Breast Cancer: Targets and Therapy

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REVIEW

Targeted Treatment for High-Risk Early-Stage Triple-Negative Breast Cancer: Spotlight on Pembrolizumab

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Abstract: Triple-negative breast cancer (TNBC) is a biologically aggressive yet heterogeneous disease that disproportionately affects younger women and women of color compared to other breast cancer subtypes. The paucity of effective targeted therapies and the prevalence of chemotherapeutic resistance in high-risk, early-stage TNBC pose significant clinical challenges. Deeper insights into the genomic and immune landscape have revealed key features of TNBC, including intrinsic genomic instability, DNA repair deficiency, and potentially an immunogenic tumor microenvironment. These advances led to landmark trials with immune checkpoint inhibitors in the advanced-stage setting, which subsequently translated into immunotherapy-based clinical trials in the early-stage setting and recent promising results. Pembrolizumab, an anti-programmed death 1 (PD-1) monoclonal antibody, was investigated in combination with platinum-, taxane- and anthracycline-based neoadjuvant chemotherapy followed by adjuvant pembrolizumab monotherapy for patients with high-risk, early-stage TNBC in the randomized, double-blind, placebo-controlled phase 3 KEYNOTE-522 trial. In July 2021, the US Food and Drug Administration (FDA) granted approval for pembrolizumab based on marked improvement in pathologic complete response rate and 3-year event-free survival compared to neoadjuvant chemotherapy alone. This advance immediately altered the longstanding treatment paradigm. Here, we review the impact of pembrolizumab plus chemotherapy for the treatment of patients with high-risk, early-stage TNBC, and discuss immunotherapy-related toxicity considerations, key immunomodulatory biomarkers under active investigation, and remaining clinical questions for future research directions.

Keywords: triple-negative breast cancer, early-stage high-risk, pembrolizumab, neoadjuvant, adjuvant, immune biomarkers

Introduction

Triple-negative breast cancer (TNBC) accounts for approximately 15–20% of all breast cancers, and is clinically defined as lacking expression of estrogen receptor (ER), progesterone expression (PR), and absence of HER2-neu overexpression. In recent years, the rapidly evolving landscape of breast cancer therapeutics has contributed to the reduction in mortality associated with breast cancer, particularly reflected by key advances in targeted therapies for ER-positive and HER2-positive tumors.[1,2] Although TNBC relapse rates have decreased over time with modern-era therapeutic approaches, TNBC remains associated with unfavorable prognosis due to the absence of well-defined molecular targets which are only recently beginning to be elucidated.[3,4] Substantial research is underway to define biomarkers for relapse and develop more effective neoadjuvant and adjuvant treatment approaches to improve long-term outcomes in patients with early-stage TNBC.

Historically, TNBC has been managed as a single breast cancer subtype. However, comprehensive molecular analyses illustrated that TNBC encompasses a complex and biologically heterogeneous disease. Gene expression profiling of breast cancers identified five distinct intrinsic molecular subtypes; the vast majority of basal-like tumors are TNBCs (>90%).[5] TNBCs are enriched for TP53 mutations.[6] Lehmann et al subsequently described six unique molecular signatures of TNBC: basal-like 1 and 2, mesenchymal and mesenchymal-stem like, immunomodulatory and luminal

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androgen receptor groups, each with differential responses to chemotherapy, and more recently, immunotherapy.[7] Additional classification efforts have reported overlapping findings.[8–10] Approximately 20% of unselected TNBC patients harbor defects in BRCA1 and 2 (germline and somatic), leading to homologous recombination DNA repair deficiency and potential PARP inhibitor sensitivity.[11] Dysregulation of actionable signaling pathways commonly occurs in TNBC, including altered RAS/RAF/MEK, PI3K/AKT/mTOR, and JAK/STAT3 pathways. Although these pathway alterations are not clearly established as oncogenic drivers in TNBC, early investigations suggest that multikinase inhibition strategies are promising.[5,12] Thus, transcriptome analysis and molecular subtyping improved our understanding of TNBC biology and provided opportunities for translational investigation. However, these advances have not yet entered routine clinical care to guide treatment decisions for patients with early-stage TNBC.

