Current situation of programmed cell death protein 1/programmed cell death ligand 1 inhibitors in advanced triple-negative breast cancer

Yuehua Liang, Xiaoran Liu, Kun Li, Huiping Li

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital & Institute, Beijing 100142, China

Correspondence to: Huiping Li. Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital & Institute, Beijing 100142, China. Email: huipingli2012@hotmail.com.

Abstract

Triple-negative breast cancer (TNBC) has the worst prognosis among all molecular types of breast cancer. Because of the strong immunogenicity of TNBC cells, programmed death 1/programmed death ligand 1 (PD-1/PD-L1) inhibitors, two kinds of immune checkpoint blockade agents, might help improve the prognosis of TNBC. However, how to better use PD-1/PD-L1 inhibitors and select patients who may benefit from treatment options remains controversial. This article summarizes published clinical studies in which PD-1/PD-L1 inhibitors were used in patients with advanced TNBC to explore how to maximize effectiveness of these medications.

Keywords: TNBC; PD-L1/PD-1; PD-L1/PD-1 inhibitor; immune checkpoint block

Submitted Mar 28, 2022. Accepted for publication Apr 26, 2022.
doi: 10.21147/j.issn.1000-9604.2022.02.07

View this article at: https://doi.org/10.21147/j.issn.1000-9604.2022.02.07

Introduction

Triple-negative breast cancer (TNBC) is a subtype of breast cancer that lacks estrogen receptor, progesterone receptor, and human epidermal growth factor 2 (HER2) overexpression or amplification as identified by immunohistochemistry or fluorescence in situ hybridization. Among patients with newly diagnosed breast cancer, about 15%–20% have TNBC (1). This subtype of breast cancer has a relatively dismal prognosis because of its rapid progression, early visceral involvement, and lack of specific therapeutic targets. Hormone receptor-positive, HER2-negative patients can be treated with aromatase inhibitors combined with cyclin-dependent kinase 4/6 inhibitors. Anti-HER2 monoclonal antibodies, antibody-drug conjugates, and small molecular tyrosine kinase inhibitors have also been developed for treatment of HER2-positive patients. Chemotherapy remains the main treatment strategy for TNBC, and a single-agent regimen or taxane-containing combination regimen is often used as first-line chemotherapy (2). Patients with TNBC have a high frequency of breast cancer susceptibility gene 1/2 (BRCA1/2) mutations, and poly(ADP-ribose) polymerase (PARP) inhibitors and platinum can improve the prognosis of patients harboring pathological BRCA1/2 mutations (3-5). Despite the benefits gained from treatment in certain patients with TNBC, the proportion of patients who benefit is relatively small; thus, more active treatment options are needed for TNBC population. Recent studies have shown a high degree of immune cell (IC) infiltration inside the tumor microenvironment (TME) caused by high immunogenicity of TNBC and high percentage of tumor cells with programmed death ligand 1 (PD-L1) expression. This makes patients with TNBC more sensitive to immune checkpoint blockade (ICB) therapy (6-10). The present article summarizes recently published clinical studies using programmed death 1 (PD-1)/PD-L1 inhibitors in patients with advanced TNBC (aTNBC) to explore how to maximize the effectiveness of these medications.
Foundation of immunotherapy of TNBC

Antitumor immunity

During the acute inflammatory phase, tumor cells undergo necrosis and release tumor antigens. Antigen-presenting cells then process and present these antigens on their surface by major histocompatibility complex class I (MHC I) molecules. The T-cell receptor (TCR) recognizes the antigen peptide-MHC complex, and the CD3 molecule then noncovalently bonds with the TCR to form a TCR-CD3 complex.

The activation signal generated by the combination of TCR and antigen is transmitted into the cell by the CD3 molecule to mediate T-cell activation; this is the activation signal of CD8+ T cells (11). Activation of T cells also depends on costimulation of the B7-CD28 complex formed by the noncovalent bond between CD28 molecules of T cells and ligands (B7) of antigen-presenting cells (12). CD28-mediated costimulatory signals can induce T-cell differentiation, proliferation, and secretion of cytokines. Tumor-infiltrating lymphocytes (TILs) specifically kill tumor cells by releasing perforin and granzyme, allowing tumor antigens to be exposed and recognized by antigen-presenting cells again and thus forming positive-feedback immune circulation of T cells.

As the tumor evolves, TME is established and chronic inflammation gradually develops. In the TME, several factors contribute to the weakness of the immune system and the functional exhaustion state of cytotoxic T lymphocytes, including 1) infiltration of immunosuppressive cells, such as regulatory T cells and marrow-derived suppressor cells; 2) overexpression of immune checkpoint molecules on the surface of tumor cells; 3) activation of immunosuppressive signal pathways in immune effector cells; and 4) hypoxia and a high-lactate environment, leading to impaired T-cell function (13,14).

PD-1/PD-L1 molecules and PD-1/PD-L1 inhibitors

Under physiological conditions, immune checkpoints play an extremely important role in maintaining immune tolerance. By abnormally expressing ligands that normally interact with immunosuppressive receptors, tumors can exploit immune checkpoint molecules to protect themselves from being eliminated by the host’s immune system (15). This is a new strategy of tumor treatment that blocks immune checkpoints and activates cellular immunity against cancer cells. The PD-1/PD-L1 signaling pathway is one of the most important immune checkpoint pathways that exerts immunosuppressive effects. When T cells infiltrate into the TME, tumor cells induce high PD-1 expression on the surface of T cells. The binding of PD-1 and PD-L1 inhibits the proliferation and activation of T cells and even leads to programmed T-cell death (Figure 1A). Tumor cells escape the host’s immune system and thrive (Figure 1B). PD-1 inhibitors bind to PD-1 molecules on the surface of T cells; likewise, PD-L1 inhibitors bind to PD-L1 molecules on the surface of tumor cells. Both stop the noncovalent binding of PD-1 and PD-L1 molecules, thereby restoring the tumor recognition and killing function of T cells (Figure 1C,D).

PD-1/PD-L1 inhibitors plus chemotherapy

Chemotherapy drugs and immunotherapy drugs may have a synergistic effect on the process of treating tumors. Chemotherapy drugs cause immunogenic cell death of tumor cells. This process is accompanied by the release of tumor antigens and damage-associated molecular patterns in TME. At the same time, chemotherapy can also regulate tumor immunity through nonimmunogenic cell death mechanisms, such as augmenting the expression of costimulatory molecules on the tumor cells; downregulating the expression of coinhibitory molecules, thereby promoting the activity of dendritic cells and the cross-presentation of antigens; eliminating the activity of immunosuppressive cells (such as marrow-derived...
suppressor cells and regulatory T cells); enhancing the recognition and lysis of tumor cells; and regulating antitumor CD4+ T cells. These mechanisms can disrupt the trajectory of the tumor’s escape from recognition by the immune system. Another approach is to properly design drugs, doses, and chemotherapy administration schedules related to antigen exposure or release, thus maximizing the patient’s immune function and mobilizing the immune system to exert an antitumor effect after using PD-1/PD-L1 inhibitors (16,17).

