Review Article

Narrative review on the role of immunotherapy in early triple negative breast cancer: unveiling opportunities and overcoming challenges

Keyang Qian[1,2,3], Qiang Liu[3,4]

[1]Department of Oncology, The Affiliated Hospital of Jiangnan University, Wuxi, China; [2]Wuxi School of Medicine, Jiangnan University, Wuxi, China; [3]Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; [4]Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

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Correspondence to: Qiang Liu, PhD. Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, 33 Yingfeng Road, Haizhu District, Guangzhou 510120, China; Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou 510120, China. Email: liuq77@mail.sysu.edu.cn.

Background and Objective: Triple negative breast cancer (TNBC) represents a highly aggressive breast cancer subtype, historically managed with chemotherapy regimens predominantly involving anthracyclines and taxanes, yielding unfavorable prognoses. This review endeavors to offer a thorough examination of the present state of treatment strategies for early stage triple negative breast cancer (eTNBC), with a particular emphasis on immunotherapy modalities, combination therapies, predictive biomarkers, and ongoing clinical trials. The principal aim of this review is to meticulously assess the available literature, ascertain significant discoveries, and engage in discussions regarding their potential implications for future research endeavors, clinical applications, and policy formulation.

Methods: This review was conducted using PubMed and Google Scholar databases, with the latest update performed in March 2023. The search strategy was designed to ensure a comprehensive analysis of the literature, with a focus on recent advancements.

Key Content and Findings: We critically assess the current eTNBC treatment landscape, covering efficacy and limitations of monotherapy, combination therapies, and predictive biomarkers. We highlight promising results from recent trials, address controversies surrounding chemotherapy, and explore optimal approaches for adjuvant and neoadjuvant therapy (NAT). Insights into personalized treatment strategies, ongoing trials, and future perspectives are provided, advancing our understanding of therapeutic options for eTNBC.

Conclusions: Through a comprehensive analysis of the literature, this review highlights the potential of immunotherapy, particularly in combination with chemotherapy, as a promising approach for treating eTNBC. However, further research is warranted to optimize treatment strategies, refine patient selection criteria, and identify reliable biomarkers for predicting response to immune checkpoint inhibitors (ICIs). The findings of this review hold significant implications for future research, clinical practice, and policy-making, offering valuable insights into the current challenges and advancements in eTNBC treatment. Ultimately, this knowledge can contribute to improved patient outcomes, enhanced quality of life, and the development of more effective therapeutic approaches for eTNBC.

Keywords: Early stage triple negative breast cancer (eTNBC); immune checkpoint inhibitors (ICIs); pembrolizumab; chemoimmunotherapy; programmed cell death-ligand 1 (PD-L1)

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Introduction

Triple negative breast cancer (TNBC) is a highly aggressive and challenging subtype of breast cancer that accounts for around 15% to 20% of all breast carcinomas (1). Notably, the prognosis for TNBC patients is worse than those with hormone receptor-positive breast cancers, with a three-fold higher risk of relapse within five years of diagnosis (2). While chemotherapy is the standard of care for TNBC patients, about only 30% of patients achieve a complete response (3). Moreover, up to 50% of patients diagnosed with early stage TNBC face the disheartening reality of disease recurrence, while a staggering 37% of these individuals tragically lose their lives within just five years following surgery. The mortality associated with breast cancer in TNBC surpasses that of hormone receptor-positive or human epidermal growth factor receptor 2 (HER2)-positive breast cancer by a significant margin (4). Even after radiotherapy, some TNBC patients' recurrence rates did not decrease as significantly as other subtypes, underscoring the resistance of some of the TNBC to current treatment options (5).

Recent studies have revealed that TNBC can stimulate immune responses, a surprising finding given that it was previously considered a non-immunogenic tumor (6-8). TNBC has a higher tumor mutational burden (TMB) compared to other subtypes of breast cancer, and increased levels of tumor-infiltrating lymphocytes (TILs) in the tumor microenvironment (9,10). Furthermore, TNBC shows relatively high expression of programmed cell death-ligand 1 (PD-L1), providing a basis for immunotherapy as a promising option against TNBC (11).

Studies have demonstrated that high PD-L1 expression on TNBC cells and immune cells (ICs), high TMB, and increased proliferation of TILs in the breast tumor microenvironment are linked to increased responsiveness to immunotherapy with immune checkpoint inhibitors (ICIs) (8,12,13). These findings highlight the potential of immunotherapy as a promising option against TNBC and pave the way for further research in this field (1-3,5,7-14). Currently, two classes of ICIs have been approved for clinical use: (I) programmed cell death protein 1 (PD-1)/PD-L1 and (II) cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (14). By exploiting the unique features of the tumor microenvironment and the molecular characteristics of TNBC, immunotherapy could provide new and effective treatment options for TNBC patients, improving overall survival (OS) rates and quality of life.

Despite these advancements, there are still significant challenges and knowledge gaps in the field of immunotherapy for early-stage TNBC. The optimal use of immunotherapy in this patient population, including the timing, combination strategies, and predictive biomarkers, remains an area of active research and debate. Therefore, a comprehensive review of the current literature is crucial to identify opportunities and address these challenges.

This review aims to uncover the transformative potential of immunotherapy in early stage triple negative breast cancer (eTNBC). By evaluating the current treatment landscape, exploring novel strategies, and addressing key challenges, this review seeks to provide valuable insights that can revolutionize TNBC treatment and improve patient outcomes. We present this article in accordance with the Narrative Review reporting checklist (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-23-17/rc).

Methods

We conducted a literature review using PubMed and Google Scholar databases, with the latest update performed in April 2023. We also screened the reference lists of retrieved articles and proceedings from relevant cancer meetings held in the past five years to find additional sources.