Neoadjuvant anthracycline- and taxane-based chemotherapeutic regimens have remained the mainstay of systemic therapy for patients with high-risk, early-stage TNBC, and are largely unchanged over the last several years.[13] The TNBC paradox is that patients with early-stage TNBC tend to achieve higher responses to neoadjuvant chemotherapy, yet have a higher propensity for early disease recurrence with a predilection for visceral involvement.[14,15] Optimal neoadjuvant chemotherapy approaches have not been fully established, including whether the incorporation of platinum salts translates to improved long-term outcomes, and the role of adjuvant approaches beyond capecitabine.[16–19] Prognosis remains poor in patients who have residual disease after standard neoadjuvant therapy, with approximately 30–40% risk of recurrence.[19–21] Novel therapeutic approaches are urgently needed. The recent approval of pembrolizumab plus chemotherapy greatly expands the therapeutic armamentarium, thereby improving cure rates for patients with high-risk, early-stage TNBC.

Immune Checkpoint Inhibitor Studies in Early-Stage TNBC

Recent approvals in the metastatic setting have provided promising therapeutic strategies for patients with advanced TNBC, including PARP inhibitors for tumors associated with germline BRCA1/2 mutations, the antibody-drug conjugate (ADC) sacituzumab govitecan, and immune checkpoint inhibitor combinations. In March 2019, atezolizumab plus nab-paclitaxel became the first checkpoint inhibitor to be granted accelerated FDA approval for the treatment of patients with PD-L1–positive advanced TNBC (as measured by the VENTANA SP-142 companion diagnostic) based on results from the Phase III IMpassion130 trial.[22,23] The continued FDA approval of atezolizumab in this setting was contingent upon results from the IMpassion131 trial, a postmarketing requirement. The phase III IMpassion 131 trial of atezolizumab plus paclitaxel versus paclitaxel in a similar patient population failed to demonstrate an improvement in progression-free survival with the addition of atezolizumab.[24] Although the results of both trials were reviewed by the FDA Oncology Drugs Advisory Committee and initially voted in favor of maintaining this accelerated approval of atezolizumab plus nab-paclitaxel, due to a shift in treatment landscape, the FDA no longer supported accelerated approval, and the manufacturer subsequently voluntarily withdrew this indication in the United States.[25,26] In November 2020, the FDA approved pembrolizumab in combination with taxane or platinum chemotherapy for the treatment of patients with PD-L1–positive advanced TNBC [PDL-1 combined positive score (CPS) ≥10 according to the DAKO 22C3 companion diagnostic] based on the phase III KEYNOTE-355 study.[27]

These promising advances in metastatic TNBC therapeutics paved the way for designing clinical trials utilizing immune checkpoint inhibitors in the early-stage setting with varying findings [Table 1]. The phase III IMpassion031 trial demonstrated that administration of atezolizumab every 2 weeks plus anthracycline-cyclophosphamide and taxane-based chemotherapy improved the pathologic complete response (pCR) rate [58% (95% confidence interval (CI), 50 to 65) with atezolizumab *versus* 41% (95% CI, 34 to 49) with placebo in the intention-to-treat (ITT) population (Δ 17%, 95% CI, 6 to 27; one-sided p=0.0044 (significance boundary 0.0184))].[28] By contrast, the NeoTRIPaPDL1 trial of neoadjuvant carboplatin plus nab-paclitaxel with or without atezolizumab, followed by surgery and adjuvant anthracycline-based regimen, did not improve the pCR rate in the ITT analysis (48.6% pCR with atezolizumab *versus* 44.4% without atezolizumab, odds ratio (OR) 1.18; 95% CI, 0.74 to 1.89; p=0.48).[29] In the Phase II TONIC trial, anthracycline chemotherapy induction in patients with metastatic TNBC prior to administration of nivolumab yielded the highest response rate to immunotherapy (objective response rate of 35%) compared to other immunomodulating strategies, including other chemotherapeutic agents.[30] Collectively, these data suggest that anthracyclines may serve as key

Table 1 Key Neoadjuvant Immune Checkpoint Inhibitor Trials in Stage II/III TNBC

Trial	Phase	CPI	N	Treatment Arms	Primary Endpoint	pCR Rate
KEYNOTE-173 [NCT02622074]	Ib	Pembro	60	Neo Pembro run-in (cycle 1) followed by Pembro + Taxane ± Carbo followed by AC	Safety/ RP2D	60.0% [range 49–71%]
I-SPY 2 [NCT01042379]	II	Pembro	250*	Neo Pembro + Pac followed by AC vs Neo Pac followed by AC	pCR	60.0% Pembro vs 22.0% PBO[a]
NeoTRIPaPDL1 [NCT02620280]	II	Atezo	280	Neo Carbo + NabP + Atezo followed by Adj AC/(F)EC vs Neo Carbo + NabP followed by Adj AC/(F)EC	EFS	48.6% Atezo vs 44.4% PBO
GeparNuevo [NCT02685059]	II	Durva	174	Neo Durva followed by NabP + Durva followed by EC + Durva vs Neo PBO followed by NabP + PBO followed by EC + PBO	pCR	53.4% Durva vs 44.2% PBO[b]
KEYNOTE-522 [NCT03036488]	III	Pembro	1174	Neo Carbo/Pac + Pembro followed by AC/EC + Pembro followed by Adj Pembro vs Neo Carbo/Pac + PBO followed by AC/EC + PBO followed by Adj PBO	pCR/EFS	64.8% Pembro vs 51.2% PBO
IMpassion031 [NCT03197935]	III	Atezo	333	Neo NabP + Atezo followed by AC + Atezo followed by Adj Atezo vs Neo NabP + PBO followed by AC + PBO	pCR in ITT and PD-L1+[c] groups	ITT: 58.0% Atezo vs 41.0% PBO

