A narrative review of immune checkpoint inhibitors in early stage triple negative breast cancer

Ana-Alicia Beltran-Bless, Terry L. Ng

Division of Medical Oncology, Department of Medicine, The Ottawa Hospital Cancer Centre and the University of Ottawa, Ottawa, Canada

Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Terry L. Ng. The Ottawa Hospital Cancer Centre, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada. Email: teng@toh.ca.

Abstract: Triple negative breast cancer (TNBC) is an aggressive disease characterized by heterogeneous molecular and immunological characteristics that portends worse overall survival compared to other breast cancer subtypes. Until now, chemotherapy has remained the cornerstone of TNBC treatment despite recent efforts to explore new molecularly targeted therapeutic targets and personalized treatments. Given TNBC has a more immunogenic tumor microenvironment than other breast cancer subtypes, there is hope that immunotherapy will emerge as a new pillar of treatment in TNBC. Based on the IMPASSION130 and KEYNOTE-355 studies, the combination of nab-paclitaxel plus atezolizumab, and chemotherapy plus pembrolizumab, respectively, have been approved by the Food and Drug Administration for locally recurrent, unresectable, or metastatic TNBC in the first line setting. Several studies have now been published demonstrating programmed cell death-1 protein (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors given alongside neoadjuvant taxane and anthracycline-based chemotherapy with or without a platinum agent significantly improves pathologic complete response rate. The choice of chemotherapy given in cooperation with PD-1/PD-L1 checkpoint inhibitor seems to determine the amount benefit derived from immunotherapy. However, longer term follow-up is required to ascertain whether immunotherapy, specifically PD-1/PD-L1 blockade, will improve event-free survival and overall survival. Future studies are underway investigating the role of immunotherapy in the adjuvant setting and in patients with residual disease after neoadjuvant therapy. Other unanswered questions remain including the total duration of immunotherapy, and which patient population would benefit from these expensive and sometimes toxic therapies. This narrative review aims to provide insight on the current landscape of immune checkpoint inhibitors in early TNBC.

Keywords: Breast cancer; triple negative; early stage; immunotherapy

Introduction

Triple negative breast cancer (TNBC), a subset of breast cancer defined by the absence of estrogen and progesterone protein expression and human epidermal growth factor receptor 2 (HER2) expression, comprises 10-15% of all breast cancers, and is characterized by aggressive behavior and worse breast cancer specific and overall survival (OS) compared to their hormone receptor positive counterparts (1,2). The 5-year OS rates for anatomic stage I, II, and III TNBC are 87.2%, 75.3%, and 46.8% respectively and there exists a paucity of proven therapeutic options (3).

Despite the rapidly evolving treatment landscape for both hormone receptor positive and HER2-positive breast cancers, chemotherapy has remained the mainstay of treatment for early stage and locally advanced TNBC.

The current standard treatment consists of anthracycline- and taxane-based chemotherapy, used either in the neoadjuvant or adjuvant setting (4). The addition of platinum-based agents is controversial given the higher risk of myelosuppression and other toxicities with little data supporting an improvement in disease free survival (DFS) and OS in spite of evidence that pathologic complete response is increased (5-7). With its poor prognosis and limited effective treatment options, there has been an ever-growing need to develop novel strategies to cure early stage TNBC.

Immune checkpoint inhibitors (ICI) such as programmed cell death-1 protein (PD-1), programmed cell death ligand 1 (PD-L1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) have garnered much success as blockbuster therapies in other solid tumors (8-10). By preventing the binding of cancer cell immune checkpoint receptors with their partner ligands on CD8+ T cells, amongst other cells, in the tumor microenvironment (TME), checkpoint inhibitors effectively remove the breaks (inhibitory checkpoints) of the immune system to promote an effective antitumour immune response (11). Immunotherapy has long been felt to be of promise for TNBC given its higher PD-L1 expression, higher mutational burden (12-14), and increased number of tumour-infiltrating lymphocytes (TILs) (5,15). Atezolizumab, a PD-L1 inhibitor, combined with nab-paclitaxel is now an FDA approved first-line treatment in unresectable locally advanced or metastatic TNBC based on OS improvement in the subgroup with PD-L1 staining in ≥1% TILs (16). Pembrolizumab, based on KEYNOTE-355, has been approved by the FDA for first line treatment of unresectable or metastatic TNBC with a combined positive score ≥10, in combination with chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine) based on a significant improvement in progression-free survival (17). The scope of this narrative review will focus on the available data on ICIs in early stage or locally-advanced TNBC and provide an opinion on the optimal treatment strategy in this context and future research directions. We present the following article in accordance with the narrative review checklist (available at http://dx.doi.org/10.21037/pcm-20-64).

Methods

A systematic literature search was conducted on PubMed using the terms 'triple negative breast cancer' and 'immunotherapy' from 2000 through October 2020. The same search terms were used for the ClinicalTrials.

gov registry of clinical trials. Abstracts from the annual meetings for the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and San Antonio Breast Cancer Symposium (SABCS) from 2017 to 2020 were systematically searched for unpublished abstracts. Phase I-III clinical trials were included in this review that looked at the use of immunotherapy, with or without chemotherapy, in early stage TNBC. Only English studies were included.