**PD-1/PD-L1 inhibitors plus PARP inhibitors**

**BRCA1** and **BRCA2** are two tumor suppressor genes that repair double-strand DNA damage through homologous recombination. **BRCA1/2** mutations lead to defects in homologous recombination repair, increasing genomic instability and accumulation of transforming mutations. PARP inhibitors prevent single-strand DNA damage from being repaired. The use of PARP inhibitors in patients with **BRCA1/2** gene mutation causes the accumulation of DNA lesions and induces cell apoptosis, a phenomenon known as synthetic lethality. Patients harboring **BRCA1** mutation are sensitive to treatment containing PARP inhibitors (18). Chromosome instability and DNA repair defects lead to accumulation of cytoplasmic DNA. The immune system can use pattern recognition receptors to recognize damage-associated molecular patterns such as cytoplasmic DNA and recruit and activate stimulator of interferon genes to promote the expression of interferon and other proinflammatory factors. At the same time, DNA damage promotes the occurrence of type I immune response. DNA damage can also lead to activation of nuclear factor kappa B, release of inflammatory cytokines, and increased lymphocyte infiltration. **BRCA1/2** mutations are associated with increased PD-L1 expression on tumor cells and increased T-cell infiltration into the TME. Moreover, DNA damage-repair drugs can change immunogenicity inside the tumor by inducing upregulation of inducible T-cell costimulatory ligands and MHC I molecules. Patients who have TNBC with intensive expression of PD-1/PD-L1 and higher frequency of **BRCA1** mutations may benefit from combination therapy that includes both PD-1/PD-L1 inhibitors and PARP inhibitors (19).

**PD-1/PD-L1 inhibitors plus vascular endothelial growth factor receptor 2 (VEGFR2) inhibitors**

Combination of VEGFR2 inhibitors and immune checkpoint therapy may provide a new approach to the treatment of PD-L1-negative TNBC. Preclinical trials have shown that the use of angiogenesis inhibitors can increase the infiltration of CD8+ T cells in TME, leading to a stronger antitumor effect. Moreover, angiogenesis inhibitors can enhance the expression of PD-L1, which may make patients who have TNBC with low PD-L1 expression more sensitive to PD-1 inhibitor therapy (20).

**Clinical research focusing on PD-1/PD-L1 inhibitors**

Below, we summarize some clinical trials of PD-1/PD-L1 inhibitors in the treatment of TNBC published from 2016 to 2021 to explore the response of patients with TNBC to PD-1/PD-L1 inhibitor treatment and evaluate whether the expression status of PD-L1 on either tumor cells or ICs impacts the treatment outcome of PD-1/PD-L1 inhibitors.

**Single-agent PD-1/PD-L1 inhibitor therapy**

**PD-L1 inhibitors**

SAFIR02-BREAST IMMUNO and JAVELIN are two trials that showed the antitumor effects of single-agent PD-L1 inhibitor therapy. Before the results of SAFIR02-BREAST IMMUNO were reported, the efficacy of single-agent PD-L1 inhibitor therapy as maintenance therapy in the treatment of advanced breast cancer was still unknown (21,22). The study showed that PD-1/PD-L1 inhibitors can have a better antitumor effect after the tumor volume is reduced by previously administered cytotoxic drugs. Durvalumab significantly prolonged the median overall survival (mOS) of patients with TNBC by about 7 months compared with maintenance chemotherapy (21.2 vs. 14.0 months, P=0.0377). In JAVELIN, mOS of the TNBC subgroup was 9.2 months. All patients in SAFIR02-BREAST IMMUNO were chemotherapy-sensitive, whereas patients in JAVELIN were refractory or had progressed after standard-of-care therapy, indicating a better response to PD-L1 inhibitors in patients with chemotherapy-responsive TNBC. Apart from this, a survival advantage of early administration of PD-L1 inhibitors was supported by the clinical activity result of a phase I study (mOS of 17.6 vs. 7.3 months in patients receiving atezolizumab as first-line vs. second-line treatment, respectively) (23).

In the subgroup analysis of patients with TNBC in SAFIR02-BREAST IMMUNO, single-agent durvalumab prolonged the mOS of patients with PD-L1-positive metastatic TNBC by about 1 year. This illustrated a
clinical advantage of using single-agent durvalumab as maintenance therapy in patients with a high percentage of ICs expressing PD-L1 on their surface in the TME. The objective response rate (ORR) of patients with TNBC in JAVELIN was 22.2% in the PD-L1-positive subset (≥10% of ICs expressing PD-L1) and 2.6% in the PD-L1-negative subset. This demonstrated the powerful antitumor activity of PD-L1 inhibitors in the PD-L1-positive population. Two different thresholds for dividing PD-L1 expression (1%/10%) as the categorical factor for AFIR02-BREAST IMMUNO and JAVELIN were set in NCT01375842 (23), in which both patients with at least 1% ICs and those with at least 10% ICs expressing the PD-L1 molecule exhibited longer OS than the rest of patients with TNBC (10.1 vs. 6.0 months and 12.6 vs. 6.7 months, P=0.002 and P=0.006, respectively). This supports the viewpoint that the percentage of ICs expressing PD-L1 and each patient’s individual response to PD-L1 inhibitors are positively correlated, indicating the percentage of ICs expressing PD-L1 as a selection criterion for screening potential patients suitable for PD-L1 inhibitor treatment.

**PD-L1 inhibitors**

As the first trial to reveal the clinical activity of single-agent pembrolizumab for patients with heavily pretreated aTNBC, KEYNOTE-012 showed that ORR, median progression-free survival (mPFS), and mOS were 18.5%, 1.9 months, and 11.2 months, respectively, providing evidence for the correlation between a higher percentage of tumor cells expressing PD-L1 and a better clinical response (24). Soon afterwards, in cohort A of the phase II KEYNOTE-086 study involving 170 patients with TNBC, 43.5% of patients received ≥3 previous lines of therapy for advanced breast cancer (25). The mPFS of cohort A was 2.0 months in the PD-L1-positive setting [combined positive score (CPS) of ≥1] vs. 1.9 months in the PD-L1-negative setting. The mOS was 8.8 vs. 9.7 months. It seems that PD-L1 inhibitors did not show an advantage with respect to mOS or mPFS in the heavily treated population, especially in the PD-L1-positive population. Patients with heavily treated TNBC in KEYNOTE-119 were recruited to assess the clinical response to pembrolizumab monotherapy compared with investigator-choice chemotherapy, making up for the limitation of KEYNOTE-086 without setting a comparison (26). No significant improvement was detected in the ORR, mPFS, or mOS in overall patients or in patients with a CPS of ≥1 or ≥10. However, in the post-hoc analysis of patients with a CPS of ≥20, a greater response was elicited by single-agent pembrolizumab, confirming that prolongation of OS was closely associated with a higher CPS. Both KEYNOTE-086 (cohort A) and KEYNOTE-119 showed a modest ORR of 5.3% and 9.6%, respectively, similar to first-line single-agent chemotherapy, whereas cohort B of KEYNOTE-086 (which enrolled patients who received ≤3 previous lines of therapy) showed an ORR of 21.4%, illustrating an improved clinical benefit of early administration of PD-L1 inhibitors (27). Moreover, cohort B of KEYNOTE-86 showed an mOS of 18 months in the PD-L1 population, which is longer than the mOS (9.2 months) of JAVELIN (using avelumab as its medication component) (22). In addition to different drugs used in the two trials, differences in the follow-up times may have also contributed to this phenomenon. The follow-up time in KEYNOTE-068 ranged from 0.9 to 23.5 months, and that in JAVELIN ranged from 6 to 15 months.

