REVIEW ARTICLE

Immunotherapy for triple-negative breast cancer

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ABSTRACT

Breast cancer (BC) is the most common cancer and one of the leading causes of cancer death in women. Triple-negative breast cancer (TNBC) is a typical subtype of breast cancer with lack of estrogen and progesterone receptors and has low expression levels of human epidermal growth factor receptor 2 (HER2), accounting for 15%–20% of all BC cases. In comparation with other subtypes of BC, TNBC displays stronger invasiveness, higher recurrence rate and poorer prognosis. Due to lack of targeted therapies and limited benefit from chemotherapy, abundant investigations have been committed to discover effective molecular targets and treatment approaches for TNBC patients. During the past decade, emerging evidence has shown that compared to other subtypes of BC, TNBC is more immunogenic, has higher expression levels of programmed death ligand-1 (PD-L1) and higher rates of CD8+ T cell infiltration. Thus, TNBC is deemed to be most suitable for immunotherapy among all BC subtypes.

Keywords: Triple-negative Breast Cancer; Immunotherapy; Immune Checkpoint Blockade

ARTICLE INFO

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1. Introduction

Different from other cancer treatment approaches, immunotherapy eliminates tumor cells by increasing and/or rebuilding the ability of the immune system[1,2]. To date, many immunotherapy approaches have been developed, including cancer vaccines, monoclonal antibodies, chimeric antigen receptor T-cell (CAR-T) therapy, and immune checkpoint inhibitors (ICIs). Among them, ICIs reactivate the cyto-toxic T lymphocytes to reverse the suppressed immune response in cancer patients[3]. Currently, ICIs have been clinically used to treat various human cancers[4]. Nevertheless, even for the cancer types with the highest response rate to ICIs, such as melanoma and non-small-cell lung cancer (NSCLC), currently less than 30% of cancer patients respond to ICIs[5]. Thus, discovery of predictive biomarkers for immunotherapy responses is significant. Several such biomarkers have been approved in clinical use by Food and Drug Administration (FDA), including PD-L1 expression[6], tumor mutation burden (TMB)[7], and mismatch repair deficiency (dMMR)[8].

In general, the "hot" tumors with high levels of immune infiltration likely respond better to ICIs compared to the "cold" tumors with low levels of immune infiltration[9]. Most BC tumors were

deemed to be "cold" tumors for their low TMB and lack of neoantigens[10–12]. However, triple-negative breast cancer (TNBC), which is the most invasive BC subtype and characterized by lack of estrogen and progesterone receptors and the low expression of human epidermal growth factor receptor 2 (HER2), often displays high TMB, PD-L1 expression and infiltration levels of tumor infiltrating lymphocytes (TILs)[13]. In addition, TNBC has a significantly higher mutation rate of *TP53* than other BC subtypes: 80% in TNBC versus 33% in general BC[14]. Our previous study has shown that *TP53* mutations can significantly enhance tumor immunity in BC[15]. These evidences collectively suggest that TNBC could be best suited for immunotherapy among all BC subtypes. In this article, we discuss current clinical trials related to immune checkpoint blockade in TNBC.

2. ICIs in advanced TNBC (Table 1)

2.1 Monotherapy

The phase Ib KEYNOTE-012 study (NCT01848834) was designed to evaluate the safety, tolerability, and antitumor activity of pembrolizumab in patients with advanced TNBC[16]. A single-agent pembrolizumab was given to patients with advanced TNBC with PD-L1-positive (expression in stroma or ≥1% of tumor cells by immunohistochemistry) in this study. All enrolled patients had previously received chemotherapy. The overall response rate (ORR) was 18.5% (95% confidence interval (CI): 6.3%–38.1%), including 1 complete response (3.7%) and 4 partial response (14.8%). The cohort B of phase II KEYNOTE-086 study (NCT02447003) was conducted for further detecting the efficacy and safety of single-agent pembrolizumab to metastatic triple-negative breast cancer (mTNBC) with PD-L1-positive (combined positive score (CPS) > 1). The ORR was 21.4% (95% CI: 13.9%–31.4%), including 4 complete response (4.8%) and 14 partial response (16.7%). The median progression-free survival (mPFS) and the median overall survival

