



# A narrative review of combination therapy of PD-1/PD-L1 blockade with standard approaches for the treatment of breast cancer: clinical application and immune mechanism

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**Objective:** In this review, we aimed to discuss the efficacy of immunotherapy of anti-programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) and potential immune mechanism combination with various standard systemic therapies for breast cancer (BC) such as chemotherapy, targeted therapy, endocrine therapy, and radiotherapy.

**Background:** Single-drug therapy of antibodies against PD-1 and its ligand, PD-L1, have only presented modest responses in patients with BC, partly due to the deficiency of tumor-infiltrating lymphocytes (TILs) and low mutation burden. Thus, the combinations of PD-1/PD-L1 blockade with other approaches which may increase the immune therapy effect are being studied. Moreover, an understanding of the immune mechanism of PD-1/PD-L1 blockade with other approaches will contribute to better application of clinical therapy.

**Methods:** We searched the studies that focus on PD-1/PD-L1 therapy with or without other systemic therapy and relative immune mechanisms indicated between 2000 and 2020.

**Conclusions:** Anti PD-1/L1 blockade combined with therapeutic approaches is safe and effective in BC, in particular for PD-L1 antibody atezolizumab plus nab-paclitaxel by inducing PD-1/L1 expression and the number of cytotoxic T cells. Otherwise, the toxicity also exists during clinical treatment. Future researches should be evaluated to explore the immune mechanism and vast clinical trials need to be conducted for evidential support for combination therapy of BC.

**Keywords:** Breast cancer (BC); programmed cell death protein 1 (PD-1); programmed death ligand 1 (PD-L1); combination therapy; immune mechanism

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## Introduction

Recently, immune checkpoint inhibitors have displayed remarkable curative effects in several cancer types, such as melanoma, non-small cell lung cancer, and triple-negative breast cancer (TNBC), especially antibodies against programmed cell death protein 1 (PD-1) and its ligand, programmed death ligand 1 (PD-L1), which have

been approved by the Food and Drug Administration (FDA) for the treatment of various types of cancer (1,2). Hormone receptor (HR)-positive breast cancer (BC) is the most common subtype of BC and has low anti-PD-1/PD-L1 respond, which partly due to the low number of tumor-infiltrating lymphocytes (TILs) and tumor mutation burden (3). The resistance of HR-positive BC to hormone

therapy and targeted therapy to receptor tyrosine-protein kinase erbB-2/human epidermal growth factor receptor 2 (HER2) positive BC has been intractable especially for the reactivation of proliferation and metastasis of BC cells. TNBC has been considered to receive benefit from the immune-therapy, however, little efficiency with anti-PD-1/PD-L1 antibody was observed. In addition, the contribution of the immune micro-environment in the treatment of BC remains to be extensively studied. Lower counts of TILs, immune-cell-activating cytokines, and higher immunosuppressive molecules have been detected in metastatic lesions of metastatic BC compared to the original lesions, suggesting an inert micro-environment in metastatic BC, which are more likely to escape immune surveillance harness (4,5). Thus gross immunosuppressive circuits would be reestablished by infiltrating with relative immature myeloid cells called myeloid derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), regulatory T cells (Tregs), and granulocytes that mediate the metastasis of BC to bone, lungs and brain. The potential mechanism of these cells included the inhibition of immunosuppressive receptors of PD-1 expressed in effector cells. Additionally, in HER2-positive BC and HR-positive BC, an immune pruning effect was demonstrated between lower clonal expansion and high immune surveillance (6,7). The immune antibody such as PD-1/L1 may upset the balance of benefits for immune surveillance. Notably, neoplasms develop only in the context of immune escape and weakly immune responses. Moreover, PD-L1, PD-1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expressions may be changed after systemic therapy in tumor cells, suggesting that systemic therapy could reestablish the immune surveillance and control of tumor growth (8). Thus, the possible combinations of PD-1/PD-L1 blockade with other approaches need to be investigated. Moreover, the potential immune-mechanism rationale behind the application of combination therapy with immune checkpoint inhibitors is entirely different from conventional chemotherapy and targeted therapy.

In this review, we discuss the binding curative effect and potential immune mechanism of anti-PD-1/L1 antibody with various standard systemic therapies for BC, for instance, chemotherapy, targeted therapy, endocrine therapy, and radiotherapy.