**Combination use of PD-1/PD-L1 inhibitors**

**PD-L1 inhibitors + chemotherapy**

The synergistic effect of immunotherapy and chemotherapy has been confirmed by data from clinical studies. Among them, the most far-reaching clinical study that provides strong support for the effectiveness of chemotherapy combined with immunotherapy in patients with TNBC is IMpassion130 (28). The results of the first interim analysis are as follows. In the intent-to-treat (ITT) setting, the mPFS was 7.2 months in patients receiving atezolizumab plus nab-paclitaxel (A+nP) vs. 5.5 months in patients receiving placebo plus nab-paclitaxel (P+nP) (P=0.002). In PD-L1-positive subgroup (≥1% PD-L1 expression on TILs as a percentage of the tumor area), the mPFS was 7.5 vs. 5.0 months (P<0.001). The mOS in ITT group was 21.3 vs. 17.6 months (P=0.08). In the second interim analysis (median follow-up time of 18.5 months), the mOS was 21.0 and 18.7 months, respectively (P=0.078) (29). The final result of IMpassion130 documented an mOS of 21.0 months (A+nP) vs. 18.7 months (P+nP) in the ITT population and 25.4 months (A+nP) vs. 17.9 months (P+nP) in the PD-L1-positive population (30). In the exploratory analysis, A+nP prolonged mPFS across all groups. The OS benefit in the ITT population was not statistically significant, but a clinically meaningful OS benefit was observed in the PD-L1-positive population, indicating a reasonable care strategy for patients with PD-L1-positive tumors. This was also confirmed by a meta-analysis (31). Commensurate results were also obtained in an analysis of an Asian subgroup (32), indicating that Asians can also benefit from such treatments. Atezolizumab plus
nab-paclitaxel was also administered to patients with TNBC in a phase Ib analysis with a 2-year survival follow-up (33). However, IMpassion131 (34) suggested that the treatment strategy of atezolizumab plus paclitaxel did not benefit patients with aTNBC, which differs from the results of IMpassion130 (28-30,32). In IMpassion131, the mPFS in ITT population was 5.7 months in the atezolizumab group vs. 5.6 months in the placebo group (not formally tested). The mOS was 19.2 months in the atezolizumab group vs. 22.8 months in the placebo group; this clinical activity was consistent with that in another clinical trial (paclitaxel as the backbone of chemotherapy plus durvalumab) showing an mPFS and mOS of 5.0 and 20.7 months, respectively (35). In IMpassion131, paclitaxel was probably chosen as the backbone of chemotherapy and a steroid was administered together with paclitaxel during chemotherapy, leading to the limited therapeutic effect of atezolizumab. Another analysis revealed that paclitaxel was able to specifically exterminate ICs that shoulder the main antitumor task, impairing the effectiveness of ICB therapy (36). This may be a rational explanation for the unfavorable response to paclitaxel plus atezolizumab in patients with TNBC. In addition, the patients’ baseline characteristics slightly differ between the two studies. Patients in IMpassion131 were more likely to be exposed to the same taxane, and IMpassion131 incorporated more Asian patients and fewer patients with de novo metastasis.

IMpassion130 established nab-paclitaxel plus atezolizumab as a new treatment strategy for patients with aTNBC and led the United States Food and Drug Administration (FDA) and European Medicines Agency to approve nab-paclitaxel plus atezolizumab as first-line treatment for unresectable local aTNBC (37). However, the manufacturer (Roche, Basel, Switzerland) withdrew the TNBC indication for atezolizumab after talks with the FDA (38). Additionally, the treatment failure in IMpassion131 led to withdrawal of approval of atezolizumab with paclitaxel for previously untreated metastatic TNBC (39).

PD-1 inhibitors + chemotherapy
Chemotherapy used in one study contained nab-paclitaxel, paclitaxel, and gemcitabine plus carboplatin in an effort to examine the antitumor effect displayed by taxane/non-taxane-based and platin/non-platin-based regimens in KEYNOTE-355 in untreated aTNBC patients (40). The mPFS of patients with a CPS of ≥10 was 9.7 months in the pembrolizumab plus chemotherapy group and 5.6 months in the placebo plus chemotherapy group (P=0.0014). Among patients with a CPS of ≥1, the mPFS was 7.6 vs. 5.6 months (P=0.0014, which did not reach the threshold of 0.00111) and 7.5 vs. 5.6 months in the ITT population. Adding pembrolizumab to standard chemotherapy improved mPFS of patients with TNBC in all subgroups. As the CPS increased, the mPFS gradually increased in the pembrolizumab plus chemotherapy population. Unlike the results from IMpassion130 and IMpassion131, in KEYNOTE-355, the combination of pembrolizumab plus paclitaxel was not inferior to nab-paclitaxel plus pembrolizumab in the subgroup analysis. The reason for this phenomenon may be that the median follow-up time in KEYNOTE-355 was longer than that in IMpassion131. In KEYNOTE-355, the Kaplan-Meier curves of the experimental group and the control group overlapped at the initial stage. As the follow-up time increased, the tendency of the two curves to separate became more obvious. Concerning the treatment for pre-treated aTNBC patients, TONIC trial recorded an ORR of 23% in the cisplatin cohort and 35% in the doxorubicin cohort (41), longer than that in KEYNOTE-086 (cohort A), KEYNOTE-012 and JAVELIN. The prime use of chemotherapeutic drugs may increase the extent of lymphocyte infiltration within the TME and upregulate immune-related genes involved in the PD-1/PD-L1 and T-cell cytotoxicity pathways, explaining a better response in the TONIC study than in the KEYNOTE-086 (cohort A), KEYNOTE-012 and JAVELIN.

As the CPS increased, mPFS gradually increased in the pembrolizumab plus chemotherapy population in KEYNOTE-355. To increase the efficacy of ICB therapy in patients with a high CPS, we chose trials with a relatively large sample size and available hazard ratio for mPFS in the subgroup analysis; the data of these trials are shown in Figure 2. In Figure 2, we can see that single-agent pembrolizumab shows its advantages in patients with CPS≥20. The combination of pembrolizumab and chemotherapy has shown efficacy advantages even in the ITT population. It not only illustrates that the enrichment of PD-L1 molecules in the TME can exert the superiority of PD-1 inhibitors, but also exhibits preponderance of combination of chemotherapy and PD-1 inhibitors over single-agent PD-1 inhibitor.