For inclusion, we focused on phase I–III trials that studied TNBC patients receiving neoadjuvant treatment with ICIs in combination with chemotherapy. If available, we also considered trials that reported separate results for molecularly defined subgroups in breast cancer subtypes other than TNBC (*Table 1*).

Mechanism and advantages of immunotherapy in TNBC

Immune checkpoint receptors, including PD-1/PD-L1 and CTLA-4 signaling pathways, play a crucial role in regulating T cell immune responses (15). These receptors have evolved to control the degree of inflammation at sites expressing the antigen, in order to protect normal tissue from pro-inflammatory damage (16). PD-1 is an important inhibitory protein expressed on several types of ICs, such as T cells, B cells, and antigen-presenting cells, including dendritic cells. Binding of PD-1 to PD-L1 induces apoptosis of antigen-specific T cells and down-regulates apoptosis of T regulatory cells, thereby reducing overall

Table 1 The search strategy summary

Items	Specification
Date of search	1 July 2022 to 31 March 2023
Databases and other sources searched	PubMed, Google scholar, Clinicaltrials.gov
Search terms used	"Early-stage triple negative breast cancer" OR "early-stage TNBC" OR "eTNBC" [MeSH]
	("Early-stage TNBC") AND "recurrence and mortality" [MeSH]
	("Early-stage TNBC") AND "prognosis" [MeSH]
	"Immunotherapy" OR "Immune checkpoint inhibitors" OR "Pembrolizumab" OR "Atezolizumab" OR "Durvalumab" [MeSH]
	"Neoadjuvant" [MeSH]
	"Adjuvant" [MeSH]
	"Monotherapy" [MeSH]
	"Combination therapy" [MeSH]
	("Early-stage TNBC") AND "predict" OR "forecast") [MeSH]
	"Early-stage TNBC" AND "endpoint" [MeSH]
	"Early-stage TNBC" AND "efficacy" [MeSH]
	"PD-L1" [MeSH]
	"TIL" [MeSH]
	"TMB" [MeSH]
	"ctDNA" [MeSH]
	"BRCA mutation" OR "BRCAness" [MeSH]
	"Non-pCR" [MeSH]
	"De-escalation of treatment" [MeSH]
Timeframe	2010–2023
Inclusion and exclusion criteria	Inclusion criteria: research articles, reviews and clinical trials in English about themes such as *early-stage triple negative breast cancer* and *immunotherapy*. Exclusion criteria: some papers which we considered with low reliability
Selection process	The included literature was selected by author Keyang Qian, reviewed by both authors
Any additional considerations, if applicable	Some papers were identified by reviewing reference lists of relevant publications

TNBC, triple negative breast cancer; eTNBC, early stage triple negative breast cancer; PD-L1, programmed cell death-ligand 1; TIL, tumor-infiltrating lymphocyte; TMB, tumor mutational burden; ctDNA, circulating tumor DNA.

immune response (17). The immune-resistance associated with PD-1 is dependent on the availability of the PD-L1 ligand in tumor cells (TCs). In certain types of tumors, including TNBC, the protective mechanism is exploited through overexpression of PD-L1, resulting in suppression of the immune response against the tumor (17,18). Previous studies have reported that PD-L1 expression in TC is induced through the anaplastic lymphoma kinase (ALK) signaling pathways via the signal transducer and activator of transcription 3 (STAT3) (19). The activation of STAT3 is modulated through interleukin (IL)-6, and the IL-6-STAT3 axis is considered one of the decisive pathways in tumorigenic macrophage polarization and immune suppression (20,21).

ICIs pharmacologically prevent the PD-1/PD-L1 interaction, enhancing immune surveillance and the antitumoral immune response. In recent years, ICI therapy, as a novel technology with targeted killing effects on TC, has achieved remarkable results in clinical applications. Clinical studies have demonstrated increased antitumoral immune response in patients with TNBC undergoing ICI therapy (22-24). The addition of ICIs to neoadjuvant chemotherapy has been shown to increase pathologic complete response rates in patients with TNBC (22). Moreover, the addition of ICI therapy has shown incomparable advantages over traditional chemotherapy therapy alone, including prolonged progression-free survival (PFS) and OS (25,26). Pembrolizumab is currently the only ICI approved for metastatic TNBC (mTNBC) with a PD-L1 Combined Positive Score (CPS) ≥10 when combined with frontline chemotherapy, based on the KEYNOTE-355 trial (25). From this perspective, there is a strong rationale for the administration of ICIs to eTNBC, and several randomized trials have been designed for this purpose.

Immunotherapy for TNBC: current landscape of immunotherapy trials

As we describe below, not only do these clinical studies validate our optimism for the expansion of immunotherapy to eTNBC, but they also contribute significantly to the identification of the most successful strategies (*Table 2*), providing a comprehensive analysis that propels us towards a future where immunotherapy emerges as a transformative cornerstone in the comprehensive management of this challenging disease.

Performance of ICIs as monotherapy

The efficacy of ICIs was first evaluated in patients with mTNBC, where response rates were found to be higher compared to other breast cancer subtypes. However, preliminary results of trials suggest that ICI monotherapy has limited clinical efficacy in patients with TNBC (31,32). Monotherapy with ICIs has shown response rates ranging from 5.5% in unselected patients to around 22.2% in treatment-naïve PD-L1 positive patients with TNBC (33).

The KEYNOTE-012 study (NCT01848834) evaluated the PD-1 inhibitor pembrolizumab in PD-L1-positive mTNBC and demonstrated an overall response rate (ORR) of 18.5% with a median time to response of 17.9 weeks (31). However, subsequent trials such as the phase II KEYNOTE-086 (NCT02447003) showed an ORR of only 5.3% with pembrolizumab as second-line therapy in pre-treated patients with mTNBC (32). In patients with pre-treated mTNBC, the phase III KEYNOTE-119 trial (NCT02555657) found no improvement in OS with pembrolizumab monotherapy compared to chemotherapy (34). Although a positive trend was observed for patients with a CPS ≥10 in the efficacy endpoints of ORR, PFS, and OS, the findings of these trials suggest that ICI monotherapy could offer limited survival benefits, potentially enhanced in patients with PD-L1-positive mTNBC.