Notes: *69 patients adaptively randomized to pembro and evaluable for primary endpoint: n=29 TNBC[a], n=40 hormone receptor positive, HER2 negative. [b]pCR rates in all 174 enrolled patients; [c]pCR rates in PDL1+ group: 69% Atezo vs 49% PBO.

Abbreviations: Atezo, atezolizumab; Durva, durvalumab; Pembro, pembrolizumab; A, doxorubicin; C, cyclophosphamide; Carbo, carboplatin; E, epirubicin; F, 5-fluorouracil; NabP, nab-paclitaxel; Pac, paclitaxel; PBO, placebo; Adj, Adjuvant; CPI, Checkpoint inhibitor; EFS, event free survival; Neo, neoadjuvant; pCR, pathologic complete response; RP2D, recommended phase II dose; N, number of enrolled patients; ITT, intention-to-treat; PD-L1 IC, PD-L1-expressing tumor infiltrating immune cells as percentage of tumor area using VENTANA SP142 assay (PD-L1 IC≥1% was considered positive).

chemotherapeutic agents to prime the immune response. In the phase II GeparNuevo trial, 117 patients treated with an initial 2-week "window" of single-agent durvalumab prior to neoadjuvant chemotherapy had a more pronounced improvement in pCR rate than those who received combination therapy alone (pCR 61.0% with durvalumab *versus* 41.4% with placebo, OR 2.22, 95% CI, 1.06 to 4.64, p=0.035).[31,32]

Early trials of neoadjuvant pembrolizumab plus chemotherapy showed manageable toxicity and improved antitumor activity in patients with early-stage TNBC. Pembrolizumab combined with neoadjuvant chemotherapy approximately doubled pCR rates and shifted residual cancer burden distribution to lower disease burden for evaluated cohorts in the randomized I-SPY 2 trial.[33] These results supported the need for further investigation of pembrolizumab in a larger clinical trial. The phase Ib KEYNOTE-173 trial treated patients with pembrolizumab run-in for cycle 1, followed by taxane with or without carboplatin, followed by doxorubicin and cyclophosphamide (AC), similar to the GeparNuevo study design, and demonstrated promising anti-tumor activity (as assessed by pCR rate, event-free survival (EFS) and overall survival (OS)) and manageable toxicity profile.[34] These trials established the basis for the FDA Breakthrough Therapy designation of pembrolizumab, and ultimately for the pivotal KEYNOTE-522 trial.

Pembrolizumab in Early-Stage TNBC

The phase III KEYNOTE-522 trial was the first randomized, double-blind, placebo-controlled study of pembrolizumab in early-stage TNBC in the neoadjuvant and adjuvant settings.[35] Eligible patients included those with newly diagnosed, high-risk, early-stage TNBC (defined as cT1c, N1-2 or cT2-4, N0-2 according to the American Joint Committee on Cancer, 7th edition). Patients with active autoimmune disease requiring systemic treatment within the previous 2 years, clinically significant comorbid condition or immunodeficiency, or requiring immunosuppressive therapy were excluded. In the neoadjuvant setting, a total of 1174 patients were randomized (2:1 fashion) and received pembrolizumab (200 mg *intravenously* every 3 weeks) or placebo combined with carboplatin (weekly or every 3 weeks) plus weekly paclitaxel for 4 cycles (first neoadjuvant treatment), followed by anthracycline (doxorubicin or epirubicin) plus cyclophosphamide every 3 weeks for 4 cycles (second neoadjuvant treatment). This was followed by definitive surgery, radiation therapy (if

clinically indicated), and adjuvant pembrolizumab or placebo to complete one full year of treatment. If radiation therapy was indicated per standard of care, adjuvant pembrolizumab or placebo was initiated either concurrently with radiation therapy, or at least 2 weeks post-radiation therapy. Adjuvant capecitabine was not permitted. The primary endpoints included pCR (defined as ypT0/Tis ypN0) and EFS in the ITT population. Key secondary endpoints included safety, OS and pCR in the PD-L1–positive population. PD-L1 expression was tested using the PD-L1 IHC 22C3 pharmDx assay; tumor specimens with CPS ≥ 1 were considered PD-L1 positive.