PD-1 inhibitors + PARP inhibitors
In addition to chemotherapeutic drugs, the synergy between PARP inhibitors and immune checkpoint antagonists has promoted the development of clinical studies on the combined use of the two drugs. MEDIOLA
included patients with germline BRCA1/2-mutated advanced breast cancer with no restriction on the hormone receptor expression status and two or fewer previous lines of chemotherapy (42). Single-agent durvalumab therapy was performed first, followed by a combination of olaparib and durvalumab until disease progression. The mPFS was 8.2 months in the overall population, similar to that in the OlympiAD trial (7 months for patients with olaparib monotherapy) (43). In the TNBC subset, the mPFS was only 4.9 months. Despite the poor prognosis, the imbalance of more first-line patients in the TNBC subgroup was responsible for the short mPFS (several nonresponders with early disease progression were included). The mOS was 21.5 months in the overall group and 20.5 months in the TNBC subgroup, which was numerically similar to the results of IMpassion130. The mOS of patients with one or fewer lines of chemotherapy was 23.4 months vs. 16.9 months in patients with two lines of chemotherapy, supporting an advantage of early use of durvalumab and olaparib. Notably, a remarkable ORR of 80% was documented in patients with ≥1% PD-L1-positive tumor cells. Thus, PARP inhibitors plus PD-L1 inhibitors were extremely effective in patients with a high percentage of PD-L1-positive tumor cells in the TME. Details of these trials are listed in Table 1. Because of the small sample of patients with ≥1% PD-L1-positive tumor cells, these results should be interpreted with caution, and further investigation should be performed to verify the conclusion.

**PD-1 inhibitors + PARP inhibitors**

TOPACIO/KEYNOTE-162 revealed the efficacy of a combination of PARP inhibitors and PD-1 inhibitor in patients with TNBC (44). This was a phase II clinical trial involving 55 patients with TNBC. Patients were given 200 mg of niraparib and 200 mg of pembrolizumab on the first day of each 21-day cycle. The ORR was 21% among 47 patients evaluated for effectiveness. In the exploratory subgroup analysis, ORR was 32% and 8% in the PD-L1-positive subgroup (CPS of ≥1%) and PD-L1-negative subgroup (CPS of <1%), respectively (Table 2). Without formal validation, a numerical difference was observed between the two groups. The mPFS of patients with BRCA mutation was 8.3 months, which is longer than that in the TNBC subgroup in MEDIOLA (with no consideration of deviation of BRCA mutation status during the analysis). TOPACIO revealed the superiority of niraparib plus pembrolizumab for improving PFS of patients who had TNBC with germline BRCA mutations.

To the best of our knowledge, MEDIOLA is the first trial to verify the effect of joint use of a PARP inhibitor and PD-L1 inhibitor in both patients with TNBC and patients with hormone receptor-positive breast cancer, whereas KEYNOTE-162 is the first clinical trial to focus on the effect of a combination of a PARP inhibitor and PD-1 inhibitor only in patients with TNBC. The results of these studies provide a new therapeutic schedule for patients with aTNBC, especially those with germline BRCA mutations. Starting treatment earlier can produce a better treatment effect.

**PD-1 inhibitors + VEGFR2 inhibitors**

VEGFR2 inhibitors plus immune checkpoint therapy may provide a new approach to the treatment of PD-L1-negative TNBC. A phase II clinical trial was designed to evaluate whether camrelizumab plus apatinib could benefit patients with TNBC (20). In patients who received continuous dosing of apatinib, the ORR was 43.3% (13 of 30). Compared with single-agent PD-1/PD-L1 inhibitor therapy in patients with aTNBC who had a limited ORR ranging from 5.2% to 21.4%, the combination of camrelizumab and apatinib doubled ORR in patients with TNBC regardless of the PD-L1 expression status, demonstrating favorable efficacy even in patients with PD-L1-negative TNBC (Table 2). Because of the small sample size of this trial, another trial with a larger sample size should be performed to further evaluate the effectiveness of this combination treatment.
| Study                         | Drugs                        | Subgroup | No.  | ORR (%) | mPFS (month) | mOS (month) |
|------------------------------|------------------------------|----------|------|---------|--------------|-------------|
| SAFIR02-BREAST (21)          | Durvalumab vs. maintenance chemotherapy | MBC      | 131 vs. 68 | NA       | 2.7 vs. 4.6 | 21.8 vs. 17.9 |
|                              |                              | TNBC     | 47 vs. 35 | NA       | NA          | 21.2 vs. 14.0 |
|                              |                              | PD-L1+IC≥1% | 18 vs. 14 | NA       | NA          | 27.3 vs. 12.1 |
|                              |                              | PD-L1+IC<1% | 17 vs. 12 | NA       | NA          | 19.5 vs. 14.0 |
| JAVELIN (22)                 | Avelumab                     | MBC      | 168    | 3.0     | 5.9          | 8.1         |
|                              |                              | TNBC     | 58     | 5.2     | 5.9          | 9.2         |
|                              |                              | PD-L1+IC≥10% (MBC) | 12     | 16.7    | 6.1          | 11.3        |
|                              |                              | PD-L1+IC<10% (MBC) | 124    | 1.6     | 5.9          | 6.8         |
|                              |                              | PD-L1+TC≥1% vs. <1% (MBC) | 85 vs. 51 | 2.4 vs. 3.9 | 5.9 vs. 6.0 | 6.5 vs. 8.3 |
|                              |                              | PD-L1+TC≥5% vs. <5% (MBC) | 23 vs. 113 | 4.3 vs. 2.7 | 6.0 vs. 5.9 | 6.5 vs. 7.5 |
|                              |                              | PD-L1+TC≥25% vs. <25% (MBC) | 3 vs. 133 | 0 vs. 3.0  | 6.0 vs. 5.9 | 9.2 vs. 6.8 |
| NCT01375842                 | Atezolizumab                  | TNBC     | 115    | 10.0    | 1.4          | 8.9         |
|                              |                              | TNBC (first line) vs. TNBC (second line) | 21 vs. 94 | 24.0 vs. 6.0 | 1.6 vs. 1.4 | 17.6 vs. 7.3 |
|                              |                              | PD-L1+ (IC≥1%) vs. PD-L1− (IC<1%) | 21 vs. 91 | 0 vs. 11.0 | 1.4 vs. 1.4 | 10.1 vs. 6.0 |
|                              |                              | PD-L1+ (IC≥5%) vs. PD-L1− (IC<5%) | 38 vs. 74 | 5.0 vs. 12.0 | 1.8 vs. 2.0 | 10.5 vs. 7.0 |
|                              |                              | PD-L1+ (IC≥10%) vs. PD-L1− (IC<10%) | 54 vs. 56 | 7.0 vs. 13.0 | NA          | 12.6 vs. 6.7 |
| NCT01633970                 | Atezolizumab + nab-paclitaxel | TNBC     | 33     | 39.4    | 5.5          | 14.7        |
|                              |                              | TNBC (first line) vs. TNBC (≥ second line) | 13 vs. 20 | 53.8 vs. 30.0 | 8.6 vs. 5.1 | 24.2 vs. 12.4 |
|                              |                              | PD-L1+ (IC≥1%) vs. PD-L1− (IC<1%) | 12 vs. 12 | 41.4 vs. 33.3 | 6.9 vs. 5.1 | 21.9 vs. 11.4 |
| IMpassion130 (28)*          | Nab-paclitaxel + atezolizumab/placebo | ITT      | 451 vs. 451 | 56.0 vs. 45.9 | 7.2 vs. 5.5 | 21.3 vs. 17.6 |
|                              |                              | PD-L1+ (PD-L1+IC≥1%) | 185 vs.184 | 58.9 vs. 42.6 | 7.5 vs. 5.0 | 25.0 vs. 15.5 |
| IMpassion130 (29)**         | Nab-paclitaxel + atezolizumab/placebo | ITT      | 451 vs. 451 | 56.0 vs. 45.9 | 7.2 vs. 5.5 | 21.0 vs. 18.7 |
|                              |                              | PD-L1+ (PD-L1+IC≥1%) | 185 vs.184 | 58.9 vs. 42.6 | 7.5 vs. 5.0 | 25.0 vs. 18.0 |
| IMpassion130 (30)*          | Nab-paclitaxel + atezolizumab/placebo | ITT      | 451 vs. 451 | 56.0 vs. 45.9 | 7.2 vs. 5.5 | 21.0 vs. 18.7 |
| IMpassion130 (32) (Japanese) | Nab-paclitaxel + atezolizumab/placebo | ITT      | 34 vs. 31  | 67.6 vs. 51.6 | 7.4 vs. 4.6 | NA vs. 16.8 |