Performance of ICIs as combination therapy

The advent of immunotherapy has led to a paradigm shift in the management of early and advanced TNBC, which was historically treated only with chemotherapy (35,36). Combining immunotherapy with chemotherapy has shown promising results, as demonstrated in various clinical trials summarized in *Table 1*. Of note, three trials have reported improved pathological complete response (pCR) rates with the combination of pembrolizumab and chemotherapy in eTNBC (20,35,37).

In the I-SPY2 study, the addition of a PD-1 inhibitor to neoadjuvant chemotherapy resulted in a three-fold increase in pCR rate compared to the control group (60% *vs.* 22%) (27). The phase III Keynote-522 trial served as a landmark study for the use of immunotherapy in eTNBC. This trial randomly assigned 1,174 patients with stage II or III TNBC in a 2:1 ratio to receive neoadjuvant and adjuvant therapy with pembrolizumab 200 mg every 3 weeks (N=784) or placebo (N=390) (22). Among the first 602 patients (pembrolizumab plus chemotherapy, N=401; placebo plus chemotherapy, N=201), the addition of pembrolizumab significantly increased pCR rate in the intention-to-treat (ITT) population [64.8% *vs.* 51.2%, delta 13.6%, 95% confidence interval (CI): 5.4–21.8%, P<0.001]. Interestingly, PD-L1 status did not predict pCR benefit for pembrolizumab treatment (68.9% *vs.* 54.9%; delta 14.0%, 95% CI: 5.3–23.1%). Moreover, the addition of pembrolizumab to neoadjuvant and adjuvant therapy significantly improved the 3-year event-free survival (EFS) rate from 76.8% to 84.5% (22,38). The updated analysis of the Keynote-522 trial also demonstrated a statistically significant improvement in EFS (HR, 0.63; P=0.00031) with the addition of pembrolizumab (38). Notably, patients without pCR still achieved significant EFS benefit from adjuvant pembrolizumab therapy (67.4%

Table 2 Summary of randomized studies of neoadjuvant chemoimmunotherapy in eTNBC

Characteristics	Study design	Patient population	Treatment regimen	pCR outcomes (ITT population)	pCR outcomes (PD-L1 population)	Survival outcomes
I-SPY2 (27), (NCT01042379)	Open-label, multi-center, randomized phase 2	Stage II–III, high risk BC (250, including 114 TNBC)	Pemb + P → AC (n=29) *vs.* P → AC (n=85)	pCR rates in TNBC: 60% *vs.* 22%	–	EFS HR 0.60 (TNBC patients)
KEYNOTE-173 (28), (NCT02622074)	Open-label, multicohort, phase 1b study	High-risk, early-stage, non-metastatic TNBC (n=60)	Pemb + (nab-P ± Cb) → AC (n=60)	Overall, 60% (range, 49–71%)	–	12-month EFS and OS rates ranged from 80% to 100% across cohorts
Keynote-522 (22), (NCT03036488)	Randomized, phase 3 trial	Untreated stage II–III TNBC patients (n=1,174)	Pemb + (PCb → AC/EC) (n=784) *vs.* placebo + (PCb → AC/EC) (n=390) (→ surgery → Pemb/ placebo)	64.8% *vs.* 51.2%	68.9% *vs.* 54.9%	3-year EFS: 84.5% *vs.* 76.8% (HR, 0.63, 95% CI: 0.48–0.82, P=0.0003); 3-year OS: 89.7% *vs.* 86.9% (HR, 0.72, 95% CI: 0.51–1.02, P=0.032)
NeoTRIPaPDL1 (29), (NCT02620280)	Randomized, phase 3 trial	Untreated stage II–III TNBC patients (n=280)	Atez + nab-P + Cb (n=138) *vs.* nab-P + Cb (n=142) (→ surgery → adjuvant anthracycline regimen)	48.6% *vs.* 44.4%	59.5% *vs.* 51.9%	Not reported
IMpassion031 (30), (NCT03197935)	Randomized, phase 3 trial	Untreated stage II–III TNBC patients (n=333)	Atez + (nab-P → AC) (n=165) *vs.* placebo + (nab-P → AC) (n=168) (→ surgery → adjuvant Atez/placebo)	58% *vs.* 41%	69% *vs.* 49%	EFS HR: 0.76 (95% CI: 0.40–1.40); DFS HR: 0.74 (95% CI: 0.32–1.70); OS HR: 0.69 (95% CI: 0.25–1.87)
GeparNuevo (26), (NCT02685059)	Randomized, phase 2 trial	Untreated stage I–III TNBC patients (n=174)	Durv×2w → Durv + (nab-P → EC) (n=88) *vs.* placebo + (nab-P → EC) (n=86) (→ surgery → physician's choice)	53.4% *vs.* 44.2%	–	3-year iDFS: 85.6% *vs.* 77.2%; 3-year DDFS: 91.7% *vs.* 78.4%; 3-year OS: 95.2% *vs.* 83.5%

eTNBC, early stage triple negative breast cancer; pCR, pathological complete response; ITT, intention to treat population; PD-L1, programmed cell death-ligand 1; BC, breast cancer; TNBC, triple negative breast cancer; Pemb, pembrolizumab; P, paclitaxel; AC, anthracyclines plus cyclophosphamide; EFS, event-free survival; HR, hazard ratio; CI, confidence interval; nab-P, nab-paclitaxel; Cb, carboplatin; OS, overall survival; PCb, paclitaxel & carboplatin; EC, epirubicin & cyclophosphamide; Atez, atezolizumab; DFS, disease-free survival; Durv, durvalumab; DDFS, distant disease-free survival; iDFS, invasive disease-free survival.

