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REVIEW

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Progress of PD-1/PD-L1 immune checkpoint inhibitors in the treatment of triple-negative breast cancer

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Abstract

Triple-negative breast cancer (TNBC) is a highly heterogeneous cancer with substantial recurrence potential. Currently, surgery and chemotherapy are the main treatments for this disease. However, chemotherapy is often limited by several factors, including low bioavailability, significant systemic toxicity, inadequate targeting, and multidrug resistance. Immune checkpoint inhibitors (ICIs), including those targeting programmed death protein-1 (PD-1) and its ligand (PD-L1), have been proven effective in the treatment of various tumours. In particular, in the treatment of TNBC with PD-1/PD-L1 inhibitors, both monotherapy and combination chemotherapy, as well as targeted drugs and other therapeutic strategies, have broad therapeutic prospects. In addition, these inhibitors can participate in the tumour immune microenvironment (TIME) through blocking PD-1/PD-L1 binding, which can improve immune efficacy. This article provides an overview of the use of PD-1/PD-L1 inhibitors in the treatment of TNBC and the progress of multiple therapeutic studies. To increase the survival of TNBC patients, relevant biomarkers for predicting the efficacy of PD-1/PD-L1 inhibitor therapy have been explored to identify new strategies for the treatment of TNBC.

Keywords Triple-negative breast cancer, PD-1 inhibitors, PD-L1 inhibitors, Biomarker, Immunotherapy

Introduction

According to data released by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) in 2024, breast cancer (BC) is the most frequently diagnosed cancer in women and the leading cause of cancer-related mortality among them [1]. Currently, breast cancer is categorized into various subtypes on the basis of clinical and molecular typing. The treatment of TNBC is limited because of its aggressive nature, poor prognosis, and high recurrence rate. Thus, the study of TNBC is highly important. Conventional chemotherapy remains the main strategy for treating TNBC patients. In the past few years, many efforts have been put into targeted therapies by investigators, and TNBC patients with germline BRCA mutations can benefit from targeted drugs. However, targeted therapies

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are still in the early stages [2]. PD-1 and PD-L1 inhibitors have received the attention of many scientific researchers in recent years because of their significant clinical efficacy, durable response and low toxicity. These inhibitors can prevent tumour immune evasion [3, 4]. In addition, they can restore the activation of T cells to activate the host immune system, which relies on its own immune function to suppress cancer cells. Notably, biomarkers of TNBC, such as the number of tumour-infiltrating lymphocytes (TILs), the level of PD-L1 expression, and the tumour mutational burden (TMB), are greater than those of other subtypes of breast cancer are, suggesting that the tumour microenvironment (TME) immunoreactivity of TNBC is stronger and that TNBC is considered the most immunogenic subtype of BC. Moreover, these factors may serve as predictive biomarkers for PD-1/PD-L1 immunotherapy, potentially improving patient survival [5]. Currently, immune checkpoint therapy for BC is focused on TNBC, and immunotherapy is transforming the current outlook for TNBC treatment [6]. This article provides a review of the latest advances in immunotherapy for TNBC and a reference for TNBC treatment and clinical prognosis.

Current status of treatment for TNBC

Compared with other subtypes, TNBC is highly aggressive and heterogeneous; characterized by greater proliferation and metastasis, poorer prognosis, and greater disease recurrence; and treatment of TNBC is urgently needed [7]. TNBC patients are treated with surgery, radiation and chemotherapy, as well as emerging targeted therapies and immunotherapy. Surgical treatment: Localized therapy for TNBC is particularly important, and surgery is a necessary means of localized therapy for early-stage TNBC [8]. In terms of chemotherapy, systemic chemotherapy remains the mainstay of treatment for the majority of early-stage cancers, and advanced TNBC is no exception [9]. Research has shown that albumin-bound paclitaxel (nab-paclitaxel) is more effective in combination with cisplatin treatment [10]. In 2024, the American Society of Clinical Oncology (ASCO) highlighted the potential capabilities of PD-1/PD-L1 inhibitors and research advances and revealed the effectiveness of bispecific antibodies in a wide range of cancers, marking a step forwards in cancer immunotherapy [11]. The Chinese Society of Clinical Oncology (CSCO) Breast Cancer guidelines state that patients with a wide range of breast cancers, including TNBC types, require preoperative neoadjuvant therapy. Treatment regimens usually include paclitaxel-based drugs in combination with anthracyclines or platinum-based (TP) drugs. However, changes in the chemotherapy regimen may be required for operable patients who do not respond adequately to neoadjuvant chemotherapy. For example, PD-1 inhibitors have entered clinical guidelines with good results in multiple trials (PCR and EFS improvements vs. TP) [12]. In addition, patients with advanced TNBC develop drug resistance earlier during neoadjuvant chemotherapy and have a poor prognosis that needs to be addressed [13]. Among targeted therapies, mutations in the genes BRCA1 and BRCA2 are more prevalent in TNBC [14]. After homologous recombination repair, patients with BRCA1/2-mutant TNBC have impaired DNA repair pathways and are more susceptible to drugs that interfere with DNA repair (e.g., PARP inhibitors). As a result, targeted therapeutic agents are effective in the treatment of TNBC but have increased toxicity [15]. There is an urgent need to find strategies that can reverse drug resistance to improve the efficacy of clinical treatments. Currently, for this type of breast cancer patient, the sequence of using platinum to improve therapeutic efficacy is still controversial. As PD-1 inhibitors have entered clinical guidelines at various times, whether they can also provide new guarantees for survival needs to be further studied [12].

