## Breast cancer immunotherapy: the use of PD-1/PD-L1 inhibitor in treatment of triple-negative breast cancer.

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Abstract: Breast cancer has become the most morbid and mortal malignancy in women worldwide, and although the use of adjuvant chemotherapy, radiotherapy, targeted therapy, and endocrine therapy has significantly reduced the risk of death, there are still patients who do not benefit from the available therapies, especially in patients with triple-negative breast cancer(TNBC). Immunotherapy of breast cancer with programmed cell death 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) immune checkpoint inhibitors is currently a hot topic in clinical research for the treatment of breast cancer. In this paper, we will discuss the use of PD-1/PD-L1 inhibitor in treatment of TNBC.

Keywords: triple-negative breast cancer; immunotherapy; PD-1; PD-L1;checkpoint blockade；

Breast cancer has become the most morbid and deadly malignancy in women worldwide[1]. Immunotherapy is a recently emerged treatment modality that further improves patient survival by restoring or activating the tumor-killing function of the body's immune system[2]. Programmed cell death receptor 1 (PD-1)/programmed cell death receptor ligand 1 (PD-L1) immune checkpoint inhibitors for immunotherapy of breast cancer are currently a hot topic of clinical research. In this paper, we will discuss he use of PD-1/PD-L1 inhibitor in treatment of TNBC.

**PD-1/PD-L1 expression in** **triple-negative breast cancer**

PD-1, a checkpoint protein expressed on T lymphocytes, plays an important role in tumor immune escape by binding to PD-L1, a ligand expressed by tumor cells, leading to T lymphocyte apoptosis and inhibiting T cell killing function. Among the molecular subtypes of breast cancer, the more aggressive ones are triple negative breast cancer (TNBC) and HER2-positive breast cancer.PD-1/PD-L1 expression varies with the stage and molecular subtype of breast cancer, with the highest expression in TNBC [3]. Doğukan R et al. [4] performed an immunohistochemical analysis of 61 patients with triple negative breast cancer (TNBC) and found that PD-L1 positivity was 37.7% and 47.5% in the tumor and tumor microenvironment, respectively, and that tumor PD-L1 expression was associated with tumor micro environment was positively correlated with Ki-67 score and PD-L1 positivity. Zerdes I et al. [5] found that total PD-L1 protein was found in ER-/HER2-(44.2%) and basal-like (44.9%) tumors were highly expressed and PD-L1 gene expression was higher in both ER-/HER2-. This shows that PD-1 and PD-L1 inhibitors have great potential in TNBC, and this high antigenicity could provide a good target for immunotherapy of breast cancer.

**PD-1/PD-L1 inhibitor monotherapy for breast cancer**

PD-1/PD-L1 inhibitor treatment studies have focused on triple-negative breast cancer (TNBC), and some of the more intensively studied PD-1/PD-L1 inhibitors include pembrolizumab and atezolizumab. Phase II KEYNOTE-086 cohort study A [6]evaluated pembrolizumab for monotherapy of previously treated metastatic triple-negative breast cancer and showed response times of ≥6 and ≥12 months in 75.0% and 62.5% of responders, respectively, with an ORR of 5.3%. However, the phase II KEYNOTE-086 cohort study B[7]evaluating pembrolizumab as first-line treatment for patients with PD-L1-positive mTNBC showed an ORR of 21.4%. Emens LA et al.[8] studying atezolizumab for metastatic triple-negative breast cancer and showed a median OS of 17.6 months in patients treated with first-line atezolizumab compared with 7.3 months in patients receiving second-line and other than atelelizumab. Dirix, L. Y., et al.[9] found that Avelumab showed an acceptable safety profile and clinical activity in a subset of patients with MBC, including mTNBC. Not coincidentally, the KEYNOTE-119 trial [10] suggested that pembrolizumab did not significantly improve overall survival compared to chemotherapy in previously treated patients with metastatic triple- negative breast cancer, but those with PD-L1-enriched tumours did, suggesting that PD-1/PD-L1 inhibitors are effective in the treatment of TNBC and that early treatment is more effective.