vs. 56.8% in the control arm). Based on these results, the Food and Drugs Administration (FDA) granted approval for pembrolizumab in combination with chemotherapy as neoadjuvant treatment for high-risk, eTNBC, followed by single-agent adjuvant therapy post-surgery. Similarly, the National Medical Products Administration (NMPA) approved pembrolizumab for high-risk, eTNBC with a PD-L1 CPS ≥20 in combination with chemotherapy as neoadjuvant treatment, followed by single-agent adjuvant therapy post-surgery on November 1, 2021. The IMpassion031 trial demonstrated a statistically significant improvement in pCR with atezolizumab compared to placebo (58% *vs.* 41%; P=0.004) in patients with eTNBC regardless of PD-L1 status (30).

However, the GeparNuevo trial, a phase 2 study, did not meet its primary endpoint. The results, notwithstanding a trend towards a higher pCR rate in patients with eTNBC who received bevacizumab compared to placebo, did not show a statistically significant difference (53.4% *vs.* 44.2%, P=0.287) (26).

Despite this, the clinically meaningful benefit of immunotherapy in eTNBC is evident and requires further substantiation in studies using other types of immunotherapies.

The best endpoint to evaluate the efficacy of immunotherapy for eTNBC

The use of immunotherapy in eTNBC in the neoadjuvant setting has been evaluated in several clinical trials, with pCR being the primary endpoint in most of them (22,26,37). However, other endpoints such as EFS, OS, disease-free survival (DFS), and residual cancer burden (RCB) have also been studied (22,26,27,29,30). While EFS is considered the ultimate goal of neoadjuvant therapy (NAT), it requires larger sample sizes than pCR and RCB analyses (39).

For high-risk tumors such as TNBC, pCR has been used as a surrogate endpoint that reflects treatment efficacy and supports accelerated and traditional approval (40). The use of surrogate endpoints, instead of traditional endpoints, for cancer drug trials with smaller sample sizes and shorter follow-up periods has been shown to reduce drug development time by around 11–19 months (41). Notably, Cortazar *et al.* reported that patients who achieved pCR had improved survival, particularly in aggressive tumor subtypes like TNBC and HER2+/hormone receptor (HR) – breast cancers (42).

The Keynote-522 trial demonstrated that, after a follow-up period of 39.1 months, the estimated 3-year EFS was higher in the pembrolizumab arm than in the control arm [84.5% (95% CI: 81.7–86.9%) *vs.* 76.8% (95% CI: 72.2–80.7%), respectively]. Among patients who achieved pCR, 3-year EFS rates were high regardless of treatment arm (94.4% *vs.* 92.5% in the pembrolizumab and control arms, respectively) (43). Furthermore, a pooled analysis of 6,377 patients with primary breast cancer showed that pCR was a suitable surrogate endpoint for patients with HER2+/non-luminal and TNBC (P<0.001 for both) (44).

Hence, pCR and EFS can be considered primary endpoints to evaluate the efficacy of immunotherapy in eTNBC. Surrogate endpoints like pCR, if properly validated, can support accelerated approval and reduce drug development time, especially for high-risk tumors like TNBC. Future studies should focus on identifying optimal biomarkers and endpoints to better assess the efficacy of immunotherapy in eTNBC.

Prognostic and predictive value of biomarkers related to ICI responses in TNBC

Immunotherapeutic drugs, particularly ICIs such as PD-1/PD-L1 and CTLA-4 inhibitors, are commonly used for cancer treatment. However, studies have shown that a proportion of patients with mTNBC have limited benefit from ICI treatment, and it remains unclear whether this applies to eTNBC cases. Therefore, it is essential to determine the clinical significance of biomarkers in eTNBC to develop effective therapies for this cancer subtype. PD-L1 is a major biomarker that has been extensively studied in this context. Recent investigations have focused on elucidating the testing value of PD-L1 in eTNBC (45,46).

PD-L1

PD-1 is principally expressed in different cells of the immune system, including TC and IC, as well as in the tumor microenvironment where it interacts with its ligands PD-L1 and PD-L2. The expression of PD-L1 on the surface of IC is relatively constant, whereas PD-L1 expression on the surface of TC is dynamic (47). Immunohistochemistry (IHC) is commonly used to measure PD-L1 expression, with various scoring systems employed, including TC, tumor-proportion score (TPS), IC, IC Present (ICP), and CPS (48). The US FDA has approved four PD-L1 IHC assays (28-8, 22C3, SP263, and SP142) for use.

However, the potential prognostic value of PD-L1 in TNBC remains a topic of debate. Some previous studies have suggested that PD-L1 expression may be associated with a better prognosis (49-51). Huang *et al.* demonstrated that PD-L1 expression on TILs was associated with improved survival (50), while Li *et al.* showed that PD-L1 expression on TILs was associated with better DFS in TNBC (51). In separate studies, Barrett *et al.* and Botti *et al.* observed that PD-L1 expression on TC was associated with increased OS and DFS in TNBC patients (49,52). However, other studies have failed to find any potential prognostic value of PD-L1 in TNBC (53,54). A recent meta-analysis showed no association between PD-L1 expression and prognosis in TNBC, with no significant association observed between PD-L1 expression and OS (53). In another study, Cirqueira *et al.* found no significant association between PD-L1 expression and DFS (54). The potential prognostic value of PD-L1 in TNBC remains

a contentious issue, as its expression has not consistently correlated with response to immunotherapy in clinical trials.