The first interim analysis, among the first 602 patients undergoing randomization showed that pCR rate was 64.8% [95% CI, 59.9 to 69.5] with pembrolizumab-chemotherapy *versus* 51.2% (95% CI, 44.1 to 58.3) with placebo-chemotherapy (Δ 13.6%, 95% CI, 5.4 to 21.8, p=0.00055). Pembrolizumab-chemotherapy increased pCR rates across all subgroups irrespective of PD-L1 status in the KEYNOTE-522 trial, unlike in the metastatic setting where PD-L1 status was predictive of pembrolizumab benefit. The pCR rate in the PD-L1–positive population was 68.9% with pembrolizumab-chemotherapy *versus* 54.9% with placebo-chemotherapy. By contrast, the pCR rate in the PD-L1–negative population was 45.3% with pembrolizumab-chemotherapy *versus* 30.3% with placebo-chemotherapy. The 3-year EFS rate, first reported at the 2021 European Society for Medical Oncology (ESMO) Virtual Meeting and subsequently published in the *New England Journal of Medicine*, was 84.5% with pembrolizumab-chemotherapy *versus* 76.8% with placebo-chemotherapy, a 7.7% absolute improvement in EFS with addition of pembrolizumab.[36,37] In the pembrolizumab-treated group, 15.7% (n=123 of 784) of patients experienced any disease-related event or death compared to 23.8% (n=93 of 390) in the placebo-treated group [hazard ratio (HR) 0.63, 95% CI, 0.48 to 0.82, p=0.00031]. The distant recurrence rate was 7.7% (n=60 of 784) in the pembrolizumab-treated group *versus* 13.1% (n=51 of 390) in the placebo-treated group. Patients who achieved pCR had 94.4% EFS rate with pembrolizumab-containing regimen and 92.5% EFS with placebo, whereas patients with residual disease after neoadjuvant therapy had 67.4% EFS rate with pembrolizumab and 56.8% EFS with placebo. This suggests that adjuvant pembrolizumab is potentially most critical in the non-pCR setting. In the PD-L1–positive population, EFS events occurred in 14.9% of pembrolizumab-treated group *versus* 21.5% of placebo-treated group (HR 0.67, 95% CI, 0.49 to 0.92). In the PD-L1 negative population, EFS events occurred in 19.5% of pembrolizumab-treated group *versus* 36.2% of placebo-treated group (HR 0.48, 95% CI, 0.28 to 0.85). There was a trend toward OS improvement with the addition of pembrolizumab (89.7% *versus* 86.9%), although the data remain immature. Distant progression- or recurrence-free survival (RFS) was 87.0% with pembrolizumab *versus* 80.7% with placebo. On July 26, 2021, the FDA approved pembrolizumab for the treatment of patients with high-risk, early-stage TNBC.[38]

The incidence of treatment-related adverse events (TRAEs) of grade ≥3 across all treatment phases was 77.1% in the pembrolizumab-chemotherapy group and 73.3% in the placebo-chemotherapy group, including death in 0.5% (n=4 patients) treated with pembrolizumab and 0.3% (n=1 patient) treated with placebo. Deaths in the pembrolizumab group were attributed to sepsis, pneumonitis, pulmonary embolism, and autoimmune encephalitis. Most TRAEs and adverse events (AEs) of interest occurred in the neoadjuvant phase, were of low grade, and were largely attributed to chemotherapy. AEs of interest occurred in 38.9% of patients treated with pembrolizumab and 18.3% of patients treated with placebo. AEs of interest that were grade ≥3 occurred in 12.9% and 1.8% of patients treated with pembrolizumab and placebo, respectively, and commonly included severe skin reactions (3.8%), infusion reactions (2.6%), and adrenal insufficiency (1.3%) in the pembrolizumab-treated group. TRAEs that led to treatment discontinuation of any therapy occurred in 27.7% in the pembrolizumab-treated group and 14.1% in the placebo-treated group. Specifically, grade 3–5 immune-related AEs (irAEs) occurred in 14.9% of the pembrolizumab-treated group and 2.1% of the placebo-treated group, and led to treatment discontinuation in 10.9% and 2.6% of patients, respectively. In the adjuvant setting, grade 3–5 irAEs occurred in 2.9% and 0.3% of patients in the pembrolizumab- and placebo-treated groups, respectively. The incorporation of an additional chemotherapy drug (carboplatin) in the neoadjuvant setting, as well as neoadjuvant followed by adjuvant immunotherapy drug (pembrolizumab) requires that improved efficacy must be considered in the context of added toxicity, and comprehensive patient education of irAEs will be an essential aspect of clinical care. Therefore, rare and potentially long-lasting irAEs will need to be closely monitored in the future.