Immunotherapy in early stage TNBC

Pembrolizumab: anti-PD-1

In I-SPY2, a multi-arm, adaptively randomized phase 2 trial of 250 women compared neoadjuvant pembrolizumab (200 mg IV administered every 3 weeks for 4 cycles) in combination with weekly paclitaxel 80 mg/m^2, followed by 4 cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC) every two to three weeks alone *vs.* standard taxane- and anthracycline-based neoadjuvant chemotherapy in stage II or III hormone receptor positive or TNBC. PD-L1 was not tested in this population. The addition of pembrolizumab almost tripled the pathological complete response (pCR) rate in the TNBC subgroup from 22% in the control arm (n=80) to 60% in the investigational arm (n=29). In an exploratory analysis, there was no significant difference in 3-year event free survival between the pembrolizumab and control arms, although it should be noted that only 4 of 69 patients in the pembrolizumab arm had 3 or more years of follow-up (18). The most common immune-related adverse events (irAE) in the immunotherapy group were endocrinopathies, including thyroid dysfunction of all grades in 16% (11/69) and adrenal insufficiency (AI) in 8.7% (6/69), of which 5 cases of AI were grade 3–4.

KEYNOTE-173, a phase 1b study evaluating safety and the recommended phase 2 dose (RP2D), combined neoadjuvant pembrolizumab 200 mg IV every 3 weeks with six different combinations of taxane with or without carboplatin, followed by doxorubicin and cyclophosphamide in high-risk, early stage (T1c, N1-N2 or T2-T4c, N0-N2) TNBC. In the six treatment cohorts (n=10 per cohort), all patients received a single run-in dose of pembrolizumab 200 mg IV (cycle 1) before starting chemotherapy (from cycle 2) while continuing pembrolizumab for 8 more cycles. Patients either received 4 cycles of taxane alone (Cohort A: weekly nab-paclitaxel 125 mg/m^2) or a taxane

given in combination with carboplatin (Cohort B: nab-paclitaxel 100 mg/m^2 weekly plus carboplatin AUC 6 every 3 weeks; Cohort C: nab-paclitaxel 125 mg/m^2 weekly with carboplatin AUC 5 every 3 weeks; Cohort D: nab-paclitaxel 125 mg/m^2 weekly with carboplatin AUC 2 weekly; Cohort E: paclitaxel 80 mg/m^2 weekly with carboplatin AUC 5 every 3 weeks; Cohort F: paclitaxel 80 mg/m^2 weekly with carboplatin AUC 2 weekly). This was followed by 4 cycles of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) every 3 weeks. Only cohorts A and E were deemed safe enough to meet the RP2D threshold whereas 4/10 patients experienced dose-limiting toxicities (DLTs) in cohorts B and F and 6/10 experienced DLTs in cohorts C and D. In this small cohort, pCR rate was numerically higher with platinum (58%, 90% CI: 45–70%) than without (50%, 90% CI: 22–78%) and with platinum every 3 weeks (60%, 90% CI: 43–75%) than with platinum given weekly (55%, 90% CI: 35–74%); pCR rates were higher for PD-L1 CPS ≥1% compared to PD-L1 CPS <1% (60–64% *vs.* 40%) (15). Immune-related adverse events (irAEs) occurred in 30% of patients and included colitis (5%), hepatitis (2%), infusion reactions (5%), skin reactions (5%), and most commonly hypothyroidism (8%) and hyperthyroidism (8%).

KEYNOTE-522, a phase 3 trial, randomized 1,174 stage II or III TNBC patients (2:1) to receive either pembrolizumab 200 mg every 3 weeks or placebo in combination with paclitaxel (80 mg/m^2 weekly) and carboplatin (AUC 5 every 3 weeks or AUC 1.5 weekly) for the first twelve weeks, and then in combination with doxorubicin (60 mg/m^2)/epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks for 4 cycles. After surgery, the patients would continue with either adjuvant pembrolizumab or placebo every three weeks for up to nine cycles. Pathologic CR rates improved with the addition of pembrolizumab from 51.2% to 64.8%. It showed an 18-month event-free survival rate increase from 85.3% to 91.3% with the addition of pembrolizumab, with a hazard ratio of 0.63 and 95% CI: 0.43–0.93. PD-L1 score correlated with pCR rate but the relative improvement from the addition of pembrolizumab was similar across all subgroups, regardless of PD-L1 status (19,20). In other post-hoc comparisons, the benefit from pembrolizumab was more notable in the subgroup receiving carboplatin (AUC 1.5) administered weekly [Δ18.4% (7.4 to 29.1)] than AUC 5 every 3 weeks: Δ7.7 (–5.0 to 20.6)] and there was more benefit in lymph node positive disease [Δ20.6 (8.9 to 31.9)] than in lymph node negative disease [Δ6.3 (–5.3 to 18.2)]. Treatment related adverse events were similar in both

groups with 78.0% in the pembrolizumab-chemotherapy group with grade 3 or higher toxicities compared to 73.0% in the placebo-chemotherapy group. Relevant irAEs in the pembrolizumab group compared to the placebo group included hypothyroidism (13.7% *vs.* 0.4%), hyperthyroidism (4.6% *vs.* 0.3%), severe skin reaction (4.4% *vs.* 3.8%) and adrenal insufficiency (2.3% *vs.* 1.3%).