Table 1 (continued)
Differences between PD-1 inhibitors and PD-L1 inhibitors

In a meta-analysis of 19 randomized clinical trials, patients treated with PD-1 inhibitors showed better OS and PFS than patients treated with PD-L1 inhibitors (45). This may have been due to the different targets of PD-1 inhibitors and PD-L1 inhibitors. PD-1 inhibitors impede both the binding of PD-1 and PD-L1 and the binding of PD-1 and PD-L2, whereas PD-L1 inhibitors only inhibit the binding of PD-1 and PD-L1. Studies have shown that PD-L2 and PD-1 interaction may inhibit TCR-mediated immune responses, making PD-L1 inhibitors less effective than PD-1 inhibitors (46). The above-mentioned meta-analysis showed no significant differences in safety. Another meta-analysis also showed similar overall adverse event rates for PD-1 and PD-L1 inhibitors. However, the incidence of pneumonia was significantly higher with PD-1 inhibitors than with PD-L1 inhibitors (4% and 2%, respectively; P=0.01) (47). PD-1 inhibitors were also associated with a higher mean incidence of grade ≥3 adverse events than PD-L1 inhibitors (48). We found no studies comparing the responsiveness of PD-1 inhibitors and PD-L1 inhibitors only in patients with TNBC, and we look forward to the emergence of such studies.

Biomarkers associated with response

The expression levels of PD-L1 molecules in tumor cells, ICs, and TME, as well as phenomena such as mismatch repair deficiency and microsatellite instability, can be used as detection methods for screening patients that may benefit from immune checkpoint therapy (49,50). The FDA has approved pembrolizumab for patients with microsatellite instability (51), indicating the patency of microsatellite instability as a biomarker for selecting patients sensitive to PD-1 inhibitors. However, these methods still have limitations. Studies have shown that the methylation status of PD-L1, PD-1, and PD-L2 may be related to the responsiveness of patients with TNBC to ICB therapy. At the same time, gene methylation is a stable epigenetic process and can be detected in small-volume samples, such as those from patients with advanced cancer (52). This provides a new idea for the establishment of

| Study | Drugs | Subgroup | No. | ORR (%) | mPFS (month) | mOS (month) |
|-------|-------|----------|-----|---------|--------------|-------------|
| NCT02628132 (35) | Durvalumab + weekly paclitaxel | TNBC | 12 vs. 13 | PD-L1+ (PD-L1+IC≥1%) | 75.0 vs. 53.8 | 10.8 vs. 3.8 | NA vs. 13.3 |
| IMpassion131 (34) | Paclitaxel + atezolizumab/placebo | ITT | 431 vs. 220 | PD-L1+ (PD-L1+IC≥1%) | 43.0 vs. 36.0 | 6.0 vs. 5.7 | 19.2 vs. 22.8 |
| MEDIOLA (42) | Durvalumab + olaparib | Overall population | 34 | TNBC | 63.3 | 8.2 | 21.5 |
| | | Hormone receptor positive | 17 | 58.5 | 4.9 | 20.5 |
| | | 0–1 prior lines | 20 | 70.0 | 11.7 | 23.4 |
| | | 2 prior lines | 10 | 50.0 | 6.5 | 16.9 |
| | | PD-L1+ TC≥1% vs. <1% | 10 vs. 17 | 80.0 vs. 52.9 | 6.7 vs. 8.2 | 23.9 vs. 18.8 |
| | | PD-L1+ IC≥1% vs. <1% | 17 vs. 10 | 64.7 vs. 60.0 | 6.7 vs. 8.2 | 21.5 vs. 16.9 |
| | | CD3 TILs≥458/mm² vs. <458/mm² | 13 vs. 13 | 53.8 vs. 61.5 | 6.7 vs. 8.3 | 19.2 vs. 19.2 |
| | | CD8 TILs≥458/mm² vs. <458/mm² | 13 vs. 12 | 61.5 vs. 58.3 | 9.9 vs. 7.2 | 23.9 vs. 18.6 |
| | | BRCA1 mutation | 14 | 64.3 | 4.9 | 19.2 |
| | | BRCA2 mutation | 16 | 62.5 | 9.9 | 21.5 |

PD-L1, programmed cell death ligand 1; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; aTNBC, advanced triple-negative breast cancer; MBC, metastatic breast cancer; ITT, intention-to-treatment; NA, not available; CPS, combined positive score; IC, immune cell; TILs, tumor infiltrating lymphocytes; *, the first interim analysis; **, the second interim analysis; *, final OS analysis.

Table 1 (continued)
screening immunotherapy-sensitive patients. In addition, the concentration of PD-L2 molecules in extracellular vesicles of tumors was associated with 3-year PFS and OS, suggesting that the concentration of PD-L2 molecules in