Biomarkers for Immunotherapy in TNBC

TNBC has been considered to have the highest immunogenic potential of all breast cancers, with enrichment for BRCA germline mutations and higher somatic mutational load and tumor-associated neoantigens, but are rarely associated with microsatellite instability.[39,40] Thus, TNBC is a target for immune-modulating therapies.[41] Early- and advanced-stage breast cancers differ in their tumor and immune cell microenvironments that may impact immunogenicity and offer therapeutic opportunities for the incorporation of checkpoint inhibitors. The predictive potential of conventional immune-based biomarkers to immunotherapy response also differ (eg, by disease stage). In the preclinical setting, high levels of tumor-specific $CD8^+$ T cells soon after neoadjuvant immunotherapy exposure were predictive of long-term survival.[42] Adjuvant immunotherapy resulted in lower tumor-specific $CD8^+$ T cells compared to neoadjuvant-treated mice with intact tumor. Additionally, PD-L1 mRNA expression is higher in TNBC, and is associated with improved clinical outcomes.[43] PD-L1 status is an established predictive biomarker of immune checkpoint inhibitor therapy response in metastatic TNBC. By contrast, the clinical benefit of immunotherapy-based treatment exists independently of PD-L1 expression for patients with early-stage TNBC, although patients with PD-L1–positive tumors achieved numerically higher pCR rates to immunotherapy-based treatment in the KEYNOTE-522 trial. Approximately 80% of patients in each treatment arm of the KEYNOTE-522 trial had PD-L1–positive disease according to the PD-L1 IHC 22C3 pharmDX assay.[36] PD-L1 expression in tumor cells versus immune cells resulted in varying treatment responses to immunotherapy in early-stage TNBC.[32,44] Specifically, data from the phase II GeparNuevo trial of neoadjuvant durvalumab plus chemotherapy suggested a trend for pCR rates in PD-L1 positive tumors, which was significant for PD-L1 expression in tumor cells in the durvalumab arm (p=0.045) and for PDL-1 expression in immune cells in the placebo arm (p=0.040). Tumor mutational burden (TMB) combined with immune gene expression profile also predicted pCR in this study.[45]

Tumor infiltrating lymphocytes (TILs) are a promising immunologic biomarker for response to neoadjuvant chemotherapy in early-stage TNBC.[46–51] The presence of stromal TILs (*s*TILs) is prognostic in TNBC and associated with higher pCR rates to neoadjuvant therapy. A pooled analysis of 3771 patients treated with neoadjuvant therapy indicated that a 10% increase in *s*TILs was associated with longer disease-free survival (DFS) in TNBC patients.[52] The phase III BIG 02–98 trial showed that both *s*TILs and intratumoral TILs (*i*TILs) were highest in highly proliferative tumors, and were associated with ER and HER2 negativity.[53] Increasing lymphocytic infiltration in the tumor and stroma at the time of diagnosis was significantly associated with favorable prognosis in the ER-negative/HER2-negative subgroup regardless of the chemotherapy backbone. This was particularly observed in the lymphocyte-predominant breast cancer (LPBC) subgroup, defined by approximately 50–60% of TILs in the tumor specimen. Higher TIL levels in residual disease also were associated with improved RFS and OS in TNBC.[54] Interestingly, some studies have reported heterogeneity in the predictive nature of TILs on treatment effect by TIL distribution - stromal versus intratumoral location. Specifically, in the GeparNuevo trial, although the presence of *s*TILs was associated with pCR, *i*TILs on pretreatment baseline biopsy did not seem to predict pCR.[32] This highlights the importance of further investigation of spatial immunophenotyping in TNBC given pre-treatment tumor microenvironment composition, as well as dynamic changes in TIL composition in response to therapy, may have key implications on therapeutic strategies necessary to promote immune cell recruitment and anti-tumor immune response.[51]

Despite this deeper understanding of TNBC immunobiology, further development of suitable biomarkers for immunotherapy response and benefit in patients with early-stage TNBC remains an area of significant need. The standardization of biomarker assay implementation and interpretation methodologies before introducing novel biomarkers into the clinical setting will be required. Strategies to identify and target key immune suppression regulators within the tumor microenvironment that could contribute to immunotherapy resistance or predict benefit to checkpoint inhibition and optimize tumor immunogenicity will achieve a more personalized therapeutic approach and balance the risks of immunotherapy-related toxicity.

