolizumab *versus* chemotherapy in ITT patients.[48] Nor did PD-L1 subgroup analyses show an improvement in OS among patients with CPS ⩾1 (10.7 *versus* 10.2 months, stratified HR 0.86, 95% CI 0.69–1.06, $p=.073$), or CPS ⩾ 10 tumors (12.7 *versus* 11.6 months, HR 0.78, 95% CI 0.57–1.06, $p=.057$). In ITT patients, ORRs were 9.6% *versus* 10.6%, and median DORs were 12.2 *versus* 8.3 months in the pembrolizumab *versus* chemotherapy arms.

ICIs plus chemotherapy combinations

Efficacy of first-line therapy. The activity of atezolizumab in combination with nab-paclitaxel was reported in a phase I and phase III trial in metastatic TNBC (Table 2).[40,42] The phase I GP28328 study investigated this regimen in 33 patients, showing an ORR of 39.4% (95% CI 22.9–57.9) in patients overall and a median DOR of 9.1 months (95% CI 2.0–20.9 months), with a subgroup analysis showing higher ORRs in first-line (53.8%) compared with later lines (30.0%) of therapy.[42] These findings formed the basis for a large phase III IMpassion 130 trial, which randomized patients to receive first-line atezolizumab ($n=451$) or placebo ($n=451$) plus nab-paclitaxel in both arms until progressive disease or intolerable toxicity. The coprimary endpoints of the trial were PFS and OS in both ITT and PD-L1-positive populations. At a median follow up of 12.9 months, a significant improvement in median PFS was observed in the atezolizumab *versus* placebo arm in both the ITT (7.2 *versus* 5.5 months, HR 0.80, 95% CI 0.69–0.92, $p=0.002$) and in patients with PD-L1-positive disease ($n=369$, 7.5 *versus* 5.0 months, stratified HR 0.62, 95% CI 0.49–0.78, $p<0.001$).[40] Median OS was not significantly improved in the ITT population for atezolizumab compared with placebo either at a median follow up of 12.9 months (21.3 *versus* 17.6 months, HR 0.84, 95% CI, 0.69–1.02, $p=0.08$) or 18.0 months (21.0 *versus* 18.7 months, HR 0.86, 95% CI 0.72–1.02, $p=0.078$).[40,50] In the stratified PD-L1-positive subgroup, median OS was numerically higher in the atezolizumab compared with placebo arm (25.0 *versus* 18.0 months, HR 0.71, 95% CI 0.54–0.93 with a CI that did not cross unity) at a median follow up of 18.0 months.[50] ORRs were 56.0% *versus* 45.9% in the atezolizumab *versus* placebo group [odds

ratio (OR) 1.52, 95% CI 1.16–1.97, $p = 0.002$ although nonsignificant based on prespecified criteria of $p < 0.001$], with a median DOR of 7.4 *versus* 5.6 months (HR 0.78, 95% CI 0.63–0.98) in the atezolizumab/nab-paclitaxel *versus* placebo/nab-paclitaxel groups, respectively.[40]

Safety of immune checkpoint inhibitors. Five trials reported on ICIs as monotherapy in advanced TNBC.[41,43–48] The phase I JAVELIN[45] and PCD4989g[46] trials reported low rates of avelumab and atezolizumab discontinuation due to treatment-related adverse events (TRAEs, 4.8% and 3%, respectively), with similar low rates reported for pembrolizumab in both the first-line (B, 1.2%)[43] and previously treated cohort (A, 4.1%) of KEYNOTE-086.[44] In KEYNOTE-119, adverse events (AEs) of any cause led to discontinuation of therapy in 4.5% and 5.5% of patients and grade 3/5 immune-mediated AEs or infusion reactions occurred in 3.2% and 1.0% of patients receiving pembrolizumab and chemotherapy, respectively.[48] Nine deaths due to AEs of any cause occurred in each arm (2.9% *versus* 3.1%) in patients receiving pembrolizumab versus chemotherapy.