| Study           | Drugs                  | Subgroup                               | No.   | ORR (%) | mPFS (month) | mOS (month) |
|-----------------|------------------------|----------------------------------------|-------|---------|--------------|-------------|
| KEYNOTE-012 (24)| Pembrolizumab          | TNBC                                   | 27    | NA      | 1.9          | 11.2        |
| KEYNOTE-086(A) (25) | Pembrolizumab            | mTNBC                                  | 170   | 5.3     | 2.0          | 9.0         |
|                 |                        | PD-L1+ (CPS≥1)                         | 105   | 5.7     | 2.0          | 8.8         |
|                 |                        | PD-L1− (CPS<1)                         | 64    | 4.7     | 1.9          | 9.7         |
| KEYNOTE-086(B) (27) | Pembrolizumab     | TNBC                                   | 84    | 21.4    | 2.1          | 18.0        |
| KEYNOTE-119 (26) | Pembrolizumab/ single-agent chemotherapy | TNBC (Pemb) vs. TNBC (chemo) | 312 vs. 310 | 9.6 vs. 10.6 | 2.1 vs. 3.3 | 9.9 vs. 10.8 |
|                 |                        | PD-L1+ (CPS≥1) (Pemb vs. chemo)        | 203 vs. 202 | 12.0 vs. 9.0 | 2.1 vs. 3.1 | 10.7 vs. 10.2 |
|                 |                        | PD-L1+ (CPS≥10) (Pemb vs. chemo)       | 96 vs. 98  | 18.0 vs. 9.0 | 2.1 vs. 3.4 | 12.7 vs. 11.6 |
|                 |                        | PD-L1+ (CPS≥20) (Pemb vs. chemo)       | 57 vs. 52  | 26.0 vs. 12.0 | 3.4 vs. 2.4 | 14.9 vs. 12.5 |
| KEYNOTE-355 (40) | Chemotherapy + pembrolizumab/placebo | ITT                               | 566 vs. 281 | 40.8 vs. 37.0 | 7.5 vs. 5.6 | 17.2 vs. 15.5 |
|                 |                        | PD-L1+ (CPS≥1)                         | 425 vs. 211 | 44.9 vs. 38.9 | 7.6 vs. 5.6 | 17.6 vs. 16.0 |
|                 |                        | PD-L1+ (CPS≥10)                        | 220 vs. 103 | 52.7 vs. 40.8 | 9.7 vs. 6.5 | 23.0 vs. 16.1 |
| TONIC (41)      | Nivolumab+ 1) without induction or with 2-week low-dose induction/2) irradiation (3 x 8 Gy)/2) cyclophosphamide/4) cisplatin/5) doxorubicin | Overall cohort | 66   | 20      | 1.9          | NA          |
|                 |                        | Without induction or with 2-week low-dose induction | 12  | 17      | NA          | NA          |
|                 |                        | Irradiation                            | 12    | 8.0     | NA          | NA          |
|                 |                        | Cyclophosphamide                       | 12    | 8.0     | NA          | NA          |
|                 |                        | Cisplatin                              | 13    | 23.0    | NA          | NA          |
|                 |                        | Doxorubicin                            | 17    | 35.0    | NA          | NA          |
| KEYNOTE-162 (44) | Niraparib + pembrolizumab | Full analysis                         | 47    | 21.0    | 2.3         | NA          |
|                 |                        | tBRCAwt                                | 15    | 47.0    | 8.3         | NA          |
|                 |                        | tBRCAwt                                | 27    | 11.0    | 2.1         | NA          |
|                 |                        | tBRCAunknow                           | 5     | 0       | 2.5         | NA          |
|                 |                        | PD-L1 unknown                          | 6     | 0       | NA          | NA          |
| NCT03394287 (20) | Apatinib + camrelizumab | All population                        | 40    | 32.5    | NA          | NA          |
|                 |                        | Intermittent dosing                    | 10    | 0       | 1.9         | 9.5         |
|                 |                        | Continuous dosing                     | 30    | 43.3    | 3.7         | 8.1         |

PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; TNBC, triple-negative breast cancer; CPS, combined positive score; NA, not available.
extracellular vesicles may be a useful tool for evaluating patients’ response to ICB therapy for TNBC (53). Molecules such as C-X-C motif chemokine ligand 10 (CXCL10) and transglutaminase 2 have also been found to be related to the responsiveness of TNBC to PD-1/PD-L1 inhibitors (54,55). Notably, although the performance of PD-L1 molecules as a detection tool is not satisfactory, the combined use of multiple biomarkers may increase the “arsenal” of the detection personnel. The FUTURE-C-Plus trial established a screening method based on CD8 staining, PD-L1 staining, and gene mutation detection and predicted the value of immunotherapy in patients with TNBC to a certain extent (56). Although many research findings can be translated into biomarkers for predicting the efficacy of PD-1/PD-L1 inhibitors, these assays are still awaiting clinical validation.

**Mechanisms of treatment resistance and novel treatment strategies for PD-1/PD-L1 inhibitors**

**Primary resistance**

Published clinical research data illustrated that only a subset of patients experienced prolonged survival from PD-1/PD-L1 inhibitor therapy. Lack of PD-L1 expression and insufficient TILs can lead to resistance to PD-1/PD-L1 inhibitors. However, the overexpression of PD-1 molecules on CD8+ T cells may also lead to resistance of patients to PD-1/PD-L1 inhibitors (57). At the same time, the overexpression of various inhibitory receptors such as T-cell immunoglobulin mucin 3 (TIM3), cytotoxic T-lymphocyte-associated protein 4 (CTLA4), lymphocyte activation gene 3 (LAG3), and B- and T-lymphocyte attenuator (BTLA) is associated with severe T-cell exhaustion (58). The combined use of PD-1/PD-L1 inhibitors and anti-CTLA-4/anti-TIM3/anti-LAG3/anti-BTLA therapy in patients with breast cancer may restore the function of CD8+ T cells. A recently published first-line study used ipilimumab in combination with nivolumab in patients with metastatic melanoma and noted an mPFS of 26 months (63). This vaccine, which has favorable safety and antitumor activity, is a new immunomodulating approach.

**Acquired resistance**

Patients receiving anti-PD-1/PD-L1 therapy may develop acquired resistance to ICB. Neoantigen landscape evolution occurs under the selective pressure of PD-1/PD-L1 inhibitors (64). Dynamically monitoring tumor-specific or tumor-associated antigens and finding new therapy targets could overcome this acquired resistance. β-2-microglobulin truncating mutations cause the loss of outer membrane localization of MHC I molecules, allowing the tumor to escape from T-cell-mediated immune responses by preventing T-cell recognition (65).

More research is underway to elucidate the mechanism of PD-1/PD-L1 inhibitor resistance. We expect that such research will contribute to development of new drugs and design of new therapies based on PD-1/PD-L1 inhibitors. Table 3 shows the unpublished trials from the ClinicalTrials.gov database concerning PD-1/PD-L1 inhibitors for patients with aTNBC, demonstrating novel clinical attempts to treat TNBC.

**Conclusions**

Along with the accumulation of studies focused on immune therapy, the role of PD-1/PD-L1 inhibitors in the treatment of TNBC has been recognized. Based on the present review of published articles, we came to the following conclusions. First, early administration of PD-
PD-L1 inhibitors can provide more survival benefits to patients with aTNBC. Second, the condition of PD-L1 molecule enrichment in the TME was positively correlated with the therapeutic effect of PD-1/PD-L1 inhibitors to a certain extent. Third, the combined use of PD-1/PD-L1 inhibitors has a greater advantage in improving patient outcomes than does single-agent use. Fourth, patients who have previously used cytotoxic drugs and have been shown to be sensitive to chemotherapy may experience additional survival prolongation by using PD-1/PD-L1 inhibitors. The exploration of new biomarkers for the therapeutic effect of PD-1/PD-L1 inhibitors is of great clinical significance. At the same time, the exploration of drug resistance may provide ideas for the generation of new treatment strategies.

Acknowledgements

None.