In eTNBC, similar observations have been reported. According to the phase 3 Keynote-522 study, PD-L1 positivity (22C3 clone, CPS ≥1) was observed in approximately 80% of the ITT population. The pembrolizumab-chemotherapy group showed a significantly higher percentage of patients achieving a pCR compared to the chemotherapy group. The benefit of combination immunotherapy was independent of PD-L1 expression, though PD-L1-positive patients achieving a higher pCR in both arms compared to the PD-L1-negative population.

Another phase 3 study, IMpassion031, assessed chemotherapy plus atezolizumab in early or locally advanced TNBC. PD-L1 enrichment was observed in 46% of patients, with PD-L1 positivity defined as IC ≥1% using the SP142 assay. In PD-L1-positive patients, a higher pCR was achieved in the immunotherapy group than the placebo arm (68.8% *vs.* 49.3%, P=0.021, significance boundary ≤0.0184) (30). The pCR benefits observed were independent of PD-L1 status, similar to the findings in the Keynote-522 trial.

However, in the phase 2 GeparNuevo trial, durvalumab did not show a significant improvement in pCR rates compared to placebo, despite 87% of the patients having PD-L1 expression using SP263 clones (TC ≥1% and/or IC ≥1%). Nonetheless, a trend towards an increase in pCR rates was observed in PD-L1-positive patients, and it was statistically significant for both the durvalumab (P=0.045) and placebo arm (P=0.040) (26). These findings suggest that PD-L1 may not be an ideal biomarker for predicting the response to immunotherapy in eTNBC, and its predictive value varies. The discordant results observed in several studies could be due in part to technical issues related to different antibody clones, cut-off points, and scoring systems used.

Several PD-L1 IHC assays, platforms, and scoring criteria are available, and different PD-L1 IHC assays and scoring systems may show variable results in TNBC. Moreover, scoring systems and thresholds for PD-L1 positivity lack standardization, which may further affect the assessment of PD-L1 positivity. Therefore, PD-L1 requires further rigorous studies to determine the best assay methods and scoring systems.

TILs

TILs are mononuclear IC that infiltrate tumor tissue and are present in most types of solid tumors. TILs can be categorized into interstitial (sTIL) and intratumor TILs (iTIL) based on hematoxylin and eosin (H&E) staining (55). Compared to HR+ and HER2 positive breast cancers, triple-negative breast cancer (TNBC) has a higher level of TILs (20%) (56). Compared to TNBC in the advanced T3-4 stages, that diagnosed in the early T1 and T2 stages exhibits a higher rate of TILs infiltration (57,58). In the GeparNuevo study of eTNBC, it was observed that adding durvalumab to anthracycline/taxane-based NAT significantly increased pCR rates (61.0% *vs.* 41.4%, OR =2.22, 95% CI: 1.06–4.64, P=0.035). It was also observed that the pCR rate increased significantly with the increase of sTIL (P<0.01) (26).

Breast cancer has traditionally been considered as an "immunocold" tumor, not suitable for tumor immunotherapy (59-61). However, recent developments suggest that the immune microenvironment of cold tumors can be reprogrammed and the strategy of combining with chemotherapy is currently considered to be an effective means to turn "cold" tumors into "hot" tumors (59). Previous clinical studies have shown that lymphocyte dominant TNBC (defined as truncation value >60%) for chemotherapy pCR rate was higher than that of non-lymphocyte type TNBC (62-64). Therefore, TNBC patients with high TILs may benefit from chemotherapy combined with ICIs. However, the limitation of TILs as predictive biomarkers in eTNBC is due to the lack of current evidence, and the standardization of TIL scores is a significant challenge (65). Fortunately, with the rapid development of artificial intelligence technology, this problem is gradually being solved (66,67). Moreover, the American Joint Committee on Cancer (AJCC) is discussing the integration of TILs into the traditional Tumor-Node-Metastasis (TNM) staging system of eTNBC (68). This highlights the potential research value of TILs as a predictor of eTNBC ICIs combination therapy.

TMB

TMB, a measure of the number of non-synonymous mutations carried by TCs, is considered to be a key driver of immunogenic neoantigen production. These mutations lead to increased expression of neoantigens in the presence of major histocompatibility complex (MHC) Class I antigens, thereby enhancing the recognition and killing of cancer cells by T cells. Studies have shown that in combination with anti-CTLA4 or anti-PD-1/CTLA-4 therapy, the ICIs response of tumors with high TMB

may be independent of PD-L1 expression (69). Due to the limitations of PD-L1 as a biomarker described above, establishing an independent benefit of TMB in predicting response to anti-PD-1/PD-L1 and anti-CTLA4 therapies would be a very useful clinical tool.

Currently, it is generally believed that tumors with more than 10 mutations per megabase (mut/MB) are tumors with high TMB. Under this standard, only 5% of patients with primary and metastatic breast cancer meet the condition of high tumor mutation load (70), which mainly occurs in lobular carcinoma (71). When it comes to the IMpassion130 trial, investigators found that TMB predicted increased ICIs benefit in PD-L1 positive tumors, but only in PD-L1 positive tumors (72). According to the data statistics of The Cancer Genome Atlas (TCGA) Program, the median TMB of breast cancer patients was only about 2.63 mut/MB. It is much lower than melanoma, non-small cell lung cancer, urothelial carcinoma, etc. (71,73), which may be one of the reasons why breast cancer is defined as an immunologically "cold" tumor (61). However, breast cancer, as a very heterogeneous tumor, often shows different biological behaviors in each subtype. TNBC, especially basal like subtype, carries higher TMB than hormone receptor positive type or HER2 positive type (74), and the early immune response of TNBC to ICIs is worthy of investigation. The GeparNuevo study mentioned above showed that eTNBC were more sensitive to immunotherapy and had a higher proportion of sTIL, which may suggest that the immune microenvironment of eTNBC was inherently different from that of advanced TNBC. Therefore, defining TNBC, and even the cut-off value of TMB in eTNBC, is currently the focus of discussion among breast clinical scientists. In addition, it is worth noting that in the phase II prospective study B-F1RST (NCT02848651), blood TMB (bTMB) ≥16 mut/MB is associated with higher ORR in locally advanced or metastatic non-small cell lung cancer (75). It is suggested that TMB in circulating tumor DNA (ctDNA) is worthy of further study in terms of the benefit of ICIs in eTNBC.