Durvalumab: anti PD-L1

Geparneuvo was a placebo-controlled phase II study randomizing (1:1) early stage TNBC patients (n=174) to receive durvalumab or placebo concurrently with neoadjuvant taxane followed by anthracycline-based chemotherapy. Patients received one injection of durvalumab 0.75 g IV or placebo 2 weeks before chemotherapy followed by durvalumab 1.5 g or placebo IV every 4 weeks with weekly nab-paclitaxel (125 mg/m^2) for 12 weeks, then durvalumab 1.5 g or placebo IV every 4 weeks with dose-dense epirubicin with cyclophosphamide (EC) every 2 weeks. The investigational arm achieved a higher pCR compared to the placebo arm [53.4% (95% CI: 42.5–61.4%) *vs.* 44.2% (95% CI: 33.5–55.3%)], but the difference was not statistically significant. The window treatment of durvalumab 2 weeks prior to chemotherapy was stopped after 117 patients as it was felt that the delay in starting chemotherapy was too long. Interestingly, a subgroup analysis of the cohort of patients who received window durvalumab had a significantly higher pCR rate than placebo (61% *vs.* 41.4%) (21). Exploratory biomarker analysis found that increased stromal TILs was associated with improved pCR but did not predict benefit from durvalumab. PD-L1 expression on tumor cells was associated with increased pCR in the durvalumab arm whereas PD-L1 expression on immune cells was associated with pCR in the placebo arm. A secondary study using data from Geparneuvo looked at tumor mutation burden (TMB) in 149 patient samples. Results revealed that median TMB was significantly higher in patients with pCR. A stratification of patients based on TMB and median gene expression profiles saw a pCR rate of 82% in patients with both high TMB and immune GEP in contrast to 28% in patients with low TMB and gene expression profiles (13). Immune related adverse events of special interest in the durvalumab group compared to the placebo group as specified in the trial included thyroid dysfunction (50% *vs.* 43.9%), neuropathy (5.4% *vs.* 8.5%), hepatotoxicity (7.6% *vs.* 7.3%), dermatitis (14.1% *vs.* 14.6%), and hypophysis

(1.1% *vs.* 0%).

An investigator-initiated phase I/II study tested the safety and efficacy of durvalumab at two dose-levels (3 and 10 mg/kg) given concurrently with weekly nab-paclitaxel (100 mg/m^2) for 12 weeks, followed by dose-dense AC for 4 cycles in stage I-III TNBC patients (n=57). In phase I, none of the patients experienced a DLT, and therefore 10 mg/kg was the chosen RP2D. The final pCR rate was 44% (95% CI: 30–57%). The PD-L1 positive subgroup [19/50 (38%)], defined in this study by PD-L1 staining ≥1% on immune and tumor cells (SP263 antibody), had a pCR rate of 55% (95% CI: 36–73%) compared to 21% (95% CI: 6–45%) in the PD-L1 negative subgroup. There was no significant difference in stromal TIL count between pCR and non-pCR groups. Grade 3/4 adverse events (AEs) occurred in 18/57 (31%) of patients, most frequently neutropenia (22). Possible grade 3 or 4 irAEs included Guillain-Barré syndrome, hypothyroidism, colitis, and hyperglycemia (1 patient per irAE).

Atezolizumab: anti PD-L1

IMpassion 031 (n=333), a phase III placebo-controlled randomized study showed that in early stage TNBC neoadjuvant treatment with atezolizumab (840 mg) every 2 weeks in combination with weekly nab-paclitaxel (125 mg/m^2) for 12 weeks followed by atezolizumab with dose-dense doxorubicin (60 mg/m^2)/cyclophosphamide (600 mg/m^2) every 2 weeks for 8 weeks significantly improved the pCR rate [58% (95% CI: 50–65%) *vs.* 41% (95% CI: 34–49%)] (23). Patients derived significant benefit in the PD-L1 positive subgroup [pCR 69% (95% CI: 57–79%) in the PD-L1+ population *vs.* 49% (95% CI: 38–61%) in the PD-L1- population] whereas in the PD-L1 negative subgroup, there was a numerical (48% *vs.* 34%) but non-significant difference (Δ13%, 95% CI: –1% to 28%) between the atezolizumab and placebo groups, respectively. After surgery, patients and study site personnel were unblinded. Patients in the atezolizumab arm receive up to 11 more cycles of atezolizumab 1,200 mg every 3 weeks whereas patients in the placebo arm were monitored for up to one year. Adjuvant capecitabine and other systemic regimens were allowed in the adjuvant setting at the treating physician's discretion, Serious adverse events occurred in 30% in the atezolizumab arm and 18% in the placebo arm. The most common irAEs were hypothyroidism (7% *vs.* 1%) and hyperthyroidism (3% *vs.* 0%). Other irAEs including hepatitis, pneumonitis, colitis, diabetes, encephalitis, ocular inflammatory toxicity, and

myositis occurred with a frequency of approximately 1%.