Table 3 Ongoing PD-1/PD-L1 inhibitors trials in TNBC

| Trial ID     | Status            | Phase | Cancer type                                                                 | Intervention                                                                 |
|--------------|-------------------|-------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------|
| PD-1 inhibitor |                   |       |                                                                             |                                                                              |
| NCT03504488  | Recruiting        | Phase 1/2 | Non-small cell lung cancer; TNBC; melanoma; head and neck cancer | CAB-ROR2-ADC/CAB-ROR2-ADC + a PD-1 inhibitor                                  |
| NCT03945604  | Unknown           | Phase 1 | Recurrent and metastatic TNBC                                               | SHR-1210 + apatinib + fluzoparib                                             |
| NCT04577963  | Recruiting        | Phase 1b/2 | Advanced, refractory TNBC                                                   | Fruguinitib + tislelizumab                                                  |
| NCT03362060  | Active, not recruiting | Phase 1b | Advanced, refractory TNBC                                                   | PVX-410 and pembrolizumab                                                  |
| NCT04639245  | Recruiting        | Phase 1/2 | Anatomic stage IV breast cancer (AJCC 8th); metastatic lung non-small cell carcinoma; metastatic malignant solid neoplasm; metastatic TNBC; metastatic urethelial carcinoma; prognostic stage IV breast cancer (AJCC 8th); stage IV/IVA/IVB lung cancer (AJCC 8th) | Cyclophosphamide + MAGE-A1-specific T cell receptor-transduced autologous T-cells atezolizumab |
| NCT03667716  | Recruiting        | Phase 1 | Advanced cancer; ovarian cancer; lung cancer; endometrial cancer; ovarian neoplasm; TNBC; malignant colorectal cancer | COM701/COM701 with opdivo (nivolumab)                                        |
| NCT05076682  | Recruiting        | Phase 2 | Metastatic TNBC                                                             | Choline/sodium cromoglicate with anti-PD-1 immunotherapy                    |
| NCT03394287  | Completed         | Phase 2 | Advanced TNBC                                                               | SHR-1210 + apatinib                                                         |
| PD-L1 inhibitor |                   |       |                                                                             |                                                                              |
| NCT04837209  | Recruiting        | Phase 2 | Metastatic, PD-L1 negative or immunotherapy-refractory TNBC                 | Niraparib + dostarlimab + radiation                                          |
| NCT04739670  | Not yet recruiting | Phase 2 | Metastatic TNBC                                                             | Atezolizumab + bevacizumab + gemcitabine + carboplatin                      |
| NCT04360941  | Recruiting        | Phase 1 | Metastatic AR+ TNBC                                                         | Palbociclib + avelumab                                                      |

PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TNBC, triple-negative breast cancer; AR, androgen receptor; AJCC, American Joint Committee on Cancer.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61-70.
2. Gradishar WJ, Anderson BO, Abraham J, et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2020;18: 452-78.
3. Wang N, Li K, Huang W, et al. Efficacy of platinum in advanced triple-negative breast cancer with germline BRCA mutation determined by next generation sequencing. Chin J Cancer Res 2020;32:149-62.
4. Liu X, Li H, Shao B, et al. Identification of recurrent
BRCA1 mutation and its clinical relevance in Chinese triple-negative breast cancer cohort. Cancer Med 2017;6:547-54.
5. Li H, Liu R, Shao B, et al. Phase I dose-escalation and expansion study of PARP inhibitor, fluzoparib (SHR3162), in patients with advanced solid tumors. Chin J Cancer Res 2020;32:370-82.
6. Banerji S, Cibulskis K, Rangel-Escareno C, et al. Sequence analysis of mutations and translocations across breast cancer subtypes. Nature 2012;486:405-9.
7. Mittendorf EA, Philips AV, Meric-Bernstam F, et al. PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res 2014;2:361-70.
8. Salgado R, Denkert C, Demaria S, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann Oncol 2015;26:259-71.
9. Shao B, Li CW, Lim SO, et al. Deglycosylation of PD-L1 by 2-deoxyglucose reverses PARP inhibitor-induced immunosuppression in triple-negative breast cancer. Am J Cancer Res 2018;8:1837-46.
10. Emens LA. Breast cancer immunotherapy: Facts and hopes. Clin Cancer Res 2018;24:511-20.
11. Golstein P, Griffiths GM. An early history of T cell-mediated cytotoxicity. Nat Rev Immunol 2018;18:527-35.
12. Janakiram M, Shah UA, Liu W, et al. The third group of the B7-CD28 immune checkpoint family: HHLA2, TMIGD2, B7x, and B7-H3. Immunol Rev 2017;276:527-35.
13. Sfános KS, Bruno TC, Meeker AK, et al. Human prostate-infiltrating CD8+ T lymphocytes are oligoclonal and PD-1+. Prostate 2009;69:1694-703.
14. Ahmadzadeh M, Johnson LA, Heemskerk B, et al. Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. Blood 2009;114:1537-44.
15. Yi M, Jiao D, Xu H, et al. Biomarkers for predicting efficacy of PD-1/PD-L1 inhibitors. Mol Cancer 2018;17:129.
16. Nowak AK, Robinson BW, Lake RA. Synergy between chemotherapy and immunotherapy in the treatment of established murine solid tumors. Cancer Res 2003;63:4490-6.
17. Frildlender ZG, Sun J, Singhal S, et al. Chemotherapy delivered after viral immunogene therapy augments antitumor efficacy via multiple immune-mediated mechanisms. Mol Ther 2010;18:1947-59.
18. Ali RMM, McIntosh SA, Savage KI. Homologous recombination deficiency in breast cancer: Implications for risk, cancer development, and therapy. Genes Chromosomes Cancer 2021;60:358-72.
19. Stewart RA, Pilié PG, Yap TA. Development of PARP and immune-checkpoint inhibitor combinations. Cancer Res 2018;78:6717-25.
20. Liu J, Liu Q, Li Y, et al. Efficacy and safety of camrelizumab combined with apatinib in advanced triple-negative breast cancer: an open-label phase II trial. J Immunother Cancer 2020;8:e000696.
21. Bachelot T, Fiendomized phase II SAFIR02-BREAST IMMUNO trial. Nat Med 2021;27:250-5.
22. Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN solid tumor study. Breast Cancer Res Treat 2018;167:671-86.
23. Emens LA, Cruz C, Eder JP, et al. Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with metastatic triple-negative breast cancer: A phase I study. JAMA Oncol 2019;5:74-82.
24. Nanda R, Chow LQ, Dees EC, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study. J Clin Oncol 2016;34:2460-7.
25. Adams S, Schmid P, Rugo HS, et al. Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort A of the phase II KEYNOTE-086 study. Ann Oncol 2019;30:397-404.
26. Winer EP, Lipatov O, Im SA, et al. Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:499-511.
27. Adams S, Loi S, Toppmeyer D, et al. Pembrolizumab monotherapy for previously untreated, PD-L1-positive, metastatic triple-negative breast cancer: cohort B of the phase II KEYNOTE-086 study. Ann Oncol 2019;30:405-11.
28. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018;379:2108-21.
29. Schmid P, Rugo HS, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind,
placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:44-59.
30. Emens LA, Adams S, Barrios CH, et al. First-line atezolizumab plus nab-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis. Ann Oncol 2021;32:983-93.
31. Huang W, Ran R, Shao B, et al. Prognostic and clinicopathological value of PD-L1 expression in primary breast cancer: a meta-analysis. Breast Cancer Res Treat;178:17-42.
32. Iwata H, Inoue K, Kaneko K, et al. Subgroup analysis of Japanese patients in a phase 3 study of atezolizumab in advanced triple-negative breast cancer (IMpassion130). Jpn J Clin Oncol 2019;49:1083-91.
33. Adams S, Diamond JR, Hamilton E, et al. Atezolizumab plus nab-paclitaxel in the treatment of metastatic triple-negative breast cancer with 2-year survival follow-up: A phase 1b clinical trial. JAMA Oncol 2019;5:334-42.
34. Miles D, Gligorov J, André F, et al. Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. Ann Oncol 2021;32:994-1004.
35. Ghebeh H, Al-Sayed A, Eiada R, et al. Weekly Paclitaxel given concurrently with Durvalumab has a favorable safety profile in triple-negative metastatic breast cancer. Sci Rep 2021;11:19154.
36. Zhang Y, Chen H, Mo H, et al. Single-cell analyses reveal key immune cell subsets associated with response to PD-L1 blockade in triple-negative breast cancer. Cancer Cell 2021;39:1578-93.e8.
37. FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer U. S. Food & Drug Administration. Available online: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-pd-l1-positive-unresectable-loocally-advanced-or-metastatic-triple-negative
38. Withdrawn 1 Cancer Accelerated Approvals FDA10/6/2021 Available online: https://www.fda.gov/drugs/resources-information-approved-drugs/withdrawn-cancer-accelerated-approvals
39. Ou-Yang F, Li CL, Chen CC, et al. De-glycosylated membrane PD-L1 in tumor tissues as a biomarker for responsiveness to atezolizumab (Tecentriq) in advanced breast cancer patients. Am J Cancer Res 2022;12:123-37.
40. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020;396:1817-28.
41. Voorwerk L, Slagter M, Horlings HM, et al. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. Nat Med 2019;25:920-8.
42. Domchek SM, Postel-Vinay S, Im SA, et al. Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study. Lancet Oncol 2020;21:1153-64.
43. Im SA, Xu B, Li W, et al. Olaparib monotherapy for Asian patients with a germline BRCA mutation and HER2-negative metastatic breast cancer: OlympiAD randomized trial subgroup analysis. Sci Rep 2020;10:8753.
44. Vinayak S, Tolaney SM, Schwartzberg L, et al. Open-label clinical trial of niraparib combined with pembrolizumab for treatment of advanced or metastatic triple-negative breast cancer. JAMA Oncol 2019;5:1132-40.
45. Duan J, Cui L, Zhao X, et al. Use of immunotherapy with programmed cell death 1 vs programmed cell death ligand 1 inhibitors in patients with cancer: A systematic review and meta-analysis. JAMA Oncol 2020;6:375-84.
46. Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2019;20:261-8.
47. Pillai RN, Behera M, Owonikoko TK, et al. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: A systematic analysis of the literature. Cancer 2018;124:271-7.
48. Wang Y, Zhou S, Yang F, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: A systematic review and meta-analysis. JAMA Oncol 2019;5:1008-19.
49. Ionov Y, Peinado MA, Malkhosyan S, et al. Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. Nature 1993;363:558-61.
50. Dudley J, Lin MT, Le DT, et al. Microsatellite
instability as a biomarker for PD-1 blockade. Clin Cancer Res 2016;22:813-20.