ctDNA

ctDNA is cell-independent tumor-derived fragmented DNA in blood (76). The inability of antineoplastic therapy to eliminate minimal residual disease is believed to arise from the evasive behavior of TCs harboring inherent resistance to chemotherapy (77). This elusive phenomenon eludes detection through existing routine hematology or imaging methods employed in clinical practice (78). Hence, the prospect of identifying hematogenous metastases at an earlier stage through ctDNA testing surpasses that of conventional testing, based on theoretical grounds. In a prospective phase II trial, Bratman *et al.* evaluated ctDNA in five different cohorts of patients with advanced solid tumors treated with pembrolizumab (NCT02644369) (79). Zhang *et al.* reported the largest sample size of ctDNA dynamic changes related to immunotherapy efficacy to date. The study analyzed three samples from durvalumab (± anti-CTLA4 therapy tremelimumab) before treatment (n=978) and during treatment (n=171) ctDNA samples from 16 advanced tumor types in phase I/II trials (80). The results of both studies show that dynamic detection of ctDNA is beneficial to predict the efficacy of immune checkpoint inhibition therapy. Tan *et al.* made a bold attempt to predict the efficacy of ICIs with a small sample size using ctDNA in advanced TNBC, and found that 12 mutated ctDNA genes could predict the efficacy of ICIs (56). Moreover, in the I-SPY2 trial, the personalized monitoring of ctDNA during NAT in high-risk early-stage breast cancer has the potential to enable real-time evaluation of treatment response and aid in refining pCR as a surrogate endpoint for survival. These findings underscore the considerable value of ctDNA detection in predicting the likelihood of recurrence and metastasis among patients who do not achieve pCR following NAT (81). In conclusion, ctDNA shows a certain potential in predicting the efficacy of ICIs, and of course more clinical studies are needed for corroboration.

Immunotherapy for eTNBC—controversial issues and challenges

TNBC is a highly aggressive subtype of breast cancer associated with poor outcomes and high risk of recurrence. Unfortunately, conventional chemotherapy has not been effective in treating this subtype of breast cancer, leaving an unmet medical need (82,83).

The preferred chemotherapy backbone for immunotherapy and the course of treatment in the neoadjuvant treatment stage

Conventional cytotoxic chemotherapy has been the mainstay of adjuvant/neoadjuvant treatment for TNBC for a long time. Chemotherapy drugs such as anthracyclines, taxanes, and alkylating agents are commonly used. In the neoadjuvant phase, the addition of platinum to

conventional taxanes and anthracyclines has significantly increased the pCR rate in TNBC from approximately 35% to more than 50%, underscoring the potential of platinum agents as promising therapeutic adjuncts for improved outcomes (84,85). Chemotherapy can enhance tumor immunity by inducing immunogenic cell death and promoting tumor antigen presentation. However, the potential therapeutic benefit of platinum-based combination immunochemotherapy during the adjuvant phase remains uncertain, as its efficacy has yet to be substantiated through extensive large-scale randomized controlled clinical trials (86).

TNBC is often associated with a deficiency in BRCA-driven DNA repair mechanisms. BRCA1/2 proteins have important roles in DNA replication fork stabilisation and homologous recombination (87). Germline mutations of BRCA1/2 predispose to breast cancer by impairing homologous recombination causing genomic instability, as homologous recombination repairs DNA lesions caused by platinums (88). This makes such tumors a preferred candidate for treatment with platinum agents such as carboplatin, which crosslink DNA, mostly by forming intrastrand crosslinks, ultimately leading to cell death (89). However, many new trials are incorporating carboplatin as part of the standard regimen in neoadjuvant stage (NCT05174832, NCT03281954, NCT03639948, NCT05645380), and its use is recommended irrespective of the BRCA status. Therefore, based on the available evidence, platinum-based chemotherapy regimens are not routinely recommended. The regimens could be considered only in patients with high-risk factors such as BRCA mutations (90).

Immunotherapy has emerged as a standard treatment option for TNBC. The combination of immunotherapy and chemotherapy has shown better outcomes than immunotherapeutic monotherapy (91). The integration of immunotherapy and chemotherapy can lead to synergistic antitumor effects, making it a promising approach in cancer treatment (92). In the phase 3 Keynote-522 trial and IMpassion031, neoadjuvant immunotherapy plus chemotherapy was established as the standard of care for many patients with eTNBC. The trials showed a higher pCR rate with pembrolizumab plus paclitaxel and carboplatin, especially for patients with stage III or node-positive disease, regardless of PD-L1 expression, and an improved outcome (22,30). Other studies have evaluated the efficacy of immunotherapy plus chemotherapy combination regimens in the neoadjuvant setting, with encouraging results observed in the GeparNuevo trial, KEYNOTE-173, and I-SPY2. However, atezolizumab did not significantly enhance the pCR rate when added to carboplatin and nab-paclitaxel (29). Despite the disparity in outcomes observed in certain trials, anthracycline and taxanes are the preferred chemotherapeutic agents used in combination with immunotherapy (93).

Challenges still remain in neoadjuvant treatment stage

Immunotherapy has emerged as an important treatment modality for TNBC, but challenges remain. The complexity of the interaction between cancer cells and the immune system in TNBC requires more comprehensive biomarkers to identify individuals who are more likely to benefit from immunotherapy (39). Although PD-L1 is being increasingly used as a biomarker in immunotherapy studies, it is not ideal for selecting patients for anti-PD-1/anti-PD-L1 therapies. Therefore, new biomarkers, including different assays and thresholds of PD-L1 expression, are urgently needed to predict response to immunotherapy (94,95).

