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Checkpoint Blockade for TNBC: PD-1/PD-L1 Pathway, Trial Landscapes, and Patient Selection

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Abstract. Breast cancer is the most prevalent cancer among women, and TNBC is defined by the lack of HR and HER2 expression. This disease features rapid tumor cell proliferation, high aggressiveness, and a propensity for hematogenous or lymphatic metastasis. TNBC is linked to poor prognosis and restricted therapeutic options. In TNBC management, the current landscape suffers from limited actionable targets, restricting targeted therapies and leaving chemotherapy as the mainstay for advanced disease. Historically, treatment options were confined to surgery, adjuvant chemotherapy, and radiotherapy. Recent advances in TNBC research have spurred the emergence of combination strategies, such as PD-1/PD-L1 inhibitor-based immunotherapy integrated with chemotherapy, targeted therapy, radiotherapy, and oncolytic virotherapy. Although PD-L1 expression characterizes only a minority (~20%) of TNBC, it delineates a therapeutically actionable subgroup. In this context, PD-1/PD-L1 inhibitors combined with chemotherapy constitute the prevailing first-line option for PD-L1-positive advanced disease, and their incorporation into neoadjuvant regimens has reshaped early-stage management. This article synthesizes recent developments in monotherapy and combination strategies to underpin evidence-based care for TNBC.

Keywords: triple negative breast cancer, immune checkpoint inhibitors, PD-L1

1. Introduction

Although unified by a receptor-negative profile in Perou's classification—ER-, PR-, and HER2-negative [1]—TNBC encompasses heterogeneous entities driven by specific mutational events and perturbed signaling networks. This subtype accounts for about 15–20% of breast cancer cases [2] and, compared with others, is linked to a more aggressive clinical trajectory, worse outcomes, and limited therapeutic avenues. In the previous treatment of TNBC, TNBC management relied on Surgical intervention, chemotherapy, and radiotherapy. TNBC is characterized by rapid tumor cell proliferation, high aggressiveness, and a propensity for metastasis via hematogenous or lymphatic systems. Recent advances in TNBC therapeutics have expanded combinatorial regimens, incorporating PD-1/PD-L1 inhibitors with chemotherapy, targeted therapy, radiation, and oncolytic virus therapy. Although chemotherapy remains the primary treatment for TNBC, immunotherapy may provide more options for patients with TNBC. ICIs is the most important part of immunotherapy especially PD-1/PD-L1 [3].

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TNBC, while historically grouped within a cancer type regarded as non-immunogenic, demonstrates immunogenicity and thus renders the PD-1/PD-L1 axis therapeutically actionable. In this axis, PD-1 on T cells—upon engagement by PD-L1 (B7 homolog) or PD-L2—transduces inhibitory signals that blunt effector function; pharmacologic blockade of PD-1/PD-L1 interrupts this checkpoint and can restore cytotoxic responses. Elevated PD-L1 expression spans numerous tumor types, and, relative to other breast cancer subtypes, TNBC more often expresses PD-L1 [4]. Together with high tumor mutational burden and the absence of reliable targeted therapies, these biological features underlie the poor prognosis of TNBC. Accordingly, PD-1/PD-L1-based combinations have become integral to TNBC therapy and have improved survival in advanced disease. Building on this context, we review monotherapy data and recent advances in combination strategies for TNBC [5].

2. Clinical advances of various PD-1/PD-L1 inhibitors in triple-negative breast cancer

2.1. Atezolizumab

2.1.1. Atezolizumab monotherapy

Atezolizumab, an anti-PD-L1 agent and a leading therapeutic in the PD-L1/PD-1 inhibitor class, was the first immunotherapy approved in the U.S., EU, and Japan for advanced TNBC in combination with nab-paclitaxel [6]. Based on efficacy, safety, and patient status, we elaborate separately on the therapeutic effects of second-line and first-line treatments among patients at different stages.Between September 2019 and May 2021, a multicenter study conducted at 8 Japanese medical institutions evaluated 36 patients with advanced breast cancer receiving later-line therapy receiving atezolizumab. The study revealed a median time to treatment failure (TTF) of 116 days (approximately 3.8 months), which was modestly shorter than historical data for standard chemotherapy (approximately 5.6 months). It is evident from these findings that atezolizumab monotherapy demonstrates limited efficacy [7]. The efficacy of second-line treatment remains suboptimal. However, Johns Hopkins University phase I trial in metastatic TNBC revealed significantly higher objective response rates (ORR) in treatment-naive patients (24% vs 6% in later-line therapy) with median overall survival (OS) of 17.6 months. Among PD-L1≥1% patients, ORR (12%) and median OS (10.1 months) outperformed PD-L1<1% patients (ORR 0%, OS 6.0 months), indicating promising activity in treatment-naive PD-L1-positive or immune cell-high (IC-high) tumors [8]. Atezolizumab monotherapy has demonstrated only modest clinical activity in advanced-stage TNBC populations. Therefore, atezolizumab is difficult to be used as a monotherapy for TNBC patients, so it is generally not used as a monotherapy for early clinical patients. Although monotherapy may be considered for front-line PD-L1-positive patients, combination therapy remains the mainstay approach; similarly, later-line treatment necessitates novel combination strategies to overcome resistance barriers.