Immunotherapy includes tumour cell vaccines (CVs), oncolytic viruses (OVs), adoptive cell transfer therapy (ACT), and ICIs [16]. ICIs have become a newly emerging therapeutic approach in recent years. The use of PD-1 and PD-L1 inhibitors in the treatment of TNBC has been extensively studied. The PD-1 molecule was first identified in hybridoma mouse T cells and was named PD-1 because of its association with apoptosis. PD-1 is found mainly on the surface of activated T cells, macrophages, and B lymphocytes. PD-L1 is usually found on the surface of cancer cells or immune cells. Cytotoxic T lymphocytes (CTLs) activate cytotoxicity through TCR recognition of MHC-1-like molecule-tumour antigen peptide complexes on the surface of tumour cells and kill tumour cells. PD-L1 on the surface of tumour cells binds to PD-1 on CTL cells, inhibiting CTL activation, facilitating tumour cell immune escape and promoting tumour progression. The function of $CD8^+$ T cells in the TME can be restored by blocking PD-1/PD-L1 binding, which can subsequently play an antitumour role [17]. Activated $CD4^+$ T cells (divided into Th1, Th2, Th17 and Treg cells, etc.) stimulate MHC-I antigen presentation (or cross-presentation) by cDC1s, thereby increasing their ability to trigger an anticancer response in $CD8^+$ CTL. In addition, $CD4^+$ T cells in the TME are linked to overall survival and the response to PD-1 checkpoint blockers in patients [18] (Fig. 1). Some clinical cancers, such as melanoma and NSCLC, use PD-1/PD-L1 inhibitors to inhibit the PD-1/PD-L1 signalling pathway, which effectively inhibits tumour growth and destroys tumour cells. With the development of molecular biology and the deepening of mechanisms, TNBC has been found to be the most immunogenic subtype. Therefore, the emergence of PD-1/PD-L1 inhibitors has provided new treatment