**Increased sensitivity of PD-1/PD-L1 inhibitors for breast cancer**

Although PD- 1/PD-L1 inhibitors can produce a longer treatment response time, there is still much room for ORR improvement. Tumor microenvironments can be divided into the following two types: infiltrated–excluded (I‐E) type and infiltrated‐inflamed (I‐I) type according to the distribution of tumor inflammatory cell infiltration, PD‐L1 and CD8B gene expression level in tumor[11]. Usually Type I‐E also be known as "cold tumors", which has no CTLs cells in the tumor core. Breast cancer is considered as "cold tumors". So how to increase immunogenicity and the sensitivity of PD-1/PD-L1 inhibitors for breast cancer and improve ORR becomes an important direction for subsequent research. Here are some clinical research trials. ([Table1](#表1))

*Combination of drugs*

*Combination adjuvant chemotherapy*

Chemotherapy plays a crucial role in the treatment of breast cancer by reducing the risk of recurrence and metastasis, prolonging the survival time and improving the quality of patients' survival. Fournier C et al.[12] concluded that chemotherapeutic agents can activate effector T cells and suppress immunosuppressive cells, and by combining immunotherapy with chemotherapy, tumor resistance to immune checkpoint blockers can be overcome. In a

Table 1 Statistical table of clinical research trials of PD-1/PD-L1 inhibitors combined with other methods of treating TNBC

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| --- | --- | --- | --- | --- |
| Treatment options | Medicine | Literature | NCT number | Status |
| PD-1/PD-L1  inhibitors combinated  adjuvant  chemotherapy | atezolizumab and nab-paclitaxel | [13]; | NCT02425891 | Completed |
| [14]; |
| [15]; |
| [16]; | NCT01633970 | Completed |
| atezolizumab and paclitaxel | [17] | NCT03125902 | Completed |
| atezolizumab 、cobimetinib and nab-paclitaxel or paclitaxel | [18]; | NCT02322814 | Completed |
| pembrolizumab plus eribulin | [19]; | NCT02513472 | Completed |
| pembrolizumab plus nab-paclitaxel, paclitaxel, or gemcitabine-carboplatin | [20]; | NCT02819518 | Active |
| paclitaxel with durvalumab | [21] | NCT02628132 | Completed |
| PD-1/PD-L1  inhibitors combinated  neoadjuvant  chemotherapy | pembrolizumab plus paclitaxel followed doxorubicin and cyclophosphamide | [22]; | NCT01042379 | Recruiting |
| pembrolizumab plus nab-paclitaxel or plus nab-paclitaxel and carboplatin | [23]; | NCT02622074 | Completed |
| pembrolizumab plus paclitaxel and carboplatin、or doxorubicin-cyclophosphamide or epirubicin-cyclophosphamide | [24]; | NCT03036488 | Active |
| pembrolizumab plus doxorubicin-cyclophosphamide or epirubicin-cyclophosphamide | [25]; |
| atezolizumab plus nab-paclitaxel followed by doxorubicin and cyclophosphamide | [26]; | NCT03197935 | Completed |
| PD-1/PD-L1  inhibitors combinated anti-  androgen therapy | pembrolizumab and enobosarm | [27]; | NCT02971761 | Active |
| PD-1/PD-L1  inhibitors combinated anti-  angiogenic drugs | camrelizumab combined with apatinib | [28]; | NCT03394287 | Completed |
| toripalimab plus anlotinib | [29]; | / (case report) | / |
| PD-1/PD-L1  inhibitors combinated anti-  angiogenic drugs and hemotherapy | famitinib combined with camrelizumab and chemotherapy | [30] | NCT04129996 | Active |
| PD-1/PD-L1  inhibitors combinated radiation therapy | pembrolizumab and radiotherapy | [31]; | NCT02730130 | Completed |

trial of atezolizumab in combination with nab-paclitaxel [13] and nab-paclitaxel plus placebo control for advanced triple-negative breast cancer, the median overall survival of atezolizumab +nab-paclitaxel group was 21.3 months and 17.6 months in the nab-paclitaxel +placebo group. The IMpassion130 trial [14] showed the same tendency,it also showed the similar grades in health-telated quality of life (HRQoL) in two groups. Adams, Diamond, et al. found that the combination of atezolizumab plus nab-paclitaxel had a manageable safety profile[16]. The ORR was numerically higher in previously untreated patients vs previously treated patients (53.8% in 1L vs 30.0% in 2L+) and in PD-L1–positive vs PD-L1–negative patients (41.4% vs 33.3%). In the PD-L1-positive population, compaired with nab-paclitaxel monotherapy atezolizumab plus nab-paclitaxel group was associated with more favourable OS [15].Surprisingly, paclitaxel with or without atezolizumab for unresectable locally advanced or metastatic triple-negative breast cancer show no statistically significant difference in FPS and OS, even though they had a numerical increase.