The large phase III IMpassion 130 trial assessed the safety of atezolizumab in combination with nab-paclitaxel in first-line advanced TNBC. Overall toxicity profiles were as expected based on known AEs of each study drug and no new safety signals were identified.[40] Rates of discontinuation of any treatment due to AEs (15.9% *versus* 8.2%) and grade 3/4 TRAEs (39.6% *versus* 30.1%) were higher in the atezolizumab compared with placebo arms. Three deaths (0.7%, autoimmune hepatitis, mucosal inflammation, and septic shock) in the atezolizumab arm and one (0.2%, hepatic failure) in the placebo group were considered treatment-related.

Discussion

What is the clinical impact of ICIs for advanced TNBC?

Traditionally, new anti-neoplastic agents are first tested in later lines of advanced disease, and adopted for earlier lines of treatment only if proven effective. The current standard of care for metastatic TNBC without a driver mutation (e.g. germline *BRCA1/2* mutation) is sequential chemotherapy.[19–22] In the first-line setting, a change in clinical practice is warranted if a new treatment improves OS, PFS, or quality of life (QoL) in a phase III trial compared with single agent anthracycline or taxane therapy in patients overall or compared with platinum or PARP-inhibitor therapy in patients with germline *BRCA*1/2 mutations. IMpassion 130 was the only phase III trial to evaluate the addition of atezolizumab to nab-paclitaxel in first-line TNBC. Enrolled patients were stratified based on PD-L1 status [PD-L1 expression on tumor-infiltrating ICs, PD-L1-positive ⩾1% and negative (PD-L1–) <1%] with PFS assessed in the ITT population and in patients with PD-L1-positive tumors. The study used a prespecified hierarchical testing approach so that if the coprimary endpoint of OS was significantly improved for the combination in the ITT population, patients with PD-L1-positive disease (41% of patients) would be formally tested. At the first interim analysis with a median follow up of 12.9 months, the study demonstrated a significant improvement in median PFS with the addition of atezolizumab in both ITT (net 1.7 months, HR 0.80, $p = 0.002$) and PD-L1-positive patients (net 2.5 months, HR 0.62, $p < 0.001$).[40] The study did not show significantly improved OS in the ITT population at either the first (net 3.7 months, HR 0.84, $p = 0.08$) or second (median follow-up 18.0 months, net 2.3 months, HR 0.86, $p = 0.078$) interim analyses.[50] Although the design of the IMpassion 130 trial did not support an assessment of significantly improved OS in the PD-L1-positive subpopulation, an exploratory PD-L1-positive subgroup analysis showed a numerical OS benefit in favor of atezolizumab compared with placebo at the first (net 9.5 months, HR 0.62, 95% CI 0.45–0.86) and second (net 7.0 months, HR 0.71, 95% CI 0.54–0.93) interim analyses.[50] The benefit, although not statistically significant, was clear, with tight confidence intervals that did not cross unity at either analysis suggesting that the benefit was real and clinically meaningful, leading to accelerated approval by the United States Food and Drug Administration (FDA) on 8 March 2019, and the European Commission on 29 August 2019 for patients with PD-L1-positive metastatic TNBC based on PFS benefit in that population.[51] Moreover, the National Comprehensive Cancer Network (NCCN) recently updated their guidelines to include atezolizumab plus nab-paclitaxel in PD-L1-positive metastatic TNBC patients.[21] The PFS and OS improvements observed in the PD-L1-positive subgroup of this trial support the use of atezolizumab in combination with nab-paclitaxel as the new potential standard first-line therapy for patients with PD-L1-positive metastatic TNBC.