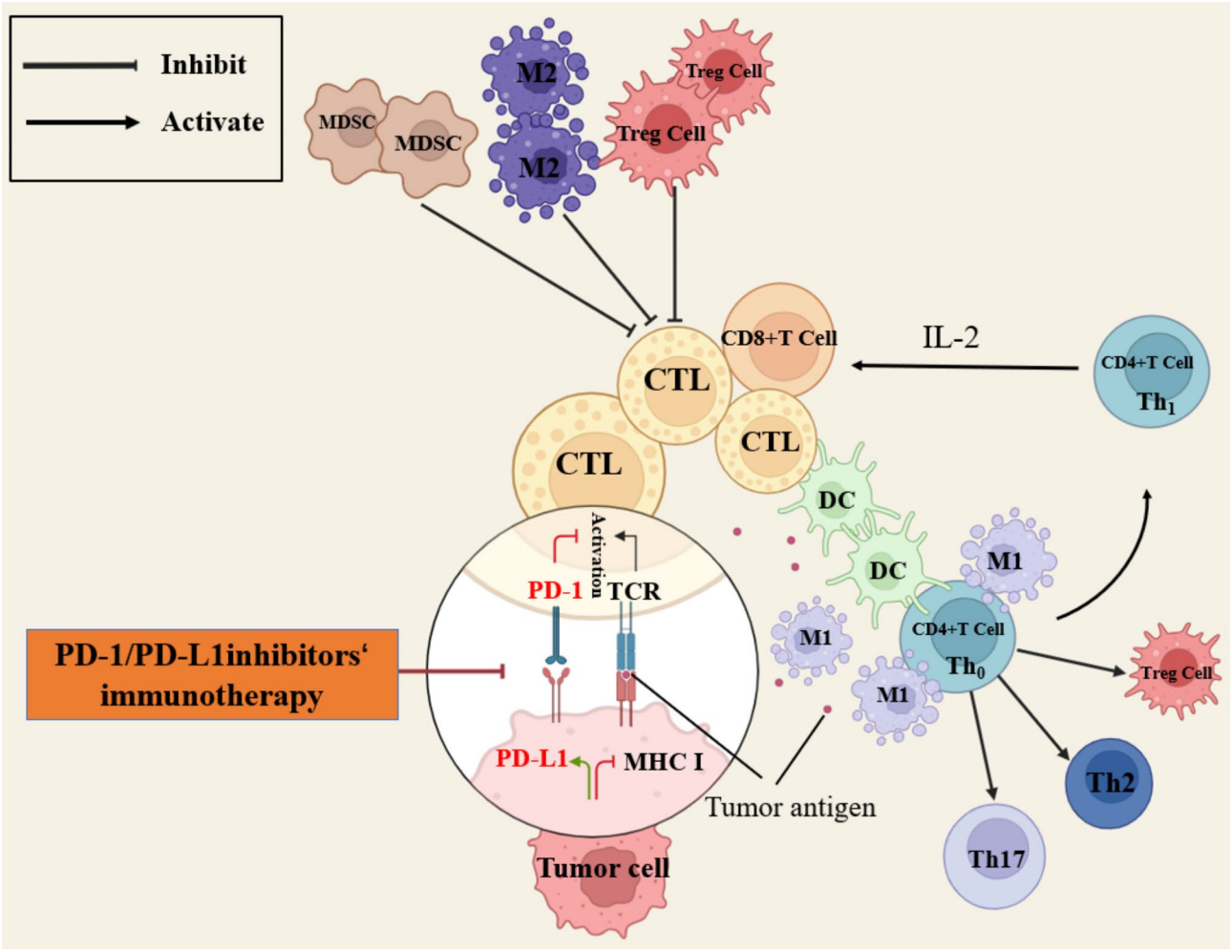

Fig. 1 Mechanisms of immune effects of PD-1/PD-L1 inhibitors in the tumour microenvironment. DC: Dendritic cells; MDSC: Myeloid-Derived Suppressor Cells; M1/M2: Macrophages 1/2 CTL: Cytotoxic T Lymphocyte; TCR: T-cell Receptor; MHC I: Major Histocompatibility Complex Class I; Treg cell: Regulatory T cells. CTL activates cytotoxicity through TCR recognition of MHC-1-like molecule-tumour antigen peptide complexes on the surface of tumour cells. PD-L1 on the surface of tumour cells binds to PD-1 on CTL cells, inhibiting CTL activation and facilitating tumour cell immune escape. PD-1/PD-L1 inhibitors can block PD-1 and PD-L1 binding, lift CTL activation restriction, and restore the anti-tumour immune effect

options for patients with all stages of TNBC, especially in combination with conventional therapeutic modalities, and has led to significant achievements in clinical practice and research.

Advances in PD-1/PD-L1 inhibitors in the treatment of TNBC

Since the identification of PD-L1 as the phagocytic checkpoint in TAMs in 2017, a new wave of immunotherapy has been established [19]. Five PD-1/PD-L1 inhibitors are currently widely used in the clinic. Pembrolizumab and atezolizumab have been more widely studied in TNBC therapies, both as single agents and in combination. Therefore, we summarize the progress of research on monotherapy combined with chemotherapy and targeted drugs. Drug safety and antitumour activity are the main concerns. This review compares various aspects, such as the median OS, median progression-free survival (PFS), objective response rate (ORR), adverse events (AEs), and pathologic complete response (PCR). This article provides an overview of the current research on inhibitors, their progress, and their potential for future clinical and basic research.

PD-1/PD-L1 inhibitor monotherapy

Although research into neoadjuvant immunotherapy has increased in recent years, most major clinical trials continue to focus on its efficacy in advanced mTNBC. The early JAVELIN study, which evaluated the activity of avelumab [20], included 168 patients with metastatic BC. Patients were treated with avelumab for approximately 10 months. The tumours were subsequently evaluated by RECIST v1.1 every 6 weeks. Finally, the study revealed that grade ≥ 3 treatment-related AEs (including

2 treatment-related deaths) occurred in 13.7% of patients, with an ORR of 3% (1 complete and 4 partial remissions), compared with 5.2% in TNBC patients. In addition, among 58 TNBC patients, who were divided into two groups on the basis of PD-L1$^+$ and PD-L1$^-$ status, the ORRs were 22.2% and 2.6%, respectively. Research has shown that single-agent avelumab treatment has a relatively high ORR in TNBC and is safe and that PD-L1$^+$ expression may be a key factor in improving treatment efficacy. Moreover, the KEYNOTE series concerns pembrolizumab drug therapy studies in solid tumours, such as TNBC, and non-small cell lung cancer (NSCLC). This trial investigated the activity of pembrolizumab in advanced mTNBC [21], evaluating both its safety and antitumour efficacy. The results revealed that common toxic reactions were similar to and milder than those in the other tumour groups. There were 5 (15.6%) grade three toxic reactions and 1 treatment-related death. The overall remission rate was 18.5% in 27 patients whose antitumour activity was evaluated. In addition, phase II clinical trials evaluated pembrolizumab as a 2nd or 3rd posttreatment in patients with mTNBC [22]. The safety of the drug pembrolizumab was likewise evaluated. A total of 61.8% of the 170 female patients enrolled in the trial were PD-L1$^+$. The overall and PD-L1-positive populations' ORRs were 5.3% and 5.7%, respectively. The disease control rates (DCRs) were 7.6% and 9.5%, respectively. In addition, approximately 103 patients experienced treatment-related AEs, with no deaths due to AEs. On the basis of the above studies, we found that only a minority of patients who received either avelumab or pembrolizumab benefited from PD-1/PD-L1 inhibitors alone in terms of long-term survival. Compared with chemotherapy, pembrolizumab and other monotherapies did not significantly improve OS in patients with advanced TNBC who previously experienced systemic therapy failure, indicating the importance of exploring combination therapy options.

In summary, in recent years, immunotherapy for TNBC has become a clinical research hotspot. PD-1 and PD-L1 inhibitors have antitumour properties and safety, and their therapeutic effects may be related to their PD-L1$^+$ status. However, the efficacy of single drugs is limited, the overall remission rate is not high, and monotherapy is hampered by an increased risk of drug resistance, which hinders the effectiveness of the treatment [12]. There is a strong need to combine drugs with multiple mechanisms of action to improve treatment efficacy.

PD-1/PD-L1 inhibitor combination therapy

PD-1/PD-L1 inhibitors and chemotherapy may act synergistically. Chemotherapy can destroy the activity of immunosuppressive cells (Treg cells/MDSCs) and can also promote the immune response by inducing the secretion of inflammatory cytokines by macrophages, increasing the expression of MHC-I, promoting the apoptosis of tumour cells, enhancing the ability to cross-express tumour antigens, and facilitating the infiltration of CD8$^+$ T cells and the maturation of dendritic cells (DCs) to improve immune efficacy. Several clinical studies are currently investigating the potential of combining immunotherapy with chemotherapy for the treatment of advanced TNBC [4]. In addition, the remission rate for monotherapy in solid tumours remains at approximately 18%, with many patients eventually developing acquired or primary resistance. To improve the effectiveness of ICIs, it is necessary to explore combination therapies that increase sensitivity.