Moreover, the appropriate chemotherapy backbone needs to be identified to improve the outcomes of immunotherapy in the treatment of eTNBC. As previously mentioned, platinum-based chemotherapy regimens increase pCR rates in TNBC during the neoadjuvant phase (30,96). However, large sample, multicenter randomized controlled trials have not yet been conducted to confirm whether the combination of platinum with immunotherapy can benefit. Additionally, more research is needed to determine the optimal duration of therapy after achieving pCR and whether immunotherapy should be combined or sequenced with other post-neoadjuvant therapies (97).

Furthermore, efforts are needed to minimize the immunotherapy-related adverse events associated with traditional chemotherapy toxicities (94,98). Since TNBC often occurs in pre-menopausal patients, concerns have been raised about the impact of immunotherapy on women's fertility potential, which needs to be adequately addressed (99).

Lastly, there is discordance among the type of endpoints being used with immunotherapy. Endpoints such as ORR, PFS, and OS have not been designed for the assessment of immunotherapies. The hope is that ongoing research will provide answers to these important questions in the near future.

Adjuvant treatment stage with residual disease after neoadjuvant immunotherapy

Presently, the availability of approved adjuvant targeted

therapies for non-pathological complete response (non-pCR) eTNBC patients who have undergone neoadjuvant immunotherapy is limited to just two options.

One option involves continuing with the same immunotherapeutic agent in the adjuvant setting that was used in the neoadjuvant phase, as seen in the Keynote-522 trial (22,43). The SWOG 1418 trial is currently testing this strategy. This randomized, open-label, phase III trial aims to compare the invasive DFS of TNBC patients treated with pembrolizumab as adjuvant therapy after failing to achieve pCR in the neoadjuvant phase. The study will stratify patients by nodal stage (ypNo *vs.* ypN+), residual tumor (≥2 *vs.* <2 cm), PD-L1 status (positive *vs.* negative), and prior adjuvant chemotherapy (100,101).

Another option involves the combination of olaparib with pembrolizumab in patients harboring germline BRCA mutations with RCB after neoadjuvant ICI containing regimens. The OlympiA trial evaluated 1 year of treatment with oral olaparib either in the adjuvant or post-neoadjuvant setting in TNBC patients harboring germline BRCA1/2 mutations. The study found that olaparib significantly improved OS and DFS outcomes (102,103). Based on these results, the US FDA approved the use of olaparib as adjuvant treatment for patients with BRCA-mutated HER2-negative high-risk early breast cancer (104).

The optimal duration of pembrolizumab treatment for patients who achieve pCR with neoadjuvant immune therapy remains a topic of controversy. Given the significant incidence of serious treatment-related adverse events (34.1%) and the unfortunate occurrence of four deaths during the neoadjuvant phase, the need for de-escalation of the treatment regimen following pCR remains unclear (22). Furthermore, the selection of an intensive regimen for non-pCR patients in the subsequent adjuvant phase is still at a crossroads. So further research is necessary to identify additional effective targeted therapies for this population.

Unleashing the power of early intervention: neoadjuvant immunotherapy as a transformative approach

The concept of early treatment in cancer management has gained significant attention, particularly in the context of immunotherapy. Neoadjuvant immunotherapy, which involves administering ICIs before surgery, has emerged as a promising approach in various tumor types. The Keynote-522 trial stands out as a notable example, as it achieved the dual endpoint of improved pCR rates and EFS in eTNBC (1).

The results from the Keynote-522 trial have provided compelling evidence for the efficacy of neoadjuvant immunotherapy in TNBC. By combining ICIs with standard chemotherapy regimens, the trial demonstrated a significant improvement in pCR rates compared to chemotherapy alone. Importantly, this improvement in response rates translated into a favorable impact on EFS, highlighting the potential of neoadjuvant immunotherapy to transform patient outcomes.

In contrast, the IMpassion031 trial, which evaluated the adjuvant use of ICIs in TNBC, did not demonstrate a significant improvement in EFS. However, it is crucial to interpret these findings in the context of the overall treatment concept. The success of neoadjuvant immunotherapy in the Keynote-522 trial suggests that the early application of immunotherapy, when the immune environment may be more favorable, holds promise for improving outcomes in TNBC.

The neoadjuvant approach allows for the modulation of the tumor microenvironment and the priming of an optimal immune response against the primary tumor. This may contribute to a more effective eradication of residual disease and a potential abscopal effect on distant metastatic sites. The concept of early treatment with neoadjuvant immunotherapy is supported by preclinical evidence and mounting clinical data, indicating its potential superiority over adjuvant administration of ICIs.

Whether BRCA gene function matters

BRCAness, a distinctive feature of homologous recombination deficiency (HRD), has emerged as an intriguing mimic of *BRCA* gene mutations in breast cancer, showcasing a phenotype resembling mutations in germline *BRCA1* and/or *BRCA2* DNA repair genes (105,106). This imitation ultimately leads to HRD, characterized by impaired homologous recombination. BRCAness, encompassing various traits associated with BRCA1 dysfunction arising from gene mutation, methylation, or deletion, results in DNA repair deficiencies. Remarkably, the DNA repair defect linked to BRCA1/2 loss becomes the Achilles' heel of these cancer cells, offering opportunities for therapeutic exploitation using DNA-damaging agents like platinum-based compounds and inhibitors of specific DNA repair pathways, such as poly ADP-ribose polymerase (PARP) inhibitors (105).