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-2062>).

## Methods

We consulted studies that focus on PD-1/PD-L1 therapy with or without other systemic therapy and relative immune mechanisms indicated between 2000 and 2020. We searched literature by the keywords of breast cancer, PD-1, PD-L1, combination therapy, and immune mechanism. Most of the studies could be found in the PubMed database. We hypothesized that the response of anti-PD-1/L1 therapy will be improved while combination with chemotherapy, targeted therapy, endocrine therapy, and radiotherapy. The immune mechanism also concluded in the combined therapy to further explore the potential therapeutic target for BC.

## Discussion

### *Anti-PD-1/L1 with paclitaxel-based chemotherapy*

Cytotoxic chemotherapy remains a standard treatment of most types of BC, which contributes to the increase of immunogenicity or the inhibition of immunosuppressive circuitries during the progression of BC. Normally, BC cells reduce the immunogenicity or develop the ability to establish immunosuppressive networks by immunoeediting and immune escape in the origin and progress of neoplasms. Adjuvant chemotherapy helps to increase immunogenicity or directly increase boost the activity of immunostimulatory or immunosuppressive cellular networks. After chemotherapy, immunomodulatory effects have been observed in BC patients, along with the inhibition of the immunosuppressive cell populations, including tumor-associated TAM, MDSC, Tregs, and the activation of the effective T cells, natural killer (NK) cells, and dendritic cells (DC), as well as the increase of CXCL10 chemokine (9-13). Moreover, adaptive PD-L1 upregulation has also been correlated with chemotherapy (14). Inhibition of the interaction between PD-L1 and PD-1 could reduce the phosphorylation of AKT and ERK and decrease multidrug resistance 1/P-glycoprotein (MDR1/P-gp) expression to increase the efficacy of doxorubicin in BC cells (15). In anthracycline treated BC, the function of toll-like receptor 4 (TLR4) polymorphisms affecting purinergic receptor P2X were impaired and correlated with decreased time-to-metastasis, suggesting an immune stimulatory effect of anthracycline via activation of the adaptive stress response involving endoplasmic reticulum (ER), and interferon (INF) signaling. The exposure of ER chaperone calreticulin

(CALR) facilitated the death of engulfment cells by binding to lipoprotein receptor-related protein 1 (LRP-1). Subsequent treatment with anthracyclines induced type I interferon (IFN) signaling that generated by autocrine/paracrine signaling, which was responsible for the secretion of potent chemotactic factor chemokine ligand 10 (CXCL 10) for T cells. Then, the chromatin-binding protein high mobility group box 1 (HMGB1), which contributes to the maturation of DCs, was released by the dead cancer cells. Meanwhile, anthracyclines triggered immunogenic cell death (ICD), and reduced the number of intratumoral and circulating MDSCs.

The administration of docetaxel to BC patients increased the amounts of circulating CTLs, decreased Treg cells, and depleted MDSCs by converting docetaxel into an active metabolite. Moreover, paclitaxel could induce TLR4, which may have the ability to boost T cell priming by DCs. Furthermore, the increased amounts of CD68<sup>+</sup> TAMs were associated with decreased recurrence-free survival and overall survival (OS) in BC patients treated with paclitaxel. In addition, paclitaxel could induce macrophages to secrete pro-inflammatory cytokines, recruit and activate dendritic cells, T cells and NK cells. Meanwhile, paclitaxel also could activate the expression of mannose-6-phosphate receptor, increasing the permeability of granzyme B. Expressions of NK cell lectin-like receptor K1 ligand were upregulated on tumor cells after chemotherapy treatment and led to a susceptibility to the therapy mediated by NK cells. Paclitaxel could also induce the expression of coordinate transcription of CD47, CD73, and PD-L1, which might increase the combination effect of paclitaxel and immune checkpoint inhibitors in BC. Accordingly, effective cytotoxic therapy, especially paclitaxel combined with immunotherapy might attract attention in the treatment of BC (16,17).