(mOS) was 2.1 months and 18 months, respectively, with durable antitumor activity. Compared to cohort A of this study, in which ORR was modest (5.3%), the antitumor activity observed in cohort B suggests an improved response to pembrolizumab in PD-L1-positive patients[17]. Moreover, the subset of patients with PD-L1-postive in cohort A showed more improvements in duration of response and OS[18]. Another clinical trial KEYNOTE-119 (NCT02555657) compared pembrolizumab with chemotherapy for second-line or third-line treatment of patients with mTNBC. The mOS in PD-L1-positive patients (CPS ≥10) was 12.7 months (95% CI: 9.9%–16.3%) for the pembrolizumab group and 11.6 months (95% CI: 8.3%–13.7%) for the chemotherapy group (hazard ratio (HR): 0.78; 95% CI: 0.57–1.06; log-rank p = 0.057). Similar results were observed in the patients with CPS ≥ 1 (the mOS for the pembrolizumab group and the chemotherapy group were 10.7 months (95% CI: 9.3–12.5) and 10.2 months (95% CI: 7.9–12.6), respectively). Although pembrolizumab monotherapy did not significantly improve OS compared to chemotherapy in this trial, in patients with CPS ≥ 20, the mOS for the pembrolizumab group was 14.9 months, suggesting that the efficacy of pembrolizumab increases with elevated PD-L1 expression. By contrast, the efficacy of chemotherapy was independent of PD-L1 expression on the tumor[19]. These results confirmed the safety and antitumor activity of pembrolizumab in patients with advanced TNBC and indicated that the expression level of PD-L1 may be associated with clinical benefit of pembrolizumab in advanced TNBC.

2.2 ICIs combined with chemotherapy

Chemotherapy agents can not only suppress the activity of immunosuppressive cells like T regulatory and myeloid-derived suppressor cells[20,21], but also activate dendritic cells and promote the proliferation of CD8+ T cells and natural killer cells[22,23]. Therefore, many clinical studies have been exploring the combination of

Table 1. ICIs in advanced TNBC

Clinical trail	Regimen	Number of patients	Enrolled patients	Results
KEYNOTE-012, phase Ib (NCT01848834)	Pembrolizumab	32	Advanced PD-L1+ TNBC	OR: 18.5% mPFS: 1.9 months mOS: 11.2 months
KEYNOTE-086A, phase II (NCT02447003)	Pembrolizumab	70	Previously treated mTNBC	ORR: Total: 5.3%; PD-L1+: 5.7%; PD-L1-: 4.7% mPFS: Total: 2.0 months; PD-L1+: 2.0 months; PD-L1-: 1.9 months mOS: Total: 9.0 months; PD-L1+: 8.8 months; PD-L1-: 9.7 months
KEYNOTE-086B, phase II (NCT02447003)	Pembrolizumab	84	Previously un-treated PD-L1+ mTNBC	ORR: 21.4% mPFS: 2.1 months mOS: 18.0 months
KEYNOTE-119, phase III (NCT02555657)	Pembrolizumab vs. investigator's choice chemotherapy (capecitabine, eribulin, gemcitabine or vinorelbine)	622	Locally advanced or mTNBC	ORR: Total: 9.6% vs. 10.6%; CPS ≥ 10: 17.7% vs. 9.2% mPFS: Total: 2.1 months vs. 3.3 months; CPS ≥ 10: 2.1 months vs. 3.4 months mOS: Total: 9.9 months vs. 10.8 months; CPS ≥ 10: 12.7 months vs. 11.6 months
IMpassion130, phase III (NCT02425891)	Atezolizumab + nab-paclitaxel vs. placebo + nab-paclitaxel	902	Previously un-treated, locally advanced or mTNBC	ORR: Total: 56% vs. 45.9%; PD-L1+: 58.9% vs. 42.6% mPFS: Total: 7.2 months vs. 5.5 months; PD-L1+: 7.5 months vs. 5.0 months mOS: Total: 21.0 months vs. 18.7 months; PD-L1+: 25.0 months vs. 18.0 months
KEYNOTE-355, phase III (NCT02819518)	Pembrolizumab + chemotherapy vs. placebo + chemo-therapy	1,372	Previously un-treated, locally recurrent, inoper-able or mTNBC	ORR: Total: 40.8% vs. 37.0%; CPS ≥ 10: 52.7% vs. 40.8% mPFS: Total: 7.5 months vs. 5.6 months; CPS ≥ 10: 9.7 months vs. 5.6 months mOS: Total: 17.2 months vs. 15.5 months; CPS ≥ 10: 23.0 months vs. 16.1 months

immunotherapy and chemotherapy in treating advanced TNBC.