NeoTRIPaPDL1 Michelangelo, a randomized, open-label study examined the activity of atezolizumab 1,200 mg every 3 weeks given concurrently with neoadjuvant carboplatin (AUC2) and nab-paclitaxel (125 mg/m^2) d1,8 every 21 days for 8 cycles in T1cN1, T2N1 and T3N0 and locally advanced TNBC (n=280). An anthracycline-based regimen was administered after surgery. The primary endpoint was event-free survival, but comparison of the secondary endpoint, pCR rate, between atezolizumab plus chemotherapy [43.5% (95% CI: 35.1–52.2%)] *vs.* chemotherapy alone [40.8% (95% CI: 32.7–49.4%)] arm failed to show a pCR benefit in the overall cohort [Odds ratio (OR) 1.11, 95% CI: 0.69-1.79, P=0.66] (24). PD-L1 status was not predictive of benefit from atezolizumab, although it was predictive of improved pCR rates overall based on multivariable analysis. Adverse events that were ≥grade 3 were documented in 77.5% patients in the atezolizumab-chemotherapy arm compared to 70% in the chemotherapy only arm. The most common irAE was hypothyroidism (5.8% *vs.* 1.4%, respectively). Other irAEs were rare (0.7–1.5%).

Discussion

Although there is no definite evidence yet that immunotherapy will lead to long-term survival improvement in early stage TNBC, the addition of ICIs to standard neoadjuvant chemotherapy significantly improves pCR (*Table 1*), a clinical endpoint that is prognostic and has the potential to predict improvement in long-term outcomes in TNBC (25). To date, IMPASSION 031 and KEYNOTE-522 are the only two randomized phase III studies to demonstrate a significant improvement in pCR rate irrespective of PD-L1 status. The interim analysis of event-free survival in KEYNOTE-522 suggests an improvement with neoadjuvant pembrolizumab, but this data is not yet mature. OS data is not yet available for either study.

In contrast, that atezolizumab did not improve pCR rate when added to carboplatin/paclitaxel over 8 cycles of treatment in NeoTRIPaPDL1 suggests the possibility that PD-(L)1 axis blockade may only confer clinical benefit when given concurrently with anthracycline and cyclophosphamide. Supporting this idea, data from the TONIC trial of nivolumab in metastatic TNBC suggests that its combination with an anthracycline is responsible for yielding higher response rates due to changes in the tumour microenvironment (26). Anthracyclines are known

Table 1 Review of immune checkpoint inhibitors in early TNBC

Trial	Regimen	Stage	PD-L1 assay/cells stained	PD-L1 status	Grade 3/4 adverse events	Serious adverse events	pCR	EFS
I-SPY2, n=250 (29 TNBC)	Paclitaxel ± pembrolizumab ×4 → AC ×4 → surgery	II–III	Not tested	N/A	41.7 *vs.* 18.3*	–	60% *vs.* 22%	Exploratory EFS similar in both groups
Keynote 173, n=60, 10 per treatment cohort	Pembrolizumab + taxane chemotherapy ± carboplatin → pembrolizumab + AC ×4	T1c, N1–N2; T2–T4c, N0–N2	PD-L1 IHC 22C3 pharmDX assay; Combined tumour cells, lymphocytes, and macrophages	+ or –; positive PD-L1: CPS ≥1	90%	40% • Febrile neutropenia • Pyrexia • Colitis • Neutropenia	60%	EFS: 12 months carboplatin *vs.* no carboplatin: 98% (90% CI: 90% to 100%) *vs.* 80% (90% CI: 49% to 93%); OS: 12 months carboplatin *vs.* no carboplatin: 98% (90% CI: 90% to 100%) *vs.* 80% (90% CI: 49% to 93%)
Keynote 522, n=1,174	Paclitaxel + carboplatin ± pembrolizumab ×4 → AC/EC ± pembrolizumab → surgery ± pembrolizumab ×9	II–III	PD-L1 IHC 22C3 pharmDX assay; combined tumour cells, lymphocytes, and macrophages	+ or –; positive PD-L1: CPS ≥1.	78.0% *vs.* 73.0%	32.5% *vs.* 19.5% • Febrile neutropenia • Anemia • Pyrexia	64.8% *vs.* 51.2%	18 months: 91.3 *vs.* 85.3 (HR 0.63)
GeparNeuvo, n=174	Durvalumab 2 weeks before chemotherapy *vs.* placebo → nabpaclitaxel ± durvalumab → EC ×4 cycles	cT2–cT4a–d	Ventana SP263 antibody; tumour cells or tumor infiltrating lymphocytes	+ or –; PD-L1 ≥1%	–	32.6% *vs.* 35.4%	61% *vs.* 41.4%	–
Putsztai *et al.* (NCT02489448), n=57	Concurrent durvalumab with weekly nab-paclitaxel (100 mg/m^2) ×12 followed by ddAC ×4	Stage I–III	Ventana SP263 antibody; immune and tumour cells	+ or –; PD-L1 positivity: staining ≥1% on immune and tumour cells	31%	–	44%	–
NeoTRIPaPDL1, n=280	Carboplatin + nab-paclitaxel ± atezolizumab → surgery → AC/EC/FEC	T1cN1, T2N1, T3N0 or locally advanced	Ventana SP142 IHC assay; not yet published	+ or –; positive PD-L1: 1+, 2+, 3+ IHC	77.5% *vs.* 70%	18.1% *vs.* 5.7%	43.5% *vs.* 40.8%	–
IMpassion031, n=333	Nab-paclitaxel ± atezolizumab ×12 weeks → AC ± atezolizumab ×4	Stage II–III	Ventana SP142 assay; tumour infiltrating immune cells	+ or –; positive PD-L1: PD-L1 expressing tumour infiltrating immune cells covering >1% of tumour area	57% *vs.* 53%	23% *vs.* 16% • Febrile neutropenia • Pneumonia • Pyrexia	58% *vs.* 41%	–