Ongoing Immunotherapy-Based Clinical Trials in Early-Stage TNBC

There are multiple ongoing clinical trials incorporating pembrolizumab and other immune-modulating strategies in early-stage TNBC [Table 2]. The NeoPACT trial is a phase II neoadjuvant study of pembrolizumab with carboplatin and docetaxel in early-stage TNBC, with pCR as the primary outcome and RFS as the secondary outcome (NCT03639948).

Table 2 Ongoing Immunotherapy-Based Clinical Trials in Early-Stage TNBC

Trial	Phase	N	Treatment Arms	Primary Endpoint
NCT04427293	WOT	12	Neo Lenvatinib + Pembro x 1 cycle	Evaluate TILs
NCT03199040	I	18	Adj neoantigen DNA vaccine + Durva vs neoantigen DNA vaccine in patients with residual TNBC	Safety
NCT04331067	Ib/II	50	Neo Cabiralizumab + Nivo and Carbo + Pac vs Neo Nivo and Carbo + Pac	% Change in TILs/TAMs / Safety
BreastVax [NCT04454528]	Ib/II	36	Neo RT followed by Pembro followed by surgery vs.Neo Pembro followed by RT followed by surgery vs Neo Pembro followed by surgery vs Upfront surgery	Feasibility
NeoPACT [NCT03639948]	II	121	Neo Pembro + Carbo + Docetaxel	pCR
NCT02957968	II	32	Neo Pembro + Decitabine followed by AC followed by Pac	Increase in TILs post Pembro + Decitabine
NCT04373031	II	30	Neo Pembro followed by Pembro + Pac followed by Pembro + AC vs Neo Pembro + C + IRX-2 induction followed by Pembro + Pac followed by IRX-2 reinduction followed by Pembro + AC	pCR
NCT03366844	II	60	Neo Pembro + RT (tumor boost) prior to surgery, breast RT or Chemo	Safety/Feasiblity / Change in TILs
P-RAD [NCT04443348]	II	120	Neo Pembro followed by Pembro + Chemo vs Neo Pembro + low dose breast RT followed by Pembro + Chemo vs Neo Pembro + high dose breast RT followed by Pembro + Chemo	Change in TILs / pCR in the axilla
c-TRAK TN [NCT03145961]	II	208	Utility of ctDNA to detect MRD after standard treatment in patients with TNBC; Adj Pembro in MRD+	ctDNA+ at 12 and 24 mths / ctDNA- or no disease recurrence at 6 mths post Pembro
SWOG S1418 [NCT02954874]	III	1155	Adj Pembro vs Observation in patients with residual TNBC	*i*DFS / PROs

Abbreviations: Durva, durvalumab; Pembro, pembrolizumab; Nivo, nivolumab; A, doxorubicin; C, cyclophosphamide; Pac, paclitaxel; Adj, Adjuvant; Chemo, chemotherapy; ctDNA, circulating tumor DNA; *i*DFS, invasive disease-free survival; MRD, minimal residual disease; N, number of enrolled patients; Neo, neoadjuvant; pCR, pathologic complete response; PROs, patient reported outcomes; RT, radiation therapy; TILs, tumor infiltrating lymphocytes; TAMs, tumor associated macrophages; WOT, window of opportunity.

Another ongoing study evaluates neoadjuvant pembrolizumab in combination with decitabine followed by standard neoadjuvant chemotherapy in early-stage TNBC (NCT02957968), which uses changes in lymphocyte infiltration into tumor and/or tumor stroma as the primary outcome. A phase Ib/II trial is currently evaluating the safety and efficacy of nivolumab plus cabiralizumab (anti-colony stimulating factor 1 receptor (CSF-1R) antibody) combined with neoadjuvant chemotherapy in early-stage TNBC to enhance TILs and reduce tissue-associated macrophages (NCT04331067). One phase II trial evaluates neoadjuvant pembrolizumab plus chemotherapy and immunotherapy induction regimen with IRX-2 in patients with early-stage TNBC (NCT04373031). IRX-2 is a cell-derived biologic agent that increased intratumoral T cell infiltration, improved dendritic cell function and resulted in radiologic tumor response in patients with previously untreated, surgically resectable head and neck cancer.[55,56] Another window trial in the neoadjuvant setting explores the use of one cycle of pembrolizumab plus multikinase inhibitor lenvatinib in untreated TNBC before surgery (NCT04427293). Lenvatinib has demonstrated antitumor activity when paired with pembrolizumab in advanced TNBC.[57]