IMpassion130 (NCT02425891) is a phase III study assessing the efficacy and safety of atezolizumab plus nab-paclitaxel in patients with unresectable, locally advanced or mTNBC. In the intention-to-treat analysis, the mPFS in the atezolizumab plus nab-paclitaxel group was 7.2 months compared with 5.5 months in the placebo plus nab-paclitaxel group (hazard ratio (HR): 0.80; 95% CI: 0.69–0.92; p = 0.002). Among patients with PD-L1-positive (tumors with ≥1% PD-L1 expression), the gap of mPFS between two groups was greater (7.5 versus 5.0 months; HR: 0.62; 95% CI: 0.49–0.78; p < 0.001)[24]. At the second interim analysis, the mOS in the ate-zolizumab plus nab-paclitaxel group was 21.0 months (95% CI: 19.0–22.6) versus 18.7 months (95% CI: 16.9–20.3) in the placebo plus nab-paclitaxel group (HR: 0.86; 95% CI: 0.72–1.02; p = 0.078), without statistical significance. Nevertheless, in the subset of PD-L1-positive patients, the mOS was significantly prolonged by atezolizumab (25.0 versus 18.0 months; HR: 0.71; 95% CI: 0.54–0.94)[25]. Nevertheless, the results of IMpassion131 study (NCT03125902) showed that atezolizumab combined with paclitaxel did not improve PFS or OS versus paclitaxel alone in mTNBC patients with PD-L1-positive[26]. Therefore, FDA withdrew atezolizumab for treating PD-L1-positive mTNBC.

KEYNOTE-355 (NCT02819518) is another

clinical trial investigating the combination of pembrolizumab and chemotherapy (namely nab-paclitaxel, paclitaxel, and gemcitabine/carboplatin) in advanced TNBC. At the second interim analysis, compared to the placebo-chemotherapy group, the pembrolizumab-chemotherapy group exhibited significantly prolonged PFS in PD-L1-positive (CPS $\geq$ 10) patients (9.7 versus 5.6 months; HR: 0.65; 95% CI: 0.49–0.86; p = 0.0012)[27]. Because of these encouraging results, FDA accelerated approval of pembrolizumab combined with chemotherapy in November, 2020 for treating mTNBC with CPS $\geq$ 10. Recently, the latest results were published. After 44.1 months of median follow-up, among the subset of CPS $\geq$ 10, the mOS was significantly improved in the pembrolizumab-chemotherapy group compared to the placebo-chemotherapy group (23.0 versus 16.1 months; HR: 0.73; 95% CI: 0.55–0.95; p = 0.0185). However, no significant difference was observed in the CPS $\geq$ 1 subset (17.6 versus 16.0 months; p = 0.1125). In the patients with CPS $\geq$ 10, the ORR in both groups were 52.7% and 40.8%, respectively. Moreover, the results of PFS were consistent with those in interim analysis[28]. It suggests a certain clinical efficacy of the combination of pembrolizumab and chemotherapy in treating advanced TNBC.

3. ICIs in early-stage TNBC (Table 2)

Early-stage TNBC accounts for 10%–20% of new diagnoses of early BC[29]. Although neoadjuvant or adjuvant treatment may improve the OS of early-stage TNBC, the recurrence rate remains high within 5 years. In this context, studies of ICIs in earlier TNBC have attracted increasing attention. GeparNuevo (NCT02685059) is a phase II study evaluating the addition of durvalumab to standard neoadjuvant in primary TNBC with the primary objective being the pathological complete response (pCR). Results showed that the pCR rate was 53.4% (95% CI: 42.5%–61.4%) in the durvalumab group versus 44.2% (95% CI: 33.5%–55.3%) in the placebo

group (p = 0.287), showing no statistical significance. In the window cohort (patients receiving monotherapy of durvalumab 2 weeks before the start of chemotherapy), the pCR rate was significantly improved in the durvalumab group (61.0% versus 41.1%; p = 0.035)[30]. KEYNOTE-522 (NCT03036488) is another phase III clinical trial investigating the addition of pembrolizumab to neoadjuvant chemotherapy. At the first interim analysis, the pCR rate was 64.8% (95% CI: 59.9%–69.5%) in the pembrolizumab-chemotherapy group and 51.2% (95% CI: 44.1%–58.3%) in the placebo-chemotherapy group ($p <$ 0.001)[31]. The latest published results showed that the event-free survival at 36 months was 84.5% (95% CI: 81.7%–86.9%) in the pembrolizumab-chemotherapy group versus 76.8% (95% CI: 72.2%–80.7%) in the placebo-chemotherapy group ($p <$ 0.001)[32]. Of note, the pCR rate in the PD-L1-positive group was increased by 14.2% (68.9% versus 54.9%), and was increased by 18.3% (45.3% versus 30.3%) in the PD-L1 negative group. It indicates that the addition of pembrolizumab could significantly increase the rate of pCR regardless of the PD-L1 expression status. Similar results were observed in the study IMpassion031 (NCT03197935) evaluating the benefit of atezolizumab in early-stage TNBC[29]. Therefore, PD-L1 expression status may not be a suitable biomarker in predicting the response rate to ICIs in early-stage TNBC. NeoTRIPaPDL1 trial (NCT02620280) evaluated the efficacy of atezolizumab combined with neoadjuvant therapy in early high-risk and locally advanced TNBC. The pCR rate showed no significant significance between the atezolizumab group and the control group (48.6% versus 44.4%; p = 0.48)[33]. Follow-up analysis based on gene expression profiles proposed that the 27-gene IO (immune oncology) score was predictive of atezolizumab benefit, suggesting the role of biological response in predicting the response of ICIs other than a single biological feature. Moreover, high angiogenesis and fatty acid/cholesterol at baseline and aberrant glutamine metabolism after cycle 1 treatment were linked to resistance in the atezolizumab group, indicating the combi-