*, selected clinically relevant adverse events; –, data not available. PD-L1, programmed cell death ligand 1; EFS, event-free survival; AC, adriamycin and cyclophosphamide; ddAC, dose dense adriamycin and cyclophosphamide; EC, epirubicin and cyclophosphamide; CPS, combined positive score; IHC, immunohistochemistry.

to stimulate direct release of antigens from tumour cells, help with antigen presentation by dendritic cells, stimulate T cells, and deplete immune suppressive cells (27). This raises the question about the function of administering PD-1/PD-L1 inhibitors concurrently with taxanes or platinum agents and whether treatment de-escalation (i.e., omitting PD-1/PD-L1 blockade with non-anthracyclines) is perhaps warranted. Counter to that, despite incorporating anthracycline-based chemotherapy with durvalumab, the GeparNuevo study did not significantly improve pCR with the addition of durvalumab. However, the study sample size was modest (n=88 durvalumab, n=86 placebo), and only had the power to detect an 18% difference in pCR.

The optimal dosage and schedule of carboplatin to be given in conjunction with immunotherapy is yet unclear. Carboplatin was used with a taxane regimen in KEYNOTE 522, KEYNOTE 173, and NeoTRIPaPDL1. A subgroup analysis from the KEYNOTE 522 study suggests that patients receiving carboplatin (AUC 1.5) given in a continuous weekly fashion derived more benefit from pembrolizumab than with carboplatin (AUC5) every 3 weeks (19). This raises the possibility that either weekly administration of lower dose carboplatin leads to some unexplained synergy with immune checkpoint blockade, or the benefits of adding immunotherapy are diminished when given with carboplatin every 3 weeks due to the use of a more efficacious backbone chemotherapy regimen. The latter hypothesis is better supported by KEYNOTE 173—although the study cohorts were small (n=10), the pCR rate was higher with carboplatin every 3 weeks than with weekly administration. On the other hand, NeoTRIPaPDL1, a negative study, used (AUC2) d1,8 every 21 days. In terms of weekly carboplatin dosing, it should be noted that the weekly carboplatin regimen in KEYNOTE 522 was reduced from AUC 2 to AUC 1.5 because in the dose-finding phase of KEYNOTE 173, 6/10 (60%) patients that received carboplatin AUC2 experienced a dose-limiting toxicity. Similarly, the GeparSixto study, which assessed the role of adding carboplatin to paclitaxel, liposomal-doxorubicin, and bevacizumab, also reduced carboplatin dose from AUC 2 to AUC 1.5 after the first 330 patients were accrued (28). In summary, whether the dose-density or dose-intensity of chemotherapy drugs influence the degree of additive or synergistic benefit with immunotherapy is unclear.

Although several of the aforementioned immunotherapy trials have integrated carboplatin into the control treatment arm, the role of platinum agents in the neoadjuvant setting is still controversial. In the Triple Negative breast cancer Trial (TNT), a biomarker-driven trial in metastatic TNBC, carboplatin only significantly improved objective response rate (compared to docetaxel) in patients with germline BRCA (gBRCA) mutation and not BRCA wild-type patients, suggesting carboplatin could provide a synergistic effect with standard neoadjuvant anthracycline and taxane chemotherapy in gBRCA carriers (29). Ironically, in the subgroup analyses of patients with germline BRCA 1 or BRCA2 mutation, carboplatin did not significantly improve the pCR rate when it was added to a paclitaxel-anthracycline based chemotherapy regimen in both the GeparSixto and BrighTNess studies (30,31). The pCR rates with and without carboplatin were 65.4% (17/26) and 66.7% (16/24) in the GeparSixto study [odds ratio 0.68, 95% CI: 0.17–2.68, P=0.004], and 50% (12/24) and 41% (9/22) in the BrighTNess study (risk difference 9.1, 95% CI: –19.6 to 37.8), respectively. On the contrary, carboplatin significantly improved pCR in the non-BRCA subgroup in both studies—in GeparSixto, the pCR rates in the presence or absence of carboplatin were 55% (66/120) and 36.4% (44/121) (OR 2.14, 95% CI: 1.28–3.58, P=0.04), and in BrighTNess, the pCR rates were 59% (80/136) and 29% (40/136) (risk difference 29.4, 95% CI: 18.1–40.7), respectively. In a randomized study comparing neoadjuvant cisplatin vs. doxorubicin and cyclophosphamide (AC) in HER-2/neu negative patients (n=118, 76 were TNBC), the pCR rate was 18% with cisplatin and 26% with AC (relative risk 0.73, 90% CI: 0.50–1.11), which supports that AC is at least as effective as a platinum agent in gBRCA mutated tumors (32). Therefore, the lack of additional benefit from carboplatin in gBRCA patients could be attributed to an increased sensitivity of gBRCA breast cancers to DNA-damaging agents, irrespective of the specific drug (i.e., carboplatin vs. anthracycline plus alkylating agent), relative to non-BRCA carriers, to the extent that the superior response to anthracycline and alkylating agents mitigates any additional benefit from platinum chemotherapy.