Several ongoing trials (NCT03366844, NCT04443348, NCT04454528) are evaluating neoadjuvant pembrolizumab and standard radiation before patients undergo chemotherapy or surgery. These trials are testing whether radiation generates

antitumor effects when combined with immunotherapy.[58] Other investigations are testing the effects of personalized neoantigen DNA vaccines combined with immunotherapy in residual TNBC (NCT03199040). The results from the SWOG S1418 trial of adjuvant pembrolizumab versus placebo in patients with residual disease after neoadjuvant chemotherapy are eagerly anticipated (NCT02954874). Additional studies incorporating precision medicine including next-generation sequencing are designed to guide adjuvant therapy. The c-TRAK TN phase II trial assesses serial circulating tumor DNA (ctDNA) to screen for minimal residual disease (MRD) after standard neoadjuvant therapy for early-stage TNBC (NCT03145961). Patients with positive ctDNA are randomized to receive adjuvant pembrolizumab versus observation alone.

Future Directions

The emergence of pembrolizumab in combination with chemotherapy has changed the treatment paradigm for patients with high-risk, curative-intent TNBC as it led to a statistically significant and clinically meaningful improvement in pCR rate and EFS. However, it is necessary to balance reduced risk of recurrence while minimizing potential toxicity, both treatment-related and financial, as we implement this regimen into routine clinical practice. When interpreting trial findings, it is important to note that the control arm in the KEYNOTE-522 trial did not receive dose-dense administration of anthracycline-based chemotherapy (doxorubicin and cyclophosphamide). Furthermore, no adjuvant capecitabine was provided to non-pCR patients, which may potentially magnify separation of the EFS curves between pembrolizumab-treated and placebo-treated patients. Future studies are necessary to determine the optimal chemotherapy backbone and dosing frequency as multiple clinical questions remain. First, dose-dense administration of AC in patients treated with adjuvant anthracycline-based chemotherapy followed by paclitaxel have shown modest benefit on DFS, particularly in those with ER-negative tumors.[59] The IMpassion031 trial treated early-stage TNBC patients with neoadjuvant dose-dense anthracycline-based therapy combined with atezolizumab.[28] The potential impact of dosing every 2 weeks versus every 3 weeks when anthracycline-based therapy is combined with immune checkpoint inhibition should be explored. Second, the incorporation of platinum agents into neoadjuvant treatment was controversial before the KEYNOTE-522 trial given the lack of consistent long-term benefit and the potential for increased myelosuppression despite improved pCR rates.[16,17,60] It is currently unknown whether all patients require the addition of carboplatin to taxane, particularly now with the incorporation of immunotherapy.[61] Third, additional work is necessary to examine whether anthracycline-sparing regimens could be utilized in some patients to avoid cardiotoxicity and short- and long-term hematologic toxicity. Recent modified neoadjuvant regimens have yielded encouraging pCR rates, including platinum–based regimens such as docetaxel plus carboplatin.[62,63] Ongoing trials are combining immunotherapy plus platinum compounds. The chemotherapy backbone likely matters for optimal immune response. Lastly, future trials should investigate upfront immunotherapy to prime the immune response before administering chemotherapy.

There are opportunities to explore de-escalation and escalation strategies in adjuvant TNBC treatment. First, patients who achieved pCR in KEYNOTE-522 had less benefit to adjuvant pembrolizumab compared to non-pCR patients based on early EFS data. Future studies should explore biomarkers for eliminating adjuvant pembrolizumab in patients who achieve a pCR because some of the benefits may be attributed to the neoadjuvant phase of immune checkpoint inhibition. Second, the optimal choice and sequence of adjuvant systemic therapy for non-pCR patients is unknown. Future work should establish how to optimally incorporate capecitabine, a current adjuvant standard-of-care chemotherapy that improves OS in the residual disease setting.[18] Clinical data in other tumor settings suggest capecitabine plus pembrolizumab is a safe combination, but future trials are needed to assess the safety and efficacy of concurrent pembrolizumab with capecitabine versus sequential therapy for TNBC patients without a pCR.[64,65] Third, the PARP inhibitors olaparib and talazoparib have been approved as an additional therapeutic option for patients with germline BRCA1/2-mutant HER-2–negative metastatic breast cancer.[66,67] One year of olaparib as adjuvant treatment following neoadjuvant or adjuvant chemotherapy in patients with high risk of recurrence significantly improved 3-year invasive DFS compared to placebo.[68] It remains unclear whether PARP inhibitors should be used as monotherapy or combined with pembrolizumab in this setting. PARP inhibitors are DNA-damaging agents that potentially boost immune response to immunotherapy by increasing tumor-specific neoantigen release, increasing TMB, and promoting PD-L1 expression.[69] The non-pCR setting also provides opportunities to explore novel investigational agents and additional combination therapies. This includes trials combining immunotherapy plus agents with novel mechanisms of action that have been approved or remain in active investigation in the metastatic setting, such as the anti-Trop2 monoclonal ADC sacituzumab govitecan, which improves OS compared to conventional chemotherapy in metastatic TNBC, or datopotamab deruxtecan.[70–73] Novel HER2-directed ADCs,