Among patients with advanced triple-negative breast cancer whose tumors expressed PD-L1 with a CPS of 10 or more, the addition of pembrolizumab to chemotherapy resulted in significantly longer overall survival than chemotherapy alone[20].A small trial[21] investigating the safety of paclitaxel in combination with durvalumab showed that its objective response rate (ORR) was observed in five patients with a median duration of 10.0 months. Median Progression-free survival (PFS) and overall survival (OS) were 5 and 20.7 months, respectively. Eribulin in combination with pembrolizumab demonstrated oncologic activity in patients with TNBC, particularly in patients with PD-L1-positive tumors, with a nearly doubled ORR compared to patients with PD-L1- negative tumors [19].

It is worth mentioning that the addition of atezolizumab to the regimen of cobimetinib combined with Nab-paclitaxel did not improve ORR in patients with mTNBC [18].

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*Combined neoadjuvant chemotherapy*

Neoadjuvant chemotherapy is systemic chemotherapy given prior to local treatment (surgery or radiotherapy) for malignant tumors and is designed to minimize the extent of radical surgical resection of operable tumors or to convert inoperable tumors to operable [32]. IMpassion031 [26] suggests that neoadjuvant treatment with atezolizumab in combination with Nab-paclitaxel and anthracycline chemotherapy in patients with early-stage TNBC significantly improves pathological complete remission rate from 41% to 58%. When pembrolizumab was combined with standard neoadjuvant chemotherapy, its pCR rates was 60% vs 22% in triple-negative cohorts, respectively [22]. Patients in the pembrolizumab combined with neoadjuvant chemotherapy group had three- year event-free survival rates of 84.5% [25], 93% [22]. Several other clinical trial studies have also demonstrated a substantial increase in pCR, event-free survival in patients with TNBC treated with neoadjuvant therapy in combination with pablizumab [23-25]. Black or African American (AA) women[33] in the durvalumab combined with neoadjuvant chemotherapy group had similar pCR rates, AA (43%) and non-AA patients (48%). Three-year EFS rates were 78.3% and 71.4% in non-AA and AA patients, respectively; 3-year OS was 87% and 81%, respectively.

*Combined anti- androgen therapy*

There is a subtype of triple-negative breast cancer that appears to be hormonally regulated and whose growth is thought to be driven by androgen receptor (AR) signaling. Treatment of AR+ TNBC patients with AR antagonists, AR inhibitors can be efficacious [34].The combination of pembrolizumab and enobosarm was well tolerated in heavily pretreated AR+ TNBC without pre-selected programmed death ligand-1 (PD- L1). The clinical benefit rate at 16 weeks was 25% [27]. Future clinical trials combining AR-targeted therapy with immune checkpoint inhibitors (ICIs) for AR+ TNBC for this type of breast cancer are worth investigating.

*Combination anti-angiogenic drugs*

Several preclinical studies have shown that anti-angiogenic agents can improve the tumor vascular network and hypoxic environment. Anlotinib transiently normalized the tumor vascular system, downregulated PD-L1 expression on vascular endothelial cells to inhibit tumor growth[35], and improved the therapeutic effect of PD-1 blockade [36]. Peng Fan et al. [37] found that effective low-dose anlotinib increased the proportion of CD4+T, CD8+T and NK cells in tumors in short- term and long-term treatment regimens, repaired the tumor immune microenvironment, and enhanced anti-PD-1 therapy. Both conventional and low-dose anti-vascular endothelial growth factor receptor 2(VEGFR2) antibody treatment normalized tumor vasculature, but low-dose VEGFR2 blockade led to more robust immune cell infiltration and activation and promoted CD8+ T cell secretion of osteopontin (OPN), which subsequently induced tumor cell production of transforming growth factor β (TGF-β), thereby upregulating immune cell on PD-1 expression on immune cells [38]. In clinical trials, the objective response rate (ORR) of camrelizumab in combination with apatinib for advanced triple-negative breast cancer [28] (TNBC) was 43.3%. Pathology reports have also been reported: using toripalimab and anlotinib to treat a advanced metaplastic breast carcinoma patient achieved partial response [29]. There is a study evaluated the effect of famitinib, camrelizumab and chemotherapy in advanced immunomodulatory TNBC patients. The objective response rate was 81.3%, and the median progression-free survival was 13.6 months[30].