Approximately 11% of unselected TNBC cases have germline *BRCA1/2* mutations,[15] and *BRCA1*-mutated TNBC shows a higher mutational load, more TILs, and increased expression of PD-L1.[52] Either PARP-inhibitor therapy or platinum-based chemotherapy are standard treatment in these patients.[21] As IMpassion 130 assessed the addition of atezolizumab to nab-paclitaxel, it is unclear how this combination compares to treatment with established therapies such as PARP-inhibitors or platinum chemotherapy. Results from the upcoming phase III IMpassion 132 (ClinicalTrials.gov identifier: NCT03371017) study combining atezolizumab with either gemcitabine-carboplatin or capecitabine alone will determine the benefits of adding atezolizumab to platinum therapy in early relapsing patients (progressing <12 months following early chemotherapy) who were excluded from IMpassion 130.[40,53] In the 15% of IMpassion 130 patients who had germline *BRCA1/2* mutations, treatment with the combination was associated with a significant PFS benefit only in those with PD-L1+ tumors and a trend toward improved OS, although patient numbers were small.[54,55] Research into ICI and PARP-inhibitor combinations is ongoing, with results from the phase I/II TOPACIO/KEYNOTE-162 trial evaluating niraparib plus pembrolizumab in patients with TNBC or ovarian cancer showing higher ORRs in patients with TNBC having germline *BRCA1/2* mutations compared with the overall population (ORR 60% *versus* 28%).[56]

For second- or later-lines of therapy for metastatic TNBC, a change in clinical practice is warranted if a new treatment improves OS and maintains or improves QoL compared with chemotherapy in a phase III trial. The PD-1-inhibitor pembrolizumab was studied in both a large phase II and a phase III trial.[44,48] KEYNOTE-086 (Cohort A) demonstrated a modest ORR (5.3%) and PFS (2.0 months) with a promising OS of 9.0 months in 170 previously treated patients.[44] The KEYNOTE-119 phase III trial compared second- or third-line pembrolizumab monotherapy to chemotherapy in patients with metastatic TNBC. There was no OS significant benefit for pembrolizumab compared with chemotherapy in the ITT (net –0.9 months, HR 0.97, 95% CI 0.82–1.15), CPS ⩾1 (net 0.5 months, HR 0.86, $p = 0.073$), or CPS ⩾10 (net 1.1 months, HR 0.78, $p = 0.057$) populations.[48] Pembrolizumab monotherapy is therefore not recommended in this setting.

Are ICI plus chemotherapy combinations for treatment of advanced TNBC safe?

ICIs have been combined with chemotherapy in a number of disease sites.[57] In IMpassion 130, the addition of atezolizumab to nab-paclitaxel showed good tolerability compared with the placebo plus nab-paclitaxel arm, with comparable rates of any grade TRAEs (96.5% *versus* 93.6%), grade 3/4 TRAEs (39.6% *versus* 30.1%), and death due to TRAEs (0.7% *versus* 0.2%).[40] Rates of discontinuation of any treatment were nearly double with the addition of atezolizumab to nab-paclitaxel (15.9%) compared with placebo plus nab-paclitaxel (8.2%), with the majority of patients in the atezolizumab arm discontinuing nab-paclitaxel compared with atezolizumab (15.9% and 6.4%, respectively) despite prespecified dose reductions protocols to manage nab-paclitaxel toxicities. The higher rates of discontinuation due to toxicity for the atezolizumab arm are reasonable, given that patients on that arm were on treatment longer and had a greater opportunity to develop an AE.

No new AEs of special interest (AESIs) were identified with the addition of atezolizumab in IMpassion 130. Higher rates of any AESIs were seen in the atezolizumab *versus* placebo arms (57.3% *versus* 41.8%),[40] although this difference was due primarily to any grade immune-related hypothyroidism (17.3% *versus* 4.3%), which can be easily monitored and managed,[58] and none of these events were grade 3/4 or led to treatment discontinuation.[40] Low rates of grade 3/4 AESIs were reported in both the atezolizumab and placebo arms (7.5% *versus* 4.3%, respectively). Two AESI-related hepatic-deaths were reported, including one receiving atezolizumab (autoimmune hepatitis) and one in the placebo plus nab-paclitaxel group (hepatic failure). Immune-related hepatitis was the most common grade 3/4 AESI (5.1% *versus* 3.0%), and other immune-related grade 3/4 AESIs in the atezolizumab arm included rash (0.9%) in addition to hyperthryoidism, pneumonitis, colitis, adrenal insufficiency, pancreatitis, and diabetes mellitus (0.2% for each). Overall, the addition of atezolizumab to nab-paclitaxel was tolerable, and did not appear to greatly increase toxicities. This combination is considered safe, although close monitoring may be required for select AESIs and clinicians should be alerted to possible hepatic toxicities, which have been shown to be effectively managed with a short course of steroids.[59]

Who will benefit from ICI plus chemotherapy combinations for advanced TNBC?