2.1.2. Atezolizumab combination therapy

Atezolizumab, as a PD-L1/PD-1 inhibitor, is predominantly administered in combination regimens rather than as monotherapy for TNBC treatment. Current clinical practice continues to favor its combination with chemotherapeutic agents, particularly carboplatin-based protocols. The TBCRC 043 Phase 2 Randomized Clinical Trial evaluated carboplatin monotherapy versus carboplatin plus atezolizumab in metastatic TNBC. This trial enrolled 106 female patients of diverse racial

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backgrounds with metastatic TNBC, among whom 35% (12 patients) received the therapy as initial therapy; the majority of participants (87 [82%]) had received prior chemotherapy, demonstrating superior efficacy for the combination arm. The median PFS was 4.1 months in the combination group compared to 2.2 months with carboplatin alone, representing a 34% reduction in disease progression risk. OS outcomes showed a median OS of 12.6 months versus 8.6 months, indicating a 40% mortality risk reduction. These findings position carboplatin-atezolizumab combination as a viable therapeutic option for metastatic TNBC, with enhanced clinical benefits observed in patients harboring specific biomarkers or exhibiting clinical features such as prior chemotherapy exposure [9].Combination chemotherapy has demonstrated superior clinical benefits. As nab-paclitaxel is currently widely utilized in breast cancer treatment, Thus, the Phase III IMpassion130 trial, designed to evaluate first-line atezolizumab combined with nab-paclitaxel, enrolled 902 treatment-naive patients with confirmed locally advanced or metastatic TNBC. In the second interim analysis, although OS did not reach statistical significance in the ITT population (HR=0.87, p=0.077), the trial demonstrated a clear clinical benefit in PFS(HR=0.80, p=0.002) [10]. Besides the combination of atezolizumab with first-line nab-paclitaxel, other chemotherapy partners for atezolizumab plus first-line chemotherapy—such as capecitabine or gemcitabine/carboplatin—are also under investigation.

Currently, Atezolizumab in combination with various chemotherapeutic agents remains under investigation, while the carboplatin-Atezolizumab regimen has become a widely accepted and implemented treatment strategy in clinical practice. Besides,among emerging therapeutic approaches, a clinical investigation evaluating the BET inhibitor RO6870810 in combination with atezolizumab failed to achieve anticipated synergistic antitumor efficacy in TNBC. Instead, the regimen exhibited increased immune-related toxicity leading to an adverse risk-benefit profile [11]. With the expanding landscape of druggable targets, ongoing research continues to explore novel combinations of atezolizumab with diverse molecular inhibitors.

Addressing whether PD-1/PD-L1 blockade enhances pathologic response in early disease, IMpassion031 reported higher pCR with neoadjuvant atezolizumab plus chemotherapy compared with placebo plus chemotherapy—57.6% versus 41.1% (absolute difference, 16.5%)—without added treatment burden [12]. Benefit was greater among PD-L1–positive tumors, defined by immune-cell staining ≥1% (68.8% vs 49.3%). For advanced TNBC, evidence from the Japanese subgroup of IMpassion130 indicated longer progression-free survival with atezolizumab plus nab-paclitaxel, particularly when PD-L1 was expressed (median 7.4 vs 4.6 months) [13]. Interim overall-survival analyses in the intention-to-treat cohort were negative; nevertheless, clinically meaningful OS gains emerged in patients whose immune cells were PD-L1–positive under atezolizumab plus nab-paclitaxel [10].