In a phase 1b trial for metastatic TNBC, the combined treatment of atezolizumab plus nab-paclitaxel showed a remarkable anti-tumor response with manageable adverse events (12). The objective response rate (ORR) and the median duration of response were 39.4% and 9.1 months, respectively. Median progression-free survival (PFS) was 5.5 months while OS was 14.7 months (12). In the phase III IMpassion130 clinical trials, PD-L1 inhibitor atezolizumab plus nab-paclitaxel was shown to improve PFS among the entire metastatic TNBC patient population (7.2 months) and the PD-L1-positive subgroup (7.5 months); however, only the PD-L1-positive group gained longer OS of 25.0 months whereas the OS of the entire cohort was 21.3 months (1). The ongoing IMpassion131 study has

provided an alternative chemotherapy backbone by evaluating atezolizumab plus paclitaxel rather than nab-paclitaxel and yielded similar results to IMpassion130 study (18). Based on the IMpassion130 and 131 study, the IMpassion132 study will enroll approximately 350 randomized patients from 100 sites globally, with the aim of verifying improvements that might be achieved in the treatment of early relapsing TNBC with an alternative chemotherapy backbone with OS as the endpoint (18). For anti-PD-1 antibody, results from the phase II “TONIC” trial demonstrated that the ORR was 20% in the overall cohort, 23% in the cisplatin cohorts, and 35% in the doxorubicin cohorts, which was followed by nivolumab. This study confirmed that short-term chemotherapy may induce the expression of PD-1/L1 and cytotoxic T cells, and increase responses to PD-1 blockade in TNBC (19). Additionally, an open-label, single-arm, phase 1b/2 trial illustrated the safety and efficacy of pembrolizumab in the combination with eribulin in TNBC (20). No dose limiting toxicities (DLT) of the combination regimen were observed in phase 1b and no deaths occurred due to the combined therapy. The most frequent immune-related adverse events of grade 3 or 4 were neutropenia and fatigue. The combined therapy presented a novel treatment approach for metastatic BC patients with comparable adverse events with either drug used when used as monotherapy. Another phase III trial, “KEYNOTE-355”, will provide data of pembrolizumab combined with paclitaxel, nab-paclitaxel, or gemcitabine/carboplatin in TNBC patients (21).

#### *Anti-PD-1/L1 with targeted therapy*

Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) have shown a dramatic effect in the treatment of HR-positive BC. It was thought that they induced cytostasis through G1 cell-cycle arrest, but a preclinical study suggested that CDK4/6i enhanced anti-tumor immunity by activating tumor cell expression of endogenous retroviral elements, suppressing the proliferation of Tregs, and promoting cytotoxic T-cell mediated clearance of tumor cells, which was further enhanced through the addition of PD-1/L1 checkpoint blockade (22,23). In addition, CDK4/6i inhibited T cell proliferation, but enhanced the activation of effective T cells, and in part modulated NFAT family proteins and their target genes (24). For the specific immune function, CDK4/6i might be a potential agent to develop synergistic effects in the combination with PD-1/

L1 blockade for the treatment of luminal A and B type BC.

In approximately 20% of BC, HER2 was overexpressed, and the use of anti-HER2 antibody (trastuzumab and pertuzumab) has been correlated with prolonged OS. Both anti-HER2 antibodies are able to induce antibody-dependent cellular cytotoxicity (ADCC), DC maturation, T cell infiltration, and the upregulation of PD-1/L1 (25,26). In murine models, the activity of HER2 antibody could enhance IFN- $\gamma$ -producing CD8<sup>+</sup> T cells, and the therapeutic effect is improved when combined with anti-PD-1 antibody (27). Data from a phase Ib/II trial showed that a 20% ORR was observed in trastuzumab-resistant PD-L1 positive tumors when treated with pembrolizumab plus trastuzumab (28). Ongoing clinical trials will further reveal whether the combination therapy of anti-HER antibody with anti-PD-1/L1 is effective in BC patients.