Neoadjuvant therapy with PD-1/PD-L1 inhibitors in combination with chemotherapy in early TNBC

Recent research has placed increasing emphasis on neoadjuvant therapy for early-stage breast cancer. KEYNOTE 522 is a phase III clinical trial [23] in which a PD-1 inhibitor was used in early-stage neoadjuvant therapy for TNBC. The efficacy of the TP-AC (neoadjuvant therapy for early TNBC also includes anthracycline-cyclophosphamide and paclitaxel-based chemotherapy) regimen (paclitaxel + carboplatin sequential doxorubicin + cyclophosphamide + epirubicin) combined with the monoclonal antibody pembrolizumab was compared with the TP-AC regimen alone for the neoadjuvant treatment of TNBC. The results revealed that the combined pembrolizumab monoclonal antibody group had a greater percentage of patients who achieved a pathologic complete response (PCR) than did the TP-AC regimen alone group (64.8% vs. 51.2%). In addition, on the basis of the above studies, the National Medical Products Administration approved the use of a pembrolizumab monoclonal antibody for the neoadjuvant treatment of TNBC. For the evaluation of atezolizumab, Impassion031, a phase III clinical trial, evaluated atezolizumab + chemotherapy for early-stage neoadjuvant treatment of TNBC [24]. Research revealed that the PCRs of the chemotherapy group + atezolizumab/placebo in the ITT population were 58% and 41%, respectively, which was a difference of 17% between the combination chemotherapy and placebo groups. In the PD-L1-positive population, the percentages of PCR-positive individuals in the combination chemotherapy group and the placebo group were 69% and 49%, respectively. In addition, it performed better in terms of safety, suggesting greater potential in the neoadjuvant treatment of early TNBC. PD-L1 expression may be an emerging marker for selecting immunosuppressive therapy. In 2024, for the neoadjuvant treatment of early TNBC, a new treatment strategy, camrelizumab combined with chemotherapy, was proposed in a randomized clinical trial. The findings indicated that adding

camrelizumab to neoadjuvant chemotherapy significantly improves pathological complete remission [25]. These studies indicate that recent studies have explored the combination of ICIs with (neo)adjuvant chemotherapy in early-stage breast cancer. Neoadjuvant ICI therapy has improved early TNBC efficacy outcomes with an acceptable safety profile; however, no significant benefit has been observed with adjuvant ICI therapy. Given the cost and validity associated with ICIs, there remains ongoing debate about the optimal strategy for integrating this approach [26].

First-line treatment with PD-1/PD-L1 inhibitors in combination with chemotherapy in advanced and recurrent metastatic TNBC

The Impassion130 trial is an immunotherapy study evaluating the efficacy and safety of atezolizumab + albumin paclitaxel (nab-paclitaxel) as a first-line treatment for advanced TNBC [27]. At the time of the first analysis, for the intent-to-treat (ITT) population, the placebo + nab-paclitaxel and atezolizumab + nab-paclitaxel groups had PFSs of approximately 5.5 months and 7.2 months, respectively. A greater PFS gap was shown in PD-L1$^+$ patients. In addition, in PD-L1-positive patients, the mOS was also prolonged by approximately 7 months [27]. Therefore, this combination was approved by the U.S. Food and Drug Administration (FDA) for patients with PD-L1$^+$ advanced TNBC primary treatment [28]. This finding offers new hope for immunosuppressive combination therapy in advanced TNBC.

On the basis of the clinical inclusion of atezolizumab, studies of pembrolizumab followed just behind. The purpose of the KEYNOTE-355 clinical phase III trial [29] was to compare the safety and efficacy of pembrolizumab combination chemotherapy with those of placebo combination chemotherapy in patients with mTNBC or previously untreated locally recurrent inoperable BC. The other group was the placebo chemotherapy group. At the time of the 2nd interim analysis, the median follow-up times were 25.9 and 26.3 months, respectively, the PFS times were 9.7 and 5.6 months, respectively, and the ITT population was 7.5 versus 5.6 months, respectively. With PD-L1 enrichment, the effect of pembrolizumab treatment increased. In July 2022 [30], a study reported that pembrolizumab monotherapy, when combined with chemotherapy, was the first immunotherapy to significantly prolong OS in patients with TNBC. These findings suggest that the study protocol is valuable in clinical practice and that pembrolizumab should be added to first-line treatment for mTNBC. These findings further support the use of immunosuppressive agents in combination with chemotherapy in advanced recurrent and mTNBC.

TORCHLIGHT is the latest phase III trial developed in China by Zefei Jiang et al. [31]. This study evaluated torlipalimab combined with nab-paclitaxel versus placebo combined with nab-paclitaxel for the treatment of female patients with recurrent or mTNBC. The combination of the two could significantly improve PFS in patients with PD-L1$^+$ recurrent or mTNBC, with an acceptable safety profile. This study represents a breakthrough in immunotherapy and provides a new treatment option for Chinese patients with advanced TNBC. The TBCRC 043 phase II randomized clinical trial is another study of mTNBC. The results showed that atezolizumab in combination with carboplatin significantly improved survival in patients with mTNBC; high TIL numbers and TMB correlated with the efficacy of ICI treatment. Patients receiving atezolizumab monotherapy after disease progression following platinum therapy had fewer toxic effects, suggesting that sequential chemotherapy and immunotherapy may be another option for patients in whom the management of clinical toxic effects is critical. However, this clinical trial was limited by the small number of patients, and further investigations in a larger cohort are needed to draw definitive conclusions [32].