Testing whether immune checkpoint blockade augments neoadjuvant response, Gianni's study added atezolizumab to nab-paclitaxel/carboplatin for high-risk, early/regionally advanced TNBC. The ITT readout showed comparable pCR (48.6% with atezolizumab vs 44.4%; OR=1.18), while exploratory findings pointed to PD-L1 dependence [14]. In a separate randomized cohort followed for two years (n=67, stage II–III), combining atezolizumab with carboplatin/paclitaxel yielded a statistically superior pCR in the modified ITT population—55.6% versus 18.8% (Δ=36.8%)—with toxicity remaining manageable; among PD-L1–positive tumors, pCR was 75% under the combination [15].Collectively, these findings highlight the complexity of clinical outcomes associated with first-line immune checkpoint blockade combined with chemotherapy in TNBC.In summary, although Atezolizumab demonstrates selective efficacy in TNBC, predominantly benefiting the PD-L1-enriched subgroup rather than the overall TNBC population, the combination

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of Atezolizumab with chemotherapy has become an established and widely adopted treatment regimen in clinical practice.

2.2. Pembrolizumab (keytruda)

2.2.1. Pembrolizumab monotherapy

Pembrolizumab has been extensively studied in recent years. In the KEYNOTE-119 trial, although the statistically nonsignificant survival benefit trend resulted in the trial failing to meet its primary endpoint, PD-L1 Combined Positive Score (CPS) has been established as a standardized integrated biomarker for immunotherapy in mTNBC based on this trial. While evidence for pembrolizumab monotherapy in unselected advanced TNBC is limited, enrichment of benefit is observed in the PD-L1–high cohort—defined by CPS ≥ 20—where survival outcomes are significantly improved compared with lower PD-L1 groups. This finding enables clinicians to more precisely avoid overtreatment with chemotherapy while maintaining therapeutic efficacy [16].

In an exploratory analysis from the KEYNOTE-119 trial investigating pembrolizumab single-agent therapy continuation in 43 subjects with metastatic HER2-negative breast carcinoma after ≥3 cycles of chemotherapy, the 4-month disease control rate (DCR) was 58.1%. The median PFS was 4.8 months. Patients with elevated baseline T-cell clonality exhibited significantly longer PFS compared to those with low clonality, demonstrating a 58% decrease in risk of progression (HR = 0.42; p = 0.03). These results indicate that pembrolizumab monotherapy induces durable clinical benefit, with elevated baseline T-cell clonality serving as a robust biomarker predictive of prolonged PFS [17].

The KEYNOTE-119 trial has inherent limitations in design precision [18]. Consequently, ongoing studies are progressively refining the treatment paradigm for pembrolizumab—evolving from initial efficacy assessment to the identification of key biomarkers, and further to mechanistic investigations into how dynamic immune microenvironmental changes modulate treatment outcomes.

2.2.2. Pembrolizumab combination therapy

Although pembrolizumab monotherapy has limited indications, its combination with chemotherapy is standard in selected settings. Addressing CPS ≥10 disease, KEYNOTE-355 showed longer PFS for pembrolizumab-chemotherapy than for placebo-chemotherapy (9.7 vs 5.6 months) [19]. In the Asian subgroup analysis reported in September 2024, patients with CPS ≥10 similarly benefited, with PFS HR=0.65, indicating an ≈35% lower hazard of progression or death and a benefit size comparable to the overall cohort. Overall survival analysis showed a ~38% reduction in death risk for PD-L1 CPS ≥10 patients and significant benefit for CPS ≥1 patients. Therefore, this therapy could indicate a novel first-line standard for this subset of patients. These results demonstrate significant clinical gains in PFS and OS with tolerable toxicity, confirming pembrolizumab-chemotherapy as an efficacious primary treatment for advanced TNBC patients regardless of PD-L1 expression levels [20].

In the neoadjuvant combination therapy for early-stage TNBC, pembrolizumab has demonstrated clinically meaningful efficacy. A phase III clinical trial conducted between September 2018 and January 2022, which enrolled 115 female patients, revealed that this drug significantly prolonged EFS by 86% compared to traditional chemotherapy regimens (3-year progression-free survival rate: 60–70%). Furthermore, the treatment achieved a pCR rate of 58%, markedly exceeding the 30–40%

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typically observed with conventional approaches. This therapeutic regimen demonstrates breakthrough potential in the neoadjuvant treatment landscape for TNBC, notably due to its favorable safety profile [21].