Another important concept is the value of pre-treatment or 'priming' with immunotherapy prior to neoadjuvant chemotherapy. Although GeparNuevo was a negative study, the subgroup that received a single dose of durvalumab during the two-week window prior to chemotherapy had a higher pCR than chemotherapy alone. Although an increase in post-treatment intratumoral TILs compared to pre-treatment levels seemed to predict benefit from durvalumab, it is difficult to determine how this applies to the subgroup that received pre-chemotherapy durvalumab since durvalumab pre-treatment was prematurely halted due to

concerns about delaying the time to starting chemotherapy. Conversely, other studies assessed the benefit of priming the immune system with chemotherapy. A phase two study in advanced NSCLC looked at a phased treatment with carboplatin/paclitaxel prior to and then concurrently with ipilimumab, compared to a concurrent-only regimen, and a control group with no immunotherapy, and found that improved progression free survival was only found in the phased regime (33). This is in keeping with the findings of TONIC, which found that after doxorubicin and cisplatin induction, there was an increase in immune-related genes and T cell infiltration and unique intratumoral T cell clones on biopsy specimens which were further increased after nivolumab (26).

In terms of clinically validated biomarkers in early stage TNBC, although PD-L1 expression is predictive of pCR rate, it does not seem to be predictive of benefit from PD-1/PD-L1 blockade, unlike in the metastatic setting where PD-L1 expression was associated with improved OS (16,19,23). One possibility is that the TME in early stage breast cancer is much more robust than in metastatic disease, and chemotherapy in the neo-/adjuvant setting is sufficient to generate a robust antitumor immune response, making PD-L1 much less relevant (5,34). An important observation across these early TNBC immunotherapy studies is that patients with lymph-node positive disease consistently derive much greater benefit from PD-L1 blockade (19,23). One hypothesis is that the presence of cancer cells at lymph node stations makes them more visible to immune surveillance systems in the body, thereby favoring a more robust antitumor response in the context of immune checkpoint blockade.

One of the biggest concerns of adding ICIs to neoadjuvant or adjuvant chemotherapy is the possibility of permanent (e.g., autoimmune diabetes or adrenal insufficiency) and sometimes life-threatening irAEs (e.g., autoimmune pneumonitis, colitis, hepatitis) in patients being treated with curative intent. Grade 3 or higher AEs were common (31–90%) with the addition of PD-(L)1 inhibitor but were not markedly more frequent than the chemotherapy arm in most randomized studies although severe AEs (SAEs) were more frequently noted (*Table 1*). Immune-related adverse effects were rare in most studies with thyroid dysfunction being the most common one.

Future directions

The published studies reviewed here will help determine the optimal neoadjuvant treatment cocktail. Although ICIs show promise, longer-term follow-up is essential to ascertain improvement in overall survival, as well as to assess the optimal drug combination(s) with immunotherapy and the ideal sequence and timing of (neo)-adjuvant chemo-immunotherapy administration.

Remaining questions include the role of adjuvant immunotherapy, optimal duration of immunotherapy, and predictive biomarkers to select patients to receive these expensive and sometimes toxic therapies. Ongoing clinical trials are looking at immunotherapy in the adjuvant setting. SWOG S1418/NRG BR-006 is a randomized, phase III trial of adjuvant pembrolizumab or observation for 12 months after surgery in high-risk TNBC with residual disease (35). A-Brave is a randomized phase III trial of adjuvant avelumab *vs.* observation in high risk TNBC who either had surgery followed by adjuvant chemotherapy or had neoadjuvant chemotherapy with residual disease upon surgical resection (36). NSABP B-59/GeparDouze is a randomized, placebo-controlled phase III trial of neoadjuvant chemotherapy (sequential paclitaxel 80 mg/m^2 with every 3 week carboplatin AUC 5 for 4 cycles, then AC/EC every 2-3 weeks for 4 cycles) with atezolizumab or placebo in patients with TNBC followed by adjuvant atezolizumab or placebo for 6 months (37). ALEXANDRA/IMpassion030 is an open-label randomized phase III trial of adjuvant chemotherapy with or without atezolizumab in operable stage II or III TNBC patients receiving adjuvant weekly paclitaxel followed by dose-dense AC/EC (38).