51. Marcus L, Lemery SJ, Keegan P, et al. FDA approval summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res 2019;25:3753-8.

52. Ralser DJ, Klümper N, Gevensleben H, et al. Molecular and immune correlates of PDCD1 (PD-1), PD-L1 (CD274), and PD-L2 (PDCD1LG2) DNA methylation in triple negative breast cancer. J Immunother 2021;44:319-24.

53. Hoffmann O, Wormland S, Bittner AK, et al. Programmed death receptor ligand-2 (PD-L2) bearing extracellular vesicles as a new biomarker to identify early triple-negative breast cancer patients at high risk for relapse. J Cancer Res Clin Oncol 2022 [Epub ahead of print]

54. Choi J, Lee HJ, Yoon S, et al. Blockade of CCL2 expression overcomes intrinsic PD-1/PD-L1 inhibitor-resistance in transglutaminase 2-induced PD-L1 positive triple negative breast cancer. Am J Cancer Res 2020;10:7175-87.

55. Shi Z, Shen J, Qiu J, et al. CXCL10 potentiates immune checkpoint blockade therapy in homologous recombination-deficient tumors. Theranostics 2021;11:7175-87.

56. Wu SY, Xu Y, Chen L, et al. Combined angiogenesis and PD-1 inhibition for immunomodulatory TNBC: concept exploration and biomarker analysis in the FUTURE-C-plus trial. Mol Cancer 2022;21:84.

57. Blackburn SD, Shin H, Freeman GJ, et al. Selective expansion of a subset of exhausted CD8 T cells by alphaPD-L1 blockade. Proc Natl Acad Sci U S A 2008;105:15016-21.

58. Thommen DS, Schreiner J, Müller P, et al. Progression of lung cancer is associated with increased dysfunction of T cells defined by coexpression of multiple inhibitory receptors. Cancer Immunol Res 2015;3:1344-55.

59. Adams S, Othus M, Patel SP, et al. A multicenter phase II trial of ipilimumab and nivolumab in unresectable or metastatic metastatic breast cancer: Cohort 36 of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART, SWOG S1609). Clin Cancer Res 2022;28:271-8.

60. Peng D, Kryczek I, Nagarsheth N, et al. Epigenetic silencing of TH1-type chemokines shapes tumour immunity and immunotherapy. Nature 2015;527:249-53.

61. George S, Miao D, Demetri GD, et al. Loss of PTEN is associated with resistance to anti-PD-1 checkpoint blockade therapy in metastatic uterine leiomyosarcoma. immunity. 2017;46:197-204.

62. Toulmonde M, Penel N, Adam J, et al. Use of PD-1 targeting, macrophage infiltration, and IDO pathway activation in sarcomas: A phase 2 clinical trial. JAMA Oncol 2018;4:93-7.

63. Kjeldsen JW, Lorentzen CL, Martinenait E, et al. A phase 1/2 trial of an immune-modulatory vaccine against IDO/PD-L1 in combination with nivolumab in metastatic melanoma. Nat Med 2021;27:2212-23.

64. Anagnostou V, Smith KN, Forde PM, et al. Evolution of neoantigen landscape during immune checkpoint blockade in non-small cell lung cancer. Cancer Discov 2017;7:264-76.

65. Zaretsky JM, Garcia-Diaz A, Shin DS, et al. Mutations associated with acquired resistance to PD-1 blockade in melanoma. N Engl J Med 2016;375:819-29.

---

Cite this article as: Liang Y, Liu X, Li K, Li H. Current situation of programmed cell death protein 1/programmed cell death ligand 1 inhibitors in advanced triple-negative breast cancer. Chin J Cancer Res 2022;34(2):117-130. doi: 10.21147/jissn.1000-9604.2022.02.07