Addressing whether PD-1 blockade enhances outcomes beyond chemotherapy, Pusztai et al. found in KEYNOTE-522 that pembrolizumab plus chemotherapy achieved superior RFS to placebo-chemotherapy (HR = 0.52; ≈48% risk reduction) [22]. The combination rebalanced tumor-clearance patterns and was associated with lower distant-recurrence risk across RFS categories (59.1% vs 50.0%). In the neoadjuvant cohort, ORR was higher with pembrolizumab-chemotherapy than with chemotherapy alone, and benefit was evident regardless of PD-L1 expression. The KEYNOTE-173 trial (Phase Ib, open-label, multicohort) further demonstrated that in subjects with early-phase elevated-risk TNBC, therapy involving chemotherapy alongside the anti-PD-1 agent pembrolizumab yielded manageable toxicity and high response rates, suggesting its potential as a standard treatment regimen [23]. The combination therapy demonstrated significant improvements in pCR rates and EFS, including a 9% absolute improvement in 5-year EFS, while maintaining a favorable safety profile [22]. The latest analyses from 2022 and 2024 demonstrated that for treatment-naive patients with stage II or III TNBC, the pembrolizumab plus chemotherapy group achieved an EFS rate of 84.5%,higher than the placebo group's 76.8%. Additionally, the pembrolizumab group showed a 60-month OS rate of 86.6%, which was also significantly superior to the placebo group's 81.7% (P=0.002) [5, 24].

Although immune-chemotherapy can increase toxicity, KEYNOTE-522 patient-reported data indicated stable quality of life, with no clinically meaningful worsening observed for pembrolizumab plus chemotherapy during initial TNBC therapy. The result indicate that the pembrolizumab regimen markedly increased PCR rates (+13.6%) and 5-year overall survival (+4.9%) while effectively maintaining patients' quality of life [5]. In conclusion,In early-stage TNBC research, whether administered as neoadjuvant combination therapy or as pembrolizumab combined with chemotherapy followed by adjuvant therapy, these regimens demonstrate significant improvements in EFS, OS, and maintenance therapy compared with chemotherapy alone.

2.3. Imfinzi (durvalumab)

2.3.1. Durvalumab monotherapy

Although no standard role has been defined for durvalumab in advanced TNBC, its use with neoadjuvant chemotherapy in early-stage disease yielded a higher pCR (95.5% vs 86.1%). Three-year outcomes—iDFS, DDFS, and OS—also showed notable between-arm differences, and in multivariable models, durvalumab’s effect remained significant irrespective of pCR [25]. Collectively, the results support durvalumab as a neoadjuvant option for high-risk early TNBC.

2.3.2. Durvalumab combination therapy

Addressing maintenance options beyond cytotoxic therapy, the phase II DORA trial enrolled metastatic TNBC patients who had received platinum in first-line treatment and compared olaparib ± durvalumab as a chemotherapy-free maintenance regimen. The combination of olaparib and durvalumab significantly prolonged PFS compared to historical controls in platinum-sensitive metastatic TNBC patients (6.1 months versus 4.0 months; P<0.0001). This highly significant improvement in PFS demonstrates a superior trend favoring the combination therapy, suggesting a potential synergistic effect between immune checkpoint inhibition and PARP inhibition [26].

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The pairing of durvalumab and paclitaxel in TNBC has been substantiated by numerous studies for its significant efficacy in the preoperative therapy of HER2-negative breast cancer. Testing immune priming in the neoadjuvant setting, GeparNuevo randomized early-stage TNBC to anthracycline–taxane chemotherapy with or without durvalumab. While overall pCR remained similar, a pre-chemo window of durvalumab monotherapy produced higher pCR (61% vs 41%), with greater effects in sTIL-high and PD-L1–positive tumors [27]. Addressing high-risk HER2-negative disease in I-SPY2, adding durvalumab and olaparib to paclitaxel (DOP) increased TNBC pCR from 27% to 47% (absolute +20%), including gains in the MP2 subgroup [28].

During early-phase TNBC, neoadjuvant treatment with durvalumab combined with weekly nab-paclitaxel and dose-dense doxorubicin/cyclophosphamide (ddAC) achieved a pCR rate of 44%. Compared to the 30-40% pCR rates typically observed with neoadjuvant chemotherapy alone in TNBC, this immunochemotherapy combination demonstrates potential synergistic efficacy. Additionally, stromal tumor-infiltrating lymphocyte (sTIL) numbers were markedly greater in the cohort attaining pCR ($p = 0.0167$), further supporting the association between immune activation and treatment response [29]. Addressing whether a TROP2-ADC–immunotherapy platform can substitute for conventional chemo-immunotherapy in early disease, the randomized phase III TROPION-Breast04 trial (2025) compares preoperative Dato-DXd plus durvalumab or postoperative durvalumab with standard treatment in newly diagnosed early-stage TNBC and HR-low/HER2- breast cancer [30]. If successful, these approaches would extend the therapeutic playbook for TNBC by integrating ADC-based regimens with immunotherapy.