The addition of platinum to neoadjuvant chemotherapy has demonstrated significant improvements in the pCR rate

among patients with early triple-negative breast cancer, as confirmed by the CALGB40603 and GeparSixto trials. However, the translation of pCR improvements into long-term survival benefits remains uncertain, potentially due to notable side effects. The establishment of platinum-based combination chemotherapy as a new standard NAT has faced challenges, as the CALGB40603 and GeparSixto trials lacked the statistical power to draw definitive conclusions regarding long-term survival benefits beyond pCR improvement (84,85).

Notably, the PARP inhibitor olaparib has demonstrated noteworthy success in improving survival outcomes, specifically freedom from invasive or distant disease, among high-risk, HER2-negative early breast cancer patients with germline BRCA1 or BRCA2 pathogenic or likely pathogenic variants (102). However, controversy surrounds the benefit of combining olaparib with ICIs in the neoadjuvant treatment stage of early triple-negative breast cancer, as clear clinical study results to support this combination are currently lacking.

Ongoing trials and future perspectives

The management of eTNBC continues to present numerous challenges, prompting the initiation of several ongoing clinical trials aimed at addressing these unanswered questions. Exciting developments in the field hold promise for the future of eTNBC treatment.

In the realm of eTNBC monotherapy, the phase III SWOG 1418 trial is currently assessing the efficacy of pembrolizumab, a PD-L1 inhibitor, in patients with residual invasive cancer measuring ≥1 cm (33). Additionally, the A-Brave trial is investigating the survival benefits of avelumab as an adjuvant treatment for high-risk eTNBC patients (34). The outcomes of these trials may expand the therapeutic options available for eTNBC patients. Dana-Farber Cancer Institute has initiated a clinical trial (NCT05812807) to explore whether eTNBC patients achieving a pCR after neoadjuvant chemotherapy with checkpoint inhibitor therapy can undergo de-escalation. Furthermore, Baylor College of Medicine has established a trial (NCT05020860) focusing on the correlation between clinical response and pathologic response in patients with early breast cancer. In the neoadjuvant stage, trials (NCT05203445, NCT05485766, NCT05209529) are underway to determine the impact of BRCA1/2 mutations on the combination of ICIs regimens.

The inclusion of immunotherapy in postoperative adjuvant regimens remains a topic of ongoing debate. Accurately predicting response rates and ultimate benefits of immunotherapy necessitates the assessment of distinct criteria. Addressing these issues, our center has undertaken two clinical studies (NCT04803539, NCT04501523) focusing on the predictive value of ctDNA in eTNBC. With over 300 patients screened and an anticipated enrollment of 1,200 patients, including 460 randomized participants, we are currently collating the data. We firmly believe that these studies will shed light on this topic in the near future.

Future perspectives

The landscape of immunotherapy in eTNBC is poised for remarkable advancements, with a myriad of captivating avenues beckoning researchers and clinicians alike. A pivotal focus lies in the integration of cutting-edge technologies, such as the analysis of ctDNA, as a predictive marker to unlock the secrets of immunotherapy response. This transformative approach holds the potential to revolutionize TNBC management, empowering clinicians to tailor treatment strategies with unparalleled precision, optimizing patient outcomes while mitigating the burden of toxicities. Moreover, meticulous exploration of the optimal chemotherapy backbone, synergistically combined with immunotherapy, and the intricate orchestration of ICIs administration timing in relation to chemotherapy, promises to unveil the true potential of these therapeutic modalities. Delving deeper into the intricate tapestry of TNBC, the influence of BRCA1/2 mutations on immunotherapy regimens emerges as a captivating enigma, warranting comprehensive investigation to unravel the intricate interplay between genetic alterations and treatment response. In parallel, the emergence of novel frontiers, such as chimeric antigen receptor-T (CAR-T) cell therapy and oncolytic viruses, tantalizes the scientific community, beckoning further scrutiny and exploration to harness their full potential in the realm of TNBC immunotherapy.

Discussion

The comprehensive analysis presented in this review sheds light on the transformative potential of immunotherapy in eTNBC. By exploring the treatment landscape, combination strategies, and predictive biomarkers, the review provides a nuanced understanding of the current state of immunotherapy in eTNBC. Notably, the incorporation of recent evidence, such as the Keynote-522

trial showcasing improved outcomes with pembrolizumab in eTNBC patients achieving pCR, enhances the relevance and applicability of the findings. However, it is important to acknowledge the limitations of the review, including its focus on eTNBC, which may restrict the generalizability of the findings to other breast cancer subtypes or advanced stages of TNBC. Additionally, the review's reliance on studies available up to June 2023 may not encompass the most recent advancements in the field. Nevertheless, this comprehensive overview serves as a valuable foundation for future research and clinical practice, propelling the field of immunotherapy in eTNBC forward.

Conclusions

Recent clinical trials have demonstrated the promising efficacy of immunotherapy in combination with chemotherapy for the treatment of eTNBC, as demonstrated in studies such as Keynote-522, IMpassion031, and GeparNuevo. However, questions still remain regarding the optimal use of immunotherapy in this setting. One critical question is whether all patients who meet the inclusion criteria should receive immunotherapy. Another question is whether a strong combination of chemotherapy in adjuvant stage is necessary. Because the addition of capecitabine or platinum may offer extra benefits to patients with TNBC, but at the cost of increased toxicity or adverse events (107). Additionally, it remains to be determined whether immunotherapy should be extended to the adjuvant stage and whether non-pCR high-risk patients should be selected for immunotherapy by neoadjuvant chemotherapy.

The analysis results of GeparNuevo suggest that TILs and TMB may be valuable in predicting the response rate of immunotherapy in NAT, but the actual benefit of patients may not be related to the complete pathological response (26,108).

As immunotherapy may bring lifelong side effects, some of which are serious, the benefits and risks must be carefully weighed (109). Therefore, identifying high-risk TNBC patients who can benefit from intensive treatment guided by ctDNA results may be critical in accurately predicting the effective rate of immunotherapy in eTNBC.

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