In summary, single-drug use results in drug resistance, and other factors affect the therapeutic effect; thus, the choice of multidrug combination can improve the therapeutic effect, but greater toxicity and multidrug-resistant refractory bacteria must still be considered. How to rationally combine drugs, the time of administration, the order of administration, and the dosage should be the focus of future experimental research.

PD-1/PD-L1 inhibitors in combination with other treatments

Although TNBC lacks a clear target, with modern medicine development, an increasing number of potential targets have been explored, and a variety of targeted drugs have been developed. Examples include PARP inhibitors for the well-known BRCA1/2 mutation, sacituzumab govitecan (SG) for the potential target human trophoblast cell–surface antigen 2 (Trop-2), antibody–drug conjugates (ADCs), and PI3K/AKT/mTOR pathway inhibitors. SG is a novel anti-Trop-2 ADC. ASCENT [33] studied the median PFS of the SG group versus the chemotherapy-only group and reported that the SG group had a better median PFS and survival rate, as well as a more reliable safety profile, which may open another era of immunotherapy for TNBC. The ESMO 2022 Congress reported on the BEGONIA phase Ib clinical trial [34], which showed that durvalumab monoclonal antibody + a novel TROP2-ADC drug (Dato-DXd) yielded favourable remission rates and safety in first-line treatment for advanced TNBC. These experiments demonstrated new promise for the combination of targeted drugs and inhibitors. For BRCA-mutant breast cancer, immunosuppression and PARP-targeted inhibitor studies are also emerging. TOPACIO [35] explored the use

of a monoclonal antibody against pembrolizumab + the PARP inhibitor niraparib for the treatment of advanced TNBC. The original intent was to expand the indications for PARP inhibitors to both BRCA-mutant and BRCA-wild-type patients as well as platinum-resistant patients. The results revealed the highest ORR for patients with BRCA gene mutations for this treatment strategy, regardless of the BRCA1 or BRCA2 mutation status or PD-L1 expression. The MEDIOLA [36–39] study evaluated the overall efficacy and safety of a PD-L1 inhibitor combined with olaparib in patients with solid tumours. The results revealed a 12-week DCR of up to 80%. In patients with advanced TNBC with BRCA mutations, the ORR was 63%. The combination of these two drugs has some antitumour activity and is expected to provide new options for TNBC treatment. However, it is in the early stages of clinical research, and further randomized controlled studies are necessary to demonstrate its efficacy and safety. In 2024, a conference on the phase II combination of the PD-1 inhibitor HX008 with niraparib noted that coadministration showed promising clinical benefits and a tolerable safety profile in MBC patients carrying germline BRCA 1/2 mutations, even in patients with brain metastases. These findings offer new hope as well as new therapeutic strategies for the treatment of breast cancer patients prone to BRCA mutations [40]. Other new therapeutic strategies regarding combination immunotherapy are also in the clinical trial phase. Radiotherapy, a conventional treatment for many types of cancer, has shown encouraging activity in patients with poor prognosis and mTNBC [41]. Among other new strategies for solid tumour immunotherapy, the use of two immune checkpoint inhibitors is expensive because of greater toxicity. Therefore, the development of bispecific antibodies by combining two different epitopes on the same or different antigens offers an option to enhance the immune response and potentially reduce toxicity. However, this study targeted relatively hot tumours, and it is worth investigating whether this emerging treatment option can also be applied to TNBC [42]. In addition, Fu et al. reported that the ginsenoside Rg3 effectively remodelled the immune microenvironment and that RG3 was associated with the reversal of drug resistance and the reduction of toxic side effects. The use of Rg3 may provide new hope for clinical treatment in the future [43] (Table 1).

Advances in triple-negative breast cancer biomarkers

In lung cancer and melanoma, the response to immunotherapeutic agents is better than that in other cancers, but the response of some tumours is generally moderate. This phenomenon cannot be separated from changes in the tumour immune microenvironment (TIME). On the basis of PD-L1 and TILs, the TIME can be classified as either "hot" or "cold", with different pathophysiological features; the "hot" type is characterized by a good immune response, including elevated PD-L1 positivity and increased density of tumour-infiltrating $CD8^+$ T cells and TILs, whereas the "cold" type is characterized by a lack of T cell activation and a poor response to