such as trastuzumab-deruxtecan with membrane-permeable topoisomerase I inhibitor payload, have promising activity in patients with advanced HER2-low expressing, HER2-negative breast cancer.[74] Preliminary data support further investigations for combining anti-HER2 therapies with immune checkpoint inhibition in HER2-low metastatic TNBC.[75]

It is crucial to consider toxicity in the curative-intent setting because some survivors develop lifelong toxicities. Short- and long-term effects related to irAEs will need to be closely monitored with the addition of pembrolizumab, including some rare and potentially life-threatening toxicities that have been observed with immune checkpoint inhibition in the metastatic setting across multiple tumor types. Clinicians must remain vigilant and promptly manage immune-related toxicities leading up to definitive surgery for unrecognized irAEs such as adrenal insufficiency, which may be life-threatening, and during survivorship care planning in the curative-intent setting. It is recommended that blood cortisol levels be monitored at time of pembrolizumab therapy initiation, prior to surgery, and as clinically indicated thereafter.[76] Some patients are cured with anthracycline- and taxane-based chemotherapy alone. Thus, this novel regimen overtreats a subset of patients, thereby adding additional toxicity risk without further clinical benefit. Future stratified analyses will be required to optimize patient selection for the inclusion of immunotherapy. Finally, financial toxicity from the rising cost of cancer therapeutics is an important consideration for patients, while access to this novel regimen in resource-limited countries may further magnify cancer care disparities. Strategies to improve the availability of cutting-edge treatments in these populations must be explored.[77]

Moving forward, it is uncertain whether pCR is the best surrogate biomarker for EFS and OS following chemo-immunotherapy. Recent studies indicate that minimal (or molecular) residual disease (MRD) may serve as a more prognostic biomarker for future clinical relapse. Early data indicate that non-pCR but MRD-negative patients may have similar outcomes to patients who achieve pCR and are MRD-negative.[78] Further studies are needed to confirm this result. Thus, MRD status rather than pCR status alone may better stratify patients at higher risk of recurrence and who may benefit from adjuvant immune checkpoint inhibition. This hypothesis was recently confirmed in a retrospective analysis of the IMvigor010 study of patients with urothelial cancer.[79] Although the study did not meet its primary endpoint in the overall population, improved DFS and OS was observed for MRD-positive patients who were treated with adjuvant atezolizumab. By contrast, MRD-negative patients treated with atezolizumab did not experience improved outcomes. Other biomarkers may help to refine adjuvant treatment strategies, including TMB, gene expression profiling, tumor microenvironment composition, and circulating immune cells. Future studies should investigate whether immune-based biomarkers can distinguish “hot” vs “cold” immune phenotypes to select patients who may benefit from combination immunotherapy to recruit additional T cells into the immune milieu and those who may not require immune checkpoint inhibition.

Conclusions

Recent clinical advances in the management of early-stage TNBC make cure a reality to more patients with early-stage, high-risk TNBC. This is a significant breakthrough for patients with the deadliest subtype of breast cancer. The approval of pembrolizumab based on the KEYNOTE-522 regimen marks a new era of neoadjuvant immunotherapy entering the clinic. The challenge moving forward is how to incorporate biomarkers and precision medicine approaches to define who will benefit from pembrolizumab rather than chemotherapy alone, and determine the optimal immunotherapy duration to balance the potential risks of toxicity. Adjuvant treatment trials are already planned or underway to better understand adaptive escalation or de-escalation strategies based on pCR and MRD status. Ultimately, the incorporation of pembrolizumab in the curative-intent setting is a significant step forward for patients with TNBC, and an opportunity for future studies to refine precision medicine approaches and optimize neoadjuvant and/or adjuvant immune checkpoint inhibition. These efforts will improve long-term outcomes for patients with TNBC.

Disclosure

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