nation of baseline values and dynamics of specific biomarkers could be more informative. Recently, researchers redefined BC subtypes using pre-treatment gene expression profiles, proteins, and clinical data from the 990 patients from I-SPY2 trial (NCT01042379). They proposed two important biomarkers associated with immune (Immune) and DNA repair (DRD), respectively, and divided TNBC into four response predictive subtypes (Immune+/DRD+, Immune+/DRD-, Immune-/DRD+, Immune-/DRD-) according to the expression status of biomarkers and response rate of treatments. The Immune+/DRD+ subtype had a very high pCR rate with both veliparib-carboplatin and pembrolizumab-chemotherapy (74% and 92%, respectively), the Immune+/DRD-subtype had the highest pCR rate to pembrolizumab-chemotherapy (80%), and the Immune-/DRD+ and the Immune-/DRD-subtype showed relatively low pCR rates to pembrolizumab-chemotherapy (33% and 20%, respectively)[34]. This study may provide a new venue to explore the prediction of the efficacy of immunotherapy in TNBC.

Table 2. ICIs in early-stage TNBC

Clinical trail	Regimen	Number of patients	Enrolled patients	Results
GeparNuevo, phase II (NCT02685059)	Durvalumab + nab-paclitaxel placebo vs. nab-paclitaxel	174	Primary cT1b-cT4a-d disease, centrally confirmed TNBC and sTILs	pCR: 53.4% vs. 44.2%
KEYNOTE-522, phase III (NCT03036488)	Pembrolizumab + chemotherapy vs. placebo + chemo-therapy	1,174	Previously untreated, non-mTNBC	pCR: Total: 64.8% vs. 51.2%; PD-L1+: 68.9% vs. 54.9%; PD-L1-: 45.3% vs. 30.3 36-month EFS rate: 84.5% vs. 76.8%
NeoTRIPaPDL1, phase II (NCT02622074)	Atezolizumab + carboplatin + nab-paclitaxel vs. carboplatin + nab-paclitaxel	280	Early high-risk and locally advanced TNBC	pCR: 48.6% vs. 44.4%
Impassion 031, phase III (NCT03197935)	Atezolizumab + nab-paclitaxel + anthracycline vs. placebo + nab-paclitaxel + anthracycline	333	Early-stage TNBC	pCR: Total: 57.6% vs. 41.1%; PD-L1+: 68.8% vs. 49.3%
I-SPY2, phase II (NCT01042379)	Pembrolizumab + chemotherapy vs. chemotherapy	114	Early-stage TNBC	pCR: 60% vs. 22%

4. Discussion

The high heterogeneity contributes to aggressive clinical behaviors and poor prognosis of TNBC[35,36]. Recently, immunotherapies have shown great success in cancer treatment. To date, FDA has approved pembrolizumab for treating advanced TNBC with CPS ≥ 10 and high risk early-stage TNBC according to the positive results of clinical trials KEYNOTE-355 and KEYNOTE-522. Despite the exciting prospect of ICIs in TNBC treatment, some major challenges deserved attention. First, how to select TNBC patients for the ICI treatment? Although several molecular features have been confirmed to be associated with the response rate to ICIs in TNBC treatment, such as PD-L1 expression, TILs, and TMB, the clinical utility of these features remains foggy because the precise cut-offs of their values are hard to determine and the detection methods are lacking of uniform standards. Recent studies like I-SPY2 and NeoTRIPaPDL1 explored the role of biological processes rather than molecular features in predicting treatment response rates. These approaches have brought a new perspective in selecting the target patients. Thus, more researches are encouraged to discover new markers for immunotherapy response.

Second, how to develop suitable treatment regimens? Monotherapy of ICIs has been proved to be safe and effective for TNBC patients but with limited effectiveness. Combination therapy may greatly improve the treatment outcomes. The GeparNuevo study showed that using pembrolizumab before chemotherapy could improve efficacy. The study KEYNOTE-355 explored different chemotherapy regimens in combination with immunotherapy, and other studies, such as I-SPY2 (combination with PARP inhibitors) and IPATunity130 (combination with AKT inhibitors) explored targeted therapy in combination with immunotherapy. Although these studies suggested the diversity of combinatory pattern and promising prospects, the detailed mechanisms remain unclear. Thus, further efforts are required to clarify the mechanisms underlying the effectiveness of combination therapies.

Conflict of interest

The authors declare that they have no competing interests.

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