Considerable work using gene expression and '-omics' approaches has revealed that TNBC is a heterogeneous disease with distinctive molecular and immunological characteristics. The molecular division of TNBC into basal-like (86%), immunomodulatory, mesenchymal/mesenchymal stem-like, and luminal androgen receptor are likely to give more context on how we should apply immunologic and targeted therapy approaches (39). Therapies that have demonstrated efficacy in metastatic TNBC targets such as PARP inhibitors and antibody-drug conjugates (i.e., Sacituzumab govitecan) are also likely to be tested in combination with ICIs in early TNBC (5,40-42). Although we certainly require combinatorial therapeutic approaches to improve outcomes for our patients, an important step forward will be identifying where treatment de-escalation would be appropriate in early stage TNBC patients so that unnecessary treatment-related toxicity can be avoided (43).

Predictive biomarkers of TNBC response to ICIs other

than PD-L1 protein expression [e.g., tumor-infiltrating lymphocytes (TILs), microsatellite instability (MSI), and tumor mutation burden (TMB) and neoantigen burden] (44), and novel immunotherapies—including other ICIs (e.g., CD47 checkpoint blockade), vaccines (e.g., death receptor 5 (DR5) DNA vaccines, antigen-loaded or gene-modified dendritic cell vaccine, personalized peptide vaccines and tumour antigen-based vaccines), and cell-based therapies (e.g., tumor-infiltrating lymphocytes, dendritic cells, natural killer cells, chimeric antigen receptor T cells, and T cell receptors)—are all under intensive investigation (45-48).

Acknowledgments

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor Jacques Raphael for the series "Management of Triple Negative Breast Cancer" published in *Precision Cancer Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review Checklist. Available at http://dx.doi.org/10.21037/pcm-20-64

Peer Review File: Available at http://dx.doi.org/10.21037/pcm-20-64

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/pcm-20-64). The series "Management of Triple Negative Breast Cancer" was commissioned by the editorial office without any funding or sponsorship. TLN reports that he has previously received honoraria from Takeda Oncology, ARIAD Pharmaceuticals, and Boehringer-Ingelheim. The authors have no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects for the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Open Access Statement: This is an Open Access article

References

1. Lin NU, Vanderplas A, Hughes ME, et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer 2012;118:5463-72.

2. Dawson SJ, Provenzano E, Caldas C. Triple negative breast cancers: clinical and prognostic implications. Eur J Cancer 2009;45 Suppl 1:27-40.

3. He J, Tsang JY, Xu X, et al. AJCC 8th edition prognostic staging provides no better discriminatory ability in prognosis than anatomical staging in triple negative breast cancer. BMC Cancer 2020;20:18.

4. Wahba HA, El-Hadaad HA. Current approaches in treatment of triple-negative breast cancer. Cancer Biol Med 2015;12:106-16.

5. Bianchini G, Balko JM, Mayer IA, et al. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol 2016;13:674-90.

6. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014;15:747-56.

7. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 2015;33:13-21.

8. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373:23-34.

9. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab vs. Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 2018;378:1277-90.

10. Reck M, Rodríguez-Abreu D, Robinson AG, et al.

Pembrolizumab vs. Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.

11. Kreamer KM. Immune Checkpoint Blockade: A New Paradigm in Treating Advanced Cancer. J Adv Pract Oncol 2014;5:418-31.

12. Barroso-Sousa R, Jain E, Cohen O, et al. Prevalence and mutational determinants of high tumor mutation burden in breast cancer. Ann Oncol 2020;31:387-94.

13. Karn T, Denkert C, Weber KE, et al. Tumor mutational burden and immune infiltration as independent predictors of response to neoadjuvant immune checkpoint inhibition in early TNBC in GeparNuevo. Ann Oncol 2020;31:1216-22.

14. Thomas A, Routh ED, Pullikuth A, et al. Tumor mutational burden is a determinant of immune-mediated survival in breast cancer. Oncoimmunology 2018;7:e1490854.

15. Schmid P, Salgado R, Park YH, et al. Pembrolizumab plus chemotherapy as neoadjuvant treatment of high-risk, early-stage triple-negative breast cancer: results from the phase 1b open-label, multicohort KEYNOTE-173 study. Ann Oncol 2020;31:569-81.

16. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med 2018;379:2108-21.

17. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy vs. placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020;396:1817-28.

18. Nanda R, Liu MC, Yau C, et al. Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer: An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial. JAMA Oncol 2020;6:676-84.

19. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 2020;382:810-21.

20. Schmid P, Park Y, Ferreira M, editor. KEYNOTE 522: Phase 3 study of neoadjuvant pembrolizumab + chemotherapy vs. placebo for early triple negative breast cancer: pathologic complete response in key subgroups and by treatment exposure and residual cancer burden. San Antonio: San Antonio Breast Cancer Symposium Coverage, 2019.

21. Loibl S, Untch M, Burchardi N, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol 2019;30:1279-88.

22. Pusztai L, Reisenbichler E, Bai Y, et al. Abstract PD1-01: Durvalumab (MEDI4736) concurrent with nab-paclitaxel and dose dense doxorubicin cyclophosphamide (ddAC) as neoadjuvant therapy for triple negative breast cancer (TNBC). Cancer Res 2020;80:PD1-01.

23. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy vs. placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet 2020;396:1090-100.

24. Gianni LH, C; Egle, D, editor. Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple negative, early high-risk and locally advanced breast cancer. NeoTRIPaPDL1 Michelangelo randomized study. San Antonio: San Antonio Breast Cancer Symposium Coverage, 2019.

25. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-72.

26. Voorwerk L, Slagter M, Horlings HM, et al. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. Nat Med 2019;25:920-8.

27. Heinhuis KM, Ros W, Kok M, et al. Enhancing antitumor response by combining immune checkpoint inhibitors with chemotherapy in solid tumors. Ann Oncol 2019;30:219-35.

28. Loibl S, Weber KE, Timms KM, et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol 2018;29:2341-7.

29. Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. Nat Med 2018;24:628-37.

30. Hahnen E, Lederer B, Hauke J, et al. Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. JAMA Oncol 2017;3:1378-85.

31. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin

alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol 2018;19:497-509.

32. Tung N, Arun B, Hacker MR, et al. TBCRC 031: Randomized Phase II Study of Neoadjuvant Cisplatin Vs. Doxorubicin-Cyclophosphamide in Germline BRCA Carriers With HER2-Negative Breast Cancer (the INFORM trial). J Clin Oncol 2020;38:1539-48.

33. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 2012;30:2046-54.

34. Szekely B, Bossuyt V, Li X, et al. Immunological differences between primary and metastatic breast cancer. Ann Oncol 2018;29:2232-9.

35. Pusztai L, Barlow WE, Ganz PA, et al. Abstract OT1-02-04: SWOG S1418/NRG -BR006: A randomized, phase III trial to evaluate the efficacy and safety of MK-3475 as adjuvant therapy for triple receptor-negative breast cancer with 1 cm residual invasive cancer or positive lymph nodes after neoadjuvant chemotherapy. Cancer Res 2018;78:OT1-02-4.

36. Conte PF, Dieci MV, Bisagni G, et al. Phase III randomized study of adjuvant treatment with the ANTI-PD-L1 antibody avelumab for high-risk triple negative breast cancer patients: The A-BRAVE trial. J Clin Oncol 2020;38:TPS598.

37. Geyer CE, Loibl S, Rastogi P, et al. NSABP B-59/GBG 96-GeparDouze: A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy (NAC) with atezolizumab or placebo in patients (pts) with triple-negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo. J Clin Oncol 2019;37:TPS605.

38. McArthur HL, Ignatiadis M, Guillaume S, et al. ALEXANDRA/IMpassion030: A phase III study of standard adjuvant chemotherapy with or without atezolizumab in early-stage triple-negative breast cancer. J Clin Oncol 2019;37:TPS598.

39. García-Teijido P, Cabal ML, Fernández IP, et al. Tumor-Infiltrating Lymphocytes in Triple Negative Breast Cancer: The Future of Immune Targeting. Clin Med Insights Oncol 2016;10:31-9.

40. Chun BM, Page DB, McArthur HL. Combination Immunotherapy Strategies in Breast Cancer. Current Breast Cancer Rep 2019;11:228-40.

41. Bardia A, Mayer IA, Vahdat LT, et al. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. N Engl J Med 2019;380:741-51.

42. Bardia A, Tolaney SM, Loirat D, et al. LBA17 ASCENT: A randomized phase III study of sacituzumab govitecan (SG) vs. treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). Ann Oncol 2020;31:S1149-50.

43. The PARADIGM study group. Prognostic value of tumor infiltrating lymphocytes in young triple negative breast cancer patients who did not receive adjuvant systemic treatment. Ann Oncol 2020;31:S303-39.

44. Cocco S, Piezzo M, Calabrese A, et al. Biomarkers in Triple-Negative Breast Cancer: State-of-the-Art and Future Perspectives. Int J Mol Sci 2020;21:4579.

45. Wang X, Qi Y, Kong X, et al. Immunological therapy: A novel thriving area for triple-negative breast cancer treatment. Cancer Lett 2019;442:409-28.

46. Pascual T, Villagrasa P, Vidal MJ, et al. Abstract OT1-01-01: SOLTI-1503 PROMETEO: Combination of talimogene laherparepvec (T-VEC) with atezolizumab in patients with residual breast cancer after standard neoadjuvant multi-agent chemotherapy. Cancer Res 2020;80:OT1-01.

47. Isakoff SJ, Adams S, Soliman HH, et al. Abstract P3-09-15: A phase 1b study of PVX-410 (PVX) vaccine plus durvalumab (DUR) as adjuvant therapy in HLA-A2+ early stage triple negative breast cancer (eTNBC) to assess safety and immune response. Cancer Res 2020;80:P3-09-15.

48. Fuentes-Antrás J, Guevara-Hoyer K, Baliu-Piqué M, et al. Adoptive Cell Therapy in Breast Cancer: A Current Perspective of Next-Generation Medicine. Front Oncol 2020;10:605633.