2.4. Nivolumab combination therapy

Asking whether monotherapy suffices, TONIC (2019) found limited benefit with nivolumab alone in metastatic TNBC, implying that combinatorial strategies are required to enhance outcomes [31]. Reflecting this, nivolumab is rarely deployed as monotherapy and more commonly combined; while approved across several advanced solid tumors, TNBC-specific activity has been reported in early-phase work [32]. In ETCTN-9844 (phase Ib; late-stage HER2-negative), entinostat + nivolumab + ipilimumab produced an ORR of 25% (5/20), including 40% in TNBC and 10% in HR-positive cohorts; CBR reached 40%, and 6-month PFS was 50% [33].

Conversely, in a phase II first-line trial, nivolumab + bevacizumab + paclitaxel showed substantial activity in TNBC, with ORR 70%, median OS 32.5 months, and manageable toxicity [34]. Taken together, these findings favor combination immunotherapy as a viable avenue in TNBC.

Phase II adaptive trial results of neoadjuvant nivolumab-based combination therapy in early-stage TNBC patients demonstrated: Regarding immune activation rates, dual ICI with anti-PD-1 + anti-CTLA-4 yielded a 7-percentage-point increase over monotherapy (60% vs. 53% of patients showing immune activation). In patients with high expression of TILs, the observed 53% MPR and 33% pCR rates confirm that dual ICI therapy offers greater clinical benefits in this subgroup. These efficacy metrics approach those achieved by neoadjuvant regimens containing conventional chemotherapy (e.g., KEYNOTE-522 study: ~35–45% pCR) [35].

In 2025, a non-comparative, open-label, randomized phase 2 trial (BCT1902/IBCSG 61-20; Neo-N) investigating neoadjuvant nivolumab combined with carboplatin and paclitaxel in early-stage TNBC demonstrated that the nivolumab lead-in group (immunotherapy before chemotherapy) achieved a pCR rate of 51%, while the concurrent nivolumab group (immunotherapy combined with chemotherapy) yielded a pCR rate of 55%. Although the superiority of the lead-in strategy remains unconfirmed, both groups achieved high pCR rates (>50%), suggesting the potential of short-course,

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anthracycline-free chemotherapy combined with immunotherapy in TNBC [36]. Currently, most nivolumab studies are in phase 1 or 2, indicating promising prospects for future development.

2.5. Toripalimab combination therapy

Current use. In TNBC, toripalimab is most often administered in combination regimens.

TORCHLIGHT (first-line metastatic/recurrent TNBC). Toripalimab plus nab-paclitaxel was compared with placebo + nab-paclitaxel and showed comparable rates of treatment-emergent adverse events. In the PD-L1–positive population, toripalimab significantly prolonged PFS (median 8.4 vs 5.6 months) and extended OS (32.8 vs 19.5 months) [37]. These findings support incorporating toripalimab into chemotherapy for PD-L1–positive metastatic or recurrent TNBC.

Early-stage (single-arm phase II). Preoperative anthracycline-based chemotherapy plus toripalimab and nab-paclitaxel yielded tpCR 55.7% and bpCR 58.6%, indicating substantial primary-tumor clearance after surgery. Relative to historical benchmarks for conventional chemotherapy(≈30–40%), the tpCR appeared higher, especially in stage III disease [38]. Takeaway. Toripalimab-based combinations may broaden the pool of benefiting TNBC patients, and pairing with other targeted agents warrants further evaluation.

3. Conclusion

PD-1/PD-L1 inhibitors face substantial challenges in TNBC management, including heterogeneity in PD-L1 expression, limited efficacy of monotherapy, acquired resistance, and imprecise biomarker stratification. Nevertheless, combination strategies with chemotherapy or targeted agents have significantly improved survival in advanced-stage patients—exemplified by regimens such as atezolizumab plus nab-paclitaxel and pembrolizumab with chemotherapy. Patients undergoing maintenance therapy also demonstrate significant clinical efficacy. In early-stage neoadjuvant settings, immune-chemotherapy combinations (e.g., KEYNOTE-522 protocol) substantially enhance pCR rates and prolong EFS. Moving forward, precision biomarkers (e.g., PD-L1 CPS, TILs, TMB), bispecific antibodies, cellular therapies, and tumor microenvironment-modulating approaches (e.g., BET inhibitors, oncolytic viruses) hold promise to overcome current limitations. These advances will drive personalized therapeutic paradigms, further extending survival and improving quality of life for TNBC patients.

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