Given the heterogeneity of TNBC, biomarkers can be particularly powerful tools for selecting patients for therapy, thereby reducing overall cost of treatment and improving overall safety. Immunogenic subtypes of TNBC contain high levels of TILs, which are an important component of the overall ICs in the tumor microenvironment, and are expected to be more responsive to ICIs.[3] PD-L1 is an established biomarker used to guide therapy in other disease settings, including advanced non-small cell lung cancer, urothelial carcinoma, head and neck squamous cell, gastric, esophageal, and cervical cancer.[60–62] In other tumor types, common immunohistochemical assays used are the Dako Link48 (Dako Colorado, Inc., Fort Collins, CO, USA) and Ventana Benchmark (Ventana Medical Systems, Oro Valley, AZ, USA), which test PD-L1 expression on TCs alone [pembrolizumab (22C3)] or both TCs and ICs [atezolizumab (SP142)]. In TNBC, atezolizumab studies defined PD-L1 positivity based on ICs alone using the Ventana SP142 assay (⩾1% expression on ICs),[40,42,46] whereas the phase II/III pembrolizumab studies defined PD-L1 positivity (CPS⩾1) based on tumor cells as well as lymphocytes and macrophages [(total TCs + ICs)/total TCs × 100] using the 22C3 antibody (pharmDx kit, Agilent, Carpinteria, CA, USA).[43,44,48,63] A *post hoc* substudy of the IMpassion130 evaluated the predictive capacity of various PD-L1 assays. The 22C3 (CPS ⩾1), SP263 (IC ⩾1%), and SP142 (IC ⩾1%) PD-L1 assays showed a PD-L1-positive prevalence of 81%, 75%, and 46%, respectively, with poor concordance for 22C3 and SP263 relative to SP142.[64] Moreover, the SP142 assay was associated with lower HRs for median PFS and OS compared with 22C3 and SP263, indicating a greater predictive capacity for atezolizumab in this setting. Given the specificity of the Ventana SP142 assay (⩾1% expression on ICs), and the FDA approval of this diagnostic test,[65] it is recommended to guide atezolizumab and nab-paclitaxel treatment in this setting.[66]

PD-L1 expression is somewhat predictive of ICI benefit in both monotherapy and combination therapy trials, although earlier phase studies assessing ORR were less consistent with regard to predictive benefit. The phase I PCD4989g study assessed atezolizumab, and indicated a potential correlation with an ORR of 12% (95% CI 6–21) in patients with PD-L1-positive disease (81.3% of patients), and no responses in PD-L1-negative disease (18.8% of patients, ORR 0%, 95% CI 0–17),[46] while the phase II KEYNOTE-086 trial cohort A evaluating pembrolizumab indicated a lack of correlation with comparable responses among PD-L1-positive (61.8% of patients, ORR 5.7%, 95% CI 2.4–12.2) and PD-L1-negative (37.6% of patients, ORR 4.7%, 95% CI 1.1–13.4) patients.[44] However, the larger phase III trials assessing OS were more clearly indicative of a correlation, although significance was not established due to the trial design limitations. KEYNOTE-119 showed greater OS benefit for pembrolizumab compared with placebo, with increasing levels of PD-L1 expression beginning in patients with CPS ⩾1 (net 0.5 months, HR 0.86, $p = 0.073$) followed by CPS ⩾10 (net 1.1 months, HR 0.78, $p = 0.057$) and CPS ⩾20 disease (exploratory, net 2.4 month, HR 0.58, 95% CI 0.38–0.88).[48] A similar correlation between PD-L1 expression and OS was seen in IMpassion130 assessing the addition of atezolizumab to chemotherapy. At a median follow up of 18.0 months, PD-L1-positive patients experienced a 7-month net OS benefit (HR 0.71, 95% CI 0.54–0.93) compared with little-to-no benefit seen in PD-L1-negative patients (net 0.1 months, HR 0.97, 95% CI 0.78–1.20).[50] Although PD-L1 expression has some predictive capacity, additional biomarkers are needed to tailor treatment. Biomarkers under investigation include TILs, tumor mutational burden, gene signatures, microsatellite instability, and mismatch repair deficiency.[66,67]