Table 1 Clinical trials using PD1/PD-L1 inhibitors in TNBC

Clinical trial	Year	Study design , Phase	Diagnostic criteria	Lines	Sample size	Trial drug	Primary endpoint	Main results
KEYNOTE-012	2016	Cohort, Ⅰb	Estrogen Receptor–negative, Progesterone Receptor–negative, HER2-negative, recurrent or metastatic breast cancer	Second line and above	111	Pembrolizumab	ORR	18.5%
KEYNOTE-086	2019	Cohort, Ⅱ	Cohort A: centrally confirmed mTNBC, ≥1 systemic therapy for metastatic disease, prior treatment with anthracycline and taxane in any disease setting; Cohort B: centrally confirmed mTNBC, no prior systemic anticancer therapy for metastatic disease	Cohort A: Second; Cohort B: First	170	Pembrolizumab	ORR	5.3%
KEYNOTE-522	2020	Randomized, Ⅲ	Centrally confirmed triple-negative breast cancer in all foci (as defined by the guidelines of the American Society of Clinical Oncology–College of American Pathologists); newly diagnosed, previously untreated, nonmetastatic disease	Neoadjuvant/adjuvant	602	Pembrolizumab	PCR	64.8%
IMpassion031	2020	Randomized, Ⅲ	Previously untreated stage II-III histologically documented TNBC	Neoadjuvant	333	Atezolizumab	PCR	58%
CamRelief	2024	Randomized, Ⅲ	Stage II or III invasive TNBC, no prior systemic therapy	Neoadjuvant	441	Camrelizumab	PCR	56.8%
IMpassion130	2018	Randomized, Ⅲ	Metastatic or inoperable locally advanced TNBC, no prior therapy for TNBC	First	451	Atezolizumab	PFS	7.2months
KEYNOTE-355	2020	Randomized, Ⅲ	Central determination of TNBC and PD-L1 expression, Previously untreated locally recurrent inoperable or metastatic disease	First	847	Pembrolizumab	PFS	9.7months
TORCHLIGHT	2024	Randomized, Ⅲ	Stage IV or recurrent/metastatic TNBC, no previous systemic therapy or only first-line cheterapy	First/Second	531	Toripalimab	PFS	8.4months
TBCRC 043	2024	Randomized, Ⅱ	Clinical stage IV or metastatic invasive TNBC negative for estrogen receptor (<10%), progesterone receptor (<10%), and ERBB2	First/Second	106	Atezolizumab	PFS	4.1months
CHANGEABLE	2024	Cohort, Ⅱ	MBC patients with histologically confirmed (suspected) pathogenic mutations in the germline of the DDR gene and previous chemotherapy line ≤2 (for metastatic disease)	Three lines and above	37	HX008+niraparib	ORR	78.6%

immunotherapy. Breast cancer is usually a "cold" tumour; however, TNBC is rated as a "hotter" breast cancer subtype because of its high TMB, PD-L1 expression and TILs [17, 44]. Therefore, identifying appropriate biomarkers may be a significant tool in the selection of treatment options for TNBC patients.

PD-L1

In many solid tumours, including advanced NSCLC, uroepithelial carcinoma and gastric cancer [45], PD-L1 has been considered a biomarker for predicting the efficacy of PD-1 and PD-L1 inhibitors. In TNBC, the KEYNOTE 012 and JAVELIN trials also confirmed the potential for PD-L1 patients to benefit from immunotherapy [20, 46]. Commonly used test kits for detecting PD-L1 include 22C3, 28 – 8, and SP263, along with DakoLink48 and the Ventana Benchmark. The Impassion130 study evaluated biomarkers as having significance in the 1st-line treatment of mTNBC by performing the Ventana SP142 IHC assay for testing PD-L1 expression (which is positive for PD-L1 when tumour-infiltrating immune cells [ICs] for any intensity of PD-L1 occupy ≥ 1% of the tumour area composed of both tumour cells and intratumoral and peripheral stroma). It was found that the PD-L1 + TNBC group demonstrated better PFS and OS, suggesting a potential predictive role for PD-L1 expression [47]. Multiple studies have since evaluated the predictive ability of various PD-L1 assays [48]. These findings suggest that the 22C3 and SP263 assays are better at screening populations that may benefit from immunotherapy. However, some studies have shown that SP142 is linked to clinical efficacy. As a result, on March 8, 2019, the FDA approved the SP142 assay kit as the diagnostic test most likely to predict benefit from the combination of atezolizumab and nab-paclitaxel. However, a recent IMpassion031 clinical trial demonstrated that atezolizumab in combination with neoadjuvant chemotherapy improved the rate of PCR in patients with early-stage TNBC, regardless of PD-L1 expression [24]. Similarly, in a randomized neoadjuvant therapy trial involving early-stage TNBC patients, those treated with chemotherapy and pembrolizumab had an increased PCR rate, which was independent of PD-L1 status. This may be attributed to dynamic changes in PD-L1 expression following neoadjuvant therapy, leading to differences in PD-L1 levels between the early and late stages of treatment [49]. These findings suggest that PD-L1 levels fluctuate during treatment and that PD-L1 expression in TNBC patients is not necessarily a criterion for the choice of immunotherapy regimen. It has been shown that immunotherapeutic expression is also associated with tissue origin. Szekely B et al. [50] compared two biomarkers, TILs and PD-L1, in metastatic tumours with primary breast cancer via IHC and reported that TIL counts and PD-L1 expression were reduced in metastases. In addition, Mariya Rozenblit [51] reported on 340 TNBC patients in whom PD-L1 was detected via the Foundation Medicine database and reported that PD-L1 positivity rates varied between metastatic sites and primary tumours, again confirming the above findings. Therefore, PD-L1 can ideally be tested for metastatic breast cancer or in primary breast tissue if testing is not effective [44].

TMB

TMB indicates the number of somatic mutations in the coding region of the tumour genome. Typically, a higher TMB results in more neoantigen products and is more readily recognized by the immune system, thus inducing an innate immune response. The TMB was shown to be a biomarker of ICI efficacy in melanoma and lung and colorectal cancers [52, 53]. The FDA promptly approved PD-1 inhibitors for solid tumours with high TMB (defined as ≥ 10 mut/mb) [54]. Although preliminary evidence suggests that high TMB may indicate a favourable response to ICIs in breast cancer, particularly in breast cancer, where TNBC and metastatic lesions with higher TMB are more likely to respond more favourably to ICIs, the statistical significance of this finding in a limited number of patients remains elusive [55]. A randomized trial investigating the effect of durvalumab in combination with anthracycline/paclitaxel chemotherapy in early TNBC patients revealed that the TMB was significantly greater in patients who achieved PCR regardless of the treatment group [56]. A study of TNBC patients was conducted to determine whether the TMB could predict the outcome of immunotherapy [57]. Patients with a high TMB had a nearly 9-month longer PFS. On the basis of these findings, researchers have suggested that the TMB may serve as a promising biomarker of immune efficacy. The investigators also reported that 59.2% of the high-TMB samples were characterized by APOBEC mutations, suggesting that TMB is a potential biomarker [55]. Although high TMB was approved by the FDA in 2020 as a biomarker for ICI therapy, its role in BC remains complex, and TMB alone may not fully predict remission [58]. There is still controversy regarding the predictive role of the TMB in BC. In recent studies, combining the TMB with other biomarkers has improved the predictive accuracy. The dual-marker combined determination method of blood tumour mutational burden (bTMB) and maximum somatic allele frequency (mSAF) has emerged as a promising way to predict the response to immunotherapy, with particular reference to advanced TNBC [59]. Notably, patients with low bTMB and mSAF values exhibited a significantly improved response to this regimen.