*Combined adenosine diphosphate ribose polymerase [PARP] inhibitor*

Polyadenosine diphosphate ribose polymerase (PARP) is involved in an important part of DNA base excision repair by inducing the polycation (ADP-ribose) of itself and other target proteins [39]. PARP inhibitors (PARPi) exploit genomic instability caused by oxidative and replicative stress, as well as defects in DNA repair pathways for the purpose of killing tumor cells[40]. Yali Wang et al.[41] found that pamiparib could induce PD-L1 expression via the JAK2 / STAT3 pathway. Seppeijiao et al. [42] demonstrated in cellular experiments that PARP inhibitors can inactivate glycogen synthase kinase 3β (GSK3β) and upregulate PD- L1 expression, and the results showed that PARPi and anti-PD-L1 therapies compared with each agent alone significantly more effective. Olaparib in combination with Durvalumab has shown good results in the treatment of BRCA-mutated metastatic breast cancer, with an 80% control rate at 12 w [43].

*Discussion*

There is a lot of research on PD-1/PD-L1 inhibitors. Strict access criteria and exclusion criteria, reasonable control drug settings, scientific rigorous assessment of patients, long follow-up period, a large number of trials, and careful measures to deal with adverse reactions are the basic guarantee for the scientific results of the experiment. Strict access criteria and exclusion criteria can help us screen out the patients who best meet the needs of the trial purpose to ensure the conduct of the trial, and at the same time reduce the adverse reactions that the test drug may have with some patients who do not meet the requirements, so as to ensure the health of patients. Reasonable control medication settings can not only make the results of the test more scientific, but also maintain the health of the control group patients as much as possible, and the proper disposal of adverse reactions is also an important part of protecting the test patients. Scientific and rigorous assessment of the patient's condition is an important part of the test, and it is necessary to avoid subjective factors biasing the test results, double-blind trials are better in this way. This requires both knowledgeable professionals and scientific criteria. Long-term follow-up and a large number of trial populations can make the trial data as complete as possible, reduce the error caused by chance, and make the experimental data more reliable,which is useful for exploring the long-term impact of interventions on patients. Even if every demand has be done,not all the results are as rosy as planned.

In the phase III IMpassion130 trial[14], combining atezolizumab with first-line nanoparticle albumin-bound-paclitaxel for advanced triple-negative breast cancer (aTNBC) showed a statistically significant progression-free survival (PFS) benefit in the intention-to-treat (ITT) and programmed death-ligand 1 (PD-L1)-positive populations, and a clinically meaningful overall survival (OS) effect in PD-L1-positive aTNBC. However, IMpassion131 evaluated first-line atezolizumab-paclitaxel in aTNBC found that combining atezolizumab with paclitaxel did not improve PFS or OS versus paclitaxel alone[17]. This means that differences in chemotherapy regimens for PD-1/PD-L1 inhibitors will affect the effectiveness of the combination. In addition,some triple schemes have emerged. Atezolizumab to the regimen of cobimetinib combined with Nab-paclitaxel did not improve ORR in patients with mTNBC[18]，while PD-1 monoclonal antibody (camrelizumab) combinate angiogenesis inhibitor (famitinib) and chemotherapy shows a positive results. This may suggest that the angiogenesis inhibitor may be a better choice when used in combination with PD-1/PD-L1 inhibitors. In addition, multiple trials support that PD-1/PD-L1-positive patients have a better response to PD-1/PD-L1 inhibitors, so stratification in the trial is also a matter of consideration. In conclusion, immunotherapy has great potential in the treatment of triple-negative breast cancer, and there is still a long way.

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