In addition to PD-L1 expression, treatment history and baseline characteristics can also influence study outcomes. An exploratory analysis of key baseline factors affecting median PFS was performed for both ITT and PD-L1-positive subpopulations of IMpassion 130. Median PFS was longer for the atezolizumab combination in the majority of patient subgroups, with select groups showing more or less benefit compared with the overall population in both analyses. In the small number of patients with lymph node only disease, the atezolizumab PFS benefit was pronounced compared with placebo in both ITT (6.2% of patients, HR 0.44, 95% CI 0.24–0.83) and PD-L1-positive (8.4% of patients, HR 0.31, 95% CI 0.13–0.77) populations.[40] A similar benefit was seen in PD-L1-positive patients with locally advanced disease (12.7% of patients, HR 0.44, 95% CI 0.22–0.89). In contrast, the PFS benefit was not very pronounced in the small number of

patients with central nervous system (CNS) metastases in both ITT (6.8% of patients, HR 0.86, 95% CI 0.50–1.49) and PD-L1-positive (2.9% of patients, HR 1.40, 95% CI 0.57–3.44) populations. Although patients with bone metastases receiving atezolizumab did not have a very pronounced PFS benefit in the ITT population (31.7% of patients, HR 1.02, 95% CI 0.79–1.31), the benefit was sound in patients with PD-L1-positive disease (27.9% of patients, HR 0.62, 95% CI 0.41–0.95). Based on results reported to date, however, caution should be used when considering subgroup analyses to guide therapy as these exploratory analyses are not powered for significance and do not control for the influence of baseline factors. Moreover, caution should be used when considering combination therapy in patients with an Eastern Cooperative Oncology Group Performance Score (ECOG PS) ≥ 2, untreated CNS metastases, and who are ineligible for taxanes, as these patients were not included in the IMpassion130 study. Taken together, clinicians should undertake an individualized approach to treatment considering clinical characteristics, treatment history, the safety and efficacy of available treatment options, and potential prognostic factors.

What are the next steps?

IMpassion130 combined the PD-L1 inhibitor atezolizumab with nab-paclitaxel for the first-line treatment of TNBC. To date, this is the only recommended ICI plus chemotherapy combination for first-line disease. However, outcomes from the phase III IMpassion132 (ClinicalTrials.gov identifier: NCT03371017) and IMpassion 131 trials (ClinicalTrials.gov identifier: NCT03125902), are due this year (Table 3). Findings from these trials will assess whether paclitaxel or non-taxane chemotherapy options such as gemcitabine-carboplatin or capecitabine can replace nab-paclitaxel as a chemotherapy companion to atezolizumab. Moreover, results from the phase III KEYNOTE-355 trial (ClinicalTrials.gov identifier: NCT02819 518) will determine whether the PD-1 inhibitor, pembrolizumab, is first safe and then active in combination with either carboplatin and gemcitabine, paclitaxel or nab-paclitaxel for advanced TNBC excluding early relapsing patients (<6 months of adjuvant chemotherapy)[68]