TILs

In recent years, increasing attention has been given to the field of immunotherapy because the TNBC immune microenvironment has been studied more intensively. TILs have become a significant biomarker in clinical tumour immunotherapy and can influence the treatment and prognosis of BC patients. TILs are lymphocytes that accumulate around the interstitium of neighbouring tissues or within the area of a lesion. For BC, TIL levels are greater in TNBC, and the other types of BC TILs are the lowest [60]. Many studies have evaluated BC TIL levels, and the results suggest that TILs have prognostic value and potential therapeutic value, especially in the context of neoadjuvant chemotherapy [61]. Interestingly, the evaluation of TILs in primary tumours in patients with TNBC receiving adjuvant or neoadjuvant chemotherapy as well as in patients with early-stage TNBC who are not receiving systemic therapy is also highly prognostic. Additionally, TILs can predict the response to TNBC immunotherapy, with higher TIL levels correlating with an improved overall response rate (ORR) in patients treated with pembrolizumab, as demonstrated in the KEYNOTE-086 study [22]. Similarly, in a study by KEYNOTE, 119 participants with high TIL levels achieved good clinical results with pembrolizumab [62]. However, the IMpassion 130 trial revealed that patients with TIL^+ tumours experienced clinical benefit (PFS/OS) only when their tumours were $PD\text{-}L1^+$ according to immunohistochemistry, confirming the importance of multimetric combinations [63]. Furthermore, TILs, especially high-density $CD8^+$ cytotoxic TILs, are positively correlated with immunotherapy. An early TNBC phase Ib clinical trial [64], KEYNOTE 173, evaluated neoadjuvant chemotherapy in combination with or without pembrolizumab monotherapy. This study revealed that higher mesenchymal expression levels of PD-L1 and TILs were associated with higher rates of overall remission and pathologic complete remission in early TNBC patients. Recent studies have indicated that specific TIL subpopulations and immunophenotypes may serve as the most reliable indicators of response. For example, $CD8^+$ intratumor TILs (iTILs) have been characterized as superior predictors of tumour immunogenicity than total sTILs [5]. $CD8^+$ tissue-resident memory (TRM) cells have also been investigated as potential biomarkers of ICI responses. For example, in mTNBC patients treated with pembrolizumab only, enriched $CD8^+$ TRM cell profiles predicted a favourable treatment response [65]. High levels of chemokines, DCs and STAT 1 signalling may be predictive of the TNBC response; for example, researchers have reported that the expansion of $MHCII^+$ and $CD8^+$ TCF 1^+ T cells is a primary indicator of the treatment response [66]. The predictive role of TILs in immunotherapy awaits further study.

Conclusions and outlook

Currently, the main reason for refractory treatment of TNBC is the lack of targets, and immune checkpoint inhibitors provide new hope for TNBC treatment. At present, JAVELIN, KEYNOTE-012 and other series have studied PD-1 and PD-L1 inhibitors, such as avelumab and pembrolizumab. Finally, researchers have shown that these drugs have a certain degree of safety. However, the therapeutic effect is limited. Therefore, PD-1 and PD-L1 inhibitors in combination with other treatment strategies have been studied extensively, and patients almost always benefit from both first-line and neoadjuvant therapy. The IMpassion130 clinical trial established atezolizumab monotherapy in combination with chemotherapeutic agents as a first-line treatment for $PD\text{-}L1^+$ TNBC. The KEYNOTE-355 study revealed that the combination of a pembrolizumab monoclonal antibody and chemotherapy was the first immunotherapy to prolong OS in TNBC patients, and pembrolizumab was added to the first-line treatment for mTNBC. In addition, the TORCHLIGHT study by Zefei Jiang's team revealed that torlipalimab monotherapy in combination with chemotherapy significantly improved PFS in patients, with an acceptable safety profile. In terms of neoadjuvant therapy, the combination chemotherapy KEYNOTE 522, Impassion031 and Impassion030 trials have demonstrated the great potential of PD-L1 inhibitors in the treatment of TNBC. With the development of medicine, in-depth research on PD-L1 inhibitors combined with targeted therapy has also been conducted. However, most related studies are still in the early clinical stage, providing only a new possibility and potential for the targeting of TNBC, and researchers need to further explore these agents for clinical application.