The HER2 signaling is also correlated with activation of the downstream PI3K/mTOR/AKT pathway, the blockade of which will enhance immune effects. The mTOR and PI3K inhibitors have been approved in metastatic BC, and the AKT inhibitor has showed promise in clinical trials. A recent study revealed that this pathway recruits MDSCs and Tregs, and also increased the constitutive expression of PD-L1 (29,30). However, other pre-clinical studies have implied that the inhibition of this pathway may decrease Tregs and promote T cell differentiation (31). In BC progression, Tregs develop an increased frequency with a Th2 cytokine micro-environment through upregulation of IL-4 and IL-10, and downregulation of circulating IFN- $\gamma$  and IL-2. Although the pre-clinical model is limited in the evaluation of combined therapy, additional anti-PD-1 may be a potential approach to enhance the benefit of PI3K/mTOR/AKT pathway blockade. Additionally, Ras-MAPK pathway activation might promote immune-evasion in TNBC, which could be further verified through clinical trials combining MEK- and PD-L1-targeted therapies (32). Additionally, HER2 treatment in BC might correlate with antibody-dependent cellular cytotoxicity (ADCC) basically via the activation of NK cells. Accordingly, BC bearing mice lacking Fc receptor (FcR)- $\gamma$  presented with regression in 29% cases, and BC patients with abnormal FcR polymorphisms were associated with reduced PFS (33).

Poly adenosine diphosphate ribose polymerase inhibitors (PARPi) have been approved by the FDA for use in metastatic BC with germline BRCA1/2 pathogenic variants (gBRCA). The OlympiAD clinical trial and EMBRACA trial both determined the direct anti-tumor effect of PARPi (34,35); however, PARPi may also have immunomodulatory

properties to improve the therapeutic efficacy of BC. In murine models, PARPi was associated with an increased number and function of cytotoxic T cells and NK cells, and induced the secretion of IFN- $\gamma$  (36,37). Moreover, in a *BRCA*-deficient murine ovarian cancer model, the PARPi olaparib could be able to induce innate and adaptive immune responses as well as increased therapeutic benefit when combined with anti-PD-1 via the stimulator of interferon genes (STING) pathway. Nevertheless, PARPi may have an immunosuppressive role in healthy immune function (36,37). A PARP-deficient murine model showed decreased switching to IgG2a, and PARP has also been shown to play an important role in normal T cell-dependent antibody responses (38). Additionally, PARP has been attributed to increases in the frequency of Tregs, and the modulation of Th1/Th2 cytokine/chemokine (39). In BC cell lines and murine models, PARPi could upregulate PD-L1 expression via the inactivation of GSK3 $\beta$  and enhance the killing function of T-cells. The combination of PARPi and anti-PD-L1 therapy has been shown to significantly improve therapeutic efficacy in BC (40). Thus, the synergistic potential of PARPi combined with anti-PD-1/L1 for the treatment of BC should be further ascertained through clinical trials (41).

Anti-angiogenesis therapy, such as inhibitors of vascular endothelial growth factor/vascular endothelial growth factor receptor 2 (VEGF/VEGFR2), is commonly used in metastatic tumors, including BC. The combination of anti-PD-L1 and anti-VEGFR2 generated high endothelial venules (HEVs) in PyMT (polyoma middle T oncoprotein) BC by activating lymphotoxin  $\beta$  receptor (LT $\beta$ R) signaling and also enhanced cytotoxic T cell (CTL) activity, which provides an evidence of anti-PD-L1 therapy with anti-angiogenesis for treating BC (42).

#### *Anti-PD-1/L1 with endocrine therapy*

In HR positive BC, endocrine modulation remains an important therapeutic approach. Up to now, the FDA has approved selective estrogen receptor modulators such as tamoxifen, aromatase inhibitors like anastrozole, exemestane, and letrozole, and a selective estrogen receptor degrader, fulvestrant (43). The expressions of PD-1/L1 are low in HR positive cancer partly bringing about low response rate of anti-PD-1/L1 therapy for BC. A trial showed the usage of pembrolizumab did not increase the OS for hormone-positive metastatic BC (3). However, another trial showed the pathologic complete response

(pCR) rate of PD-1/L1 therapy with standard neoadjuvant chemotherapy in HR positive BC was 30% *vs.* 13% of control, presenting a potential success approach to treat BC (44). Moreover, some of HR positive BC treated with endocrine therapy finally became resistance and incident metastasis with poor prognosis. The KEYNOTE-028 showed the partial response (PR) rate of HR positive metastasis BC patients received pembrolizumab (PD-1 inhibitor) was 12% and complete response (CR) was 0 (45). The JAVELIN trial demonstrated that the overall response (ORR) was 2.8% in HR positive metastasis BC patients with avelumab (PD-L1