The efficacy of ICIs combined with chemotherapy as neoadjuvant therapy has been explored in three randomized clinical trials[69–71] (Table 3). The phase II GeparNuevo trial randomized 174 patients with invasive stage cT1b to cT4a-d TNBC to receive durvalumab or placebo combined with chemotherapy, showing a pathological complete response (pCR) of 53.4% (95% CI 42.5–61.4%) for the addition of durvalumab compared with 44.2% (95% CI 33.5–55.3%) in the placebo arm.[70] Interestingly, a subgroup analysis assessing durvalumab timing showed that patients pretreated with a single durvalumab dose ($n = 117$) had a significantly higher pCR rate compared with those starting durvalumab and chemotherapy together (61.0% *versus* 37.9%, interaction $p = 0.048$). The phase II I-SPY 2 trial assessed pembrolizumab plus paclitaxel followed by doxorubicin/cyclophosphamide in 29 patients with high-risk invasive TNBC, reporting an estimated pCR rate of 60% [95% probability interval (PI) 43–78%] compared with 20% for controls (95% PI 6–33%), suggesting a >99% probability that the addition of pembrolizumab was superior to chemotherapy alone in this setting.[69] The large phase III KEYNOTE-522 trial randomized 1174 patients with locally advanced PD-L1 unselected TNBC to receive neoadjuvant pembrolizumab or placebo in combination with chemotherapy, showing a statistically significant improvement in pCR for the pembrolizumab versus placebo arms (64.8% *versus* 51.2%, $p = .0005$), with an early analysis showing a trend toward greater event-free survival at 18 months with pembrolizumab (91.3% *versus* 85.3%).[72]

Additional research into the PD-L1 inhibitors, atezolizumab and avelumab, is underway in both the neoadjuvant and adjuvant settings (Table 4), with readouts from the neoadjuvant IMpassion 031 trial (ClinicalTrials.gov identifier: NCT031 97935) expected in September 2020,[73] and the adjuvant A-Brave trial (ClinicalTrials.gov identifier: NCT02926196) expected in January 2021.[74] Pembrolizumab is also under investigation in the adjuvant setting, with results from the S1418 trial (ClinicalTrials.gov identifier: NCT02954874) expected in May 2026.[75]

Summary

Results from the IMpassion130 trial support the use of ICIs combined with nab-paclitaxel as an effective therapy for PD-L1-positive TNBC based on significant PFS improvements and a numerical increase in OS, leading to the approval of this regimen in both the United States and Europe. The addition of atezolizumab to

Table 3. Efficacy of neoadjuvant immune checkpoint inhibitor plus chemotherapy combinations in TNBC. Efficacy outcomes of immune checkpoint inhibitor trials in TNBC ordered by setting then size of trial.

Trial	Setting Line of treatment	Regimen(s)	*n*	pCR, % (95% CI)
I-SPY-2 Bayesian Model Adaptively-Rd Phase II Subset[69]	PD-L1 unselected invasive BC ⩾2.5 cm by exam or ⩾2 cm by imaging	Pembrolizumab plus paclitaxel followed by AC	29	60[a,b] (0.43–0.78)[c]
GeparNuevo Rd Phase II[70]	Uni- or bilateral invasive cT1b to cT4a-d	Durvalumab plus nab-paclitaxel followed durvalumab plus AC	88	53.4[d] (42.5–61.4) OR = 1.45 (0.80–2.63) *p* = .23
		Placebo plus nab-paclitaxel followed by placebo plus AC	86	44.2[d] (33.5–55.3)
KEYNOTE-522 Phase III[71]	Locally advanced T1c, N1-N2 T2, N0-N2 T3, N0-N2 T4a-d, N0-N2	Pembrolizumab plus paclitaxel plus carboplatin followed by pembrolizumab plus AC[e]	1,174	64.8[f] *p* = .0005
		Placebo plus paclitaxel plus carboplatin followed by placebo plus AC[e]		51.2[f]