PD-1 and PD-L1 inhibitors have gradually become important treatment options for BC immunotherapy. However, the side effects of PD-1/PD-L1 inhibitors and drug resistance also need to be addressed [12]. Some findings have shown that the adverse effects of PD-1/PD-L1 inhibitors include their accumulation in multiple organs, such as the skin, liver, endocrine tract and gastrointestinal tract, and that skin toxicity is common. Rare toxicities include encephalitis and myocarditis. In addition, several potential biomarkers, such as the TMB, PD-L1 level, and TIL count, have gradually been approved for testing. Currently, the Impassion-130 study revealed that PD-L1 expression might have predictive value for clinical efficacy, and high TMB has been accelerated by the FDA for approval as a potential biomarker for PD-L1 inhibitors. Some studies have shown that TILs also have potential therapeutic and prognostic value, and the combined evaluation of PD-L1 and TILs is becoming a promising strategy. Notably, the subtypes of TNBC, including basal-like cells and mesenchymal-like stem cells, determine

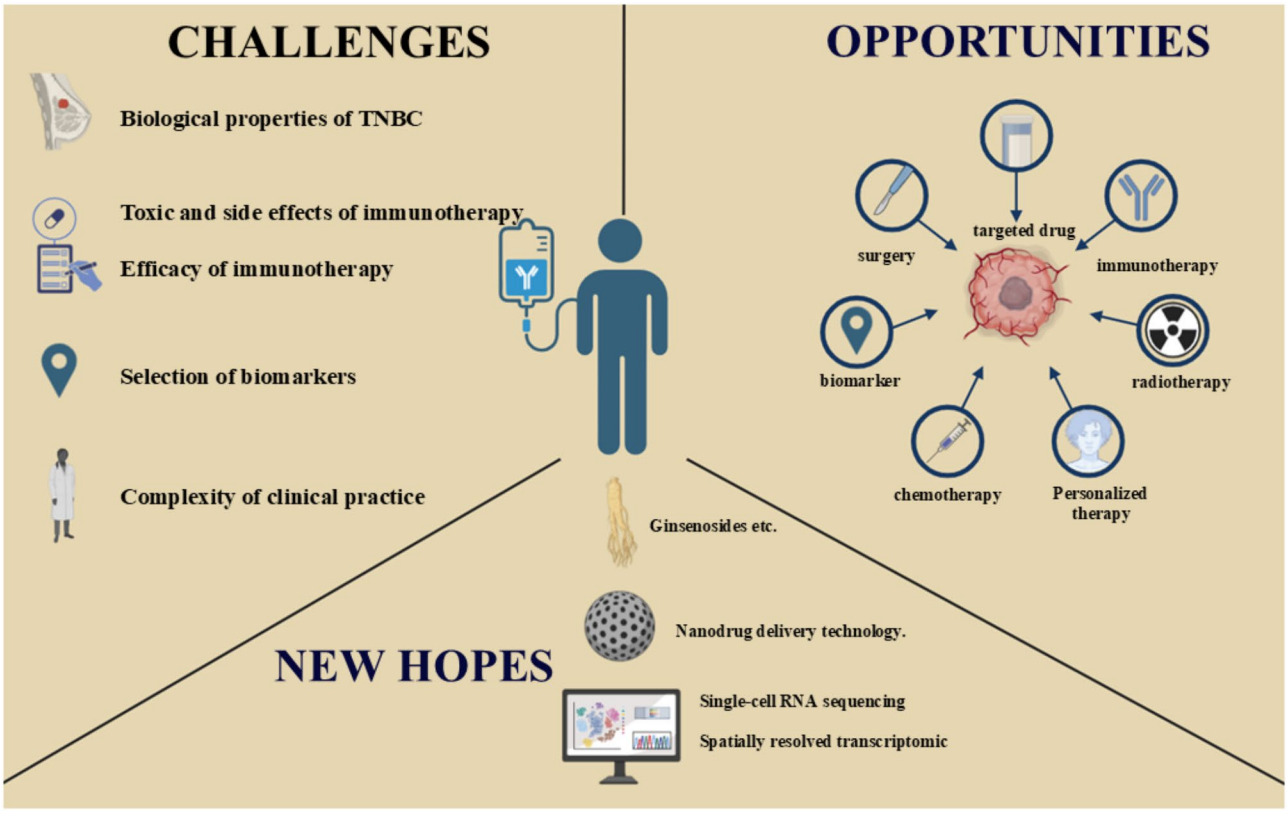

Fig. 2 PD-1/PD-L1 inhibitors' challenges and opportunities

the heterogeneity of TNBC, leading to different clinical outcomes. Therefore, reliable and thorough predictive TNBC biomarkers are still lacking, and further exploration of new biological markers is necessary.

In conclusion, the use of immunosuppressants in the treatment of TNBC still faces challenges. With input from a wide range of investigators, PD-1/PD-L1 inhibitors have entered clinical guidelines. These findings offer new opportunities to improve the therapeutic efficacy of TNBC treatment. With the development of new technologies, such as spatially resolved transcriptomics, single-cell RNA sequencing [67], nanotechnology [68] and exosome purification, novel markers, targeted drug delivery and remodelling of the immune microenvironment will offer new possibilities for improving the efficacy of immunotherapies and reducing drug resistance. In addition, RG3, a biological response modifier, can act as a regulator of the immune microenvironment. Through a series of complex biological processes, RG3 is able to transform 'cold' tumours with low immunogenicity into 'hot' tumours with high immunogenicity. This transformation process enables tumour cells to present richer biomarkers, which may provide new opportunities for improving the therapeutic efficacy of PD-1/PD-L1 inhibitors and for precision medicine in oncology (Fig. 2).

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Author H.L: Writing -Original Draft. Author Y.C: Writing-review & Editing. Author T.J(Corresponding Author): Funding Acquisition, Supervision. Author M.Z(Corresponding Author): Funding Acquisition, Supervision. All authors reviewed the manuscript.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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