[a]Probability that pembrolizumab is superior to control: 99%.
[b]ypT0/is and ypN0.
[c]95% PI.
[d]ypT0 and ypN0.
[e]Patients receive adjuvant pembrolizumab or placebo following surgery.
[f]Assessment of pCR was based on the first 602 patients randomized 2:1 to receive pembrolizumab or placebo.
AC, anthracycline (doxorubicin or epirubicin) plus cyclophosphamide; BC, breast cancer; CI, confidence interval; OR, odds ratio; pCR, pathological complete response; PI, probability interval; Rd, randomized; TNBC, triple-negative breast cancer.

chemotherapy was considered safe, with no new safety signals reported. Use should be restricted to PD-L1-positive patients, and used with caution in patients with an ECOG PS⩾2, in those with untreated CNS metastases, or in patients ineligible for taxanes as data in these patients is limited. Research into additional combinations with chemotherapy, the use of other ICI combinations, as well as use in earlier lines of therapy for TNBC is ongoing.

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Table 4. Ongoing phase III clinical trials of immune checkpoint inhibitors in TNBC. Ongoing (trials that are actively recruiting for which efficacy outcomes are not yet available) phase III trials of immune checkpoint inhibitors for first-line disease or earlier as listed at CT.gov on 27 July 2018 ordered by line of therapy and estimated primary completion date.

PD-(L)1 inhibitor (Target)	Trial ID (NCT#)	Patient population	Experimental regimen	Comparator	Primary endpoint(s)	Estimated PCD
Early, neoadjuvant						
Atezolizumab (PD-L1)	IMpassion-031 (NCT03197935)	cT2-cT4, cN0-cN3, cM0	Atezolizumab plus CT → surgery → atezolizumab	Placebo plus chemotherapy → surgery → observation	pCR	Sept 2020
Atezolizumab (PD-L1)	NeoTRIPaPDL1 (NCT02620280)	Locally Advanced	Atezolizumab plus chemotherapy → surgery → chemotherapy	chemotherapy → surgery → chemotherapy	EFS	May 2022
Atezolizumab (PD-L1)	NSABP B-59/GBG 96-GeparDouze (NCT03281954)	N0, T2-T3 cN1+ or cN2-N3, T1c/T2-T3	Atezolizumab plus chemotherapy → surgery → atezolizumab	Placebo plus chemotherapy → surgery → placebo	pCR, EFS	Dec 2023
Early, adjuvant						
Avelumab (PD-L1)	A-Brave (NCT02926196)	Nonmetastatic	Avelumab	Observation	DFS	June 2021
Atezolizumab (PD-L1)	IMpassion-030 (NCT03498716)	Stage II-III	Atezolizumab plus chemotherapy	Chemotherapy	iDFS	Jan 2022
Pembrolizumab (PD-1)	S1418 (NCT02954874)	⩾1 cm residual IBC or >pN1mic	Pembrolizumab	Observation	iDFS	May 2026
Advanced, first line						
Atezolizumab (PD-L1)	IMpassion-132 (NCT03371017)	Recurrent	Atezolizumab plus chemotherapy	Placebo plus chemotherapy	OS	July 2019
Pembrolizumab (PD-1)	KEYNOTE-355 (NCT02819518)	Unresectable Stage III-IV	Pembrolizumab plus chemotherapy	Chemotherapy	PFS, OS	Dec 2019
JS-001 (PD-1)	KEYSTONE (NCT03777579)	Stage IV	JS-001 plus nab-paclitaxel	Placebo plus nab-paclitaxel	PFS	Dec 2019
Atezolizumab (PD-L1)	IMpassion-131 (NCT03125902)	Unresectable Stage III-IV	Atezolizumab plus paclitaxel	Placebo plus paclitaxel	PFS	Jan 2020

DFS, disease-free survival; EFS, event-free survival; IBC, invasive breast cancer; iDFS, invasive disease-free survival; NCT#, ClinicalTrials.gov identifier; OS, overall survival, pCR, pathological complete response; PCD, primary completion date; PD-1, programmed cell death receptor-1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; →, followed by; TNBC, triple-negative breast cancer.

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Supplemental material

Supplemental material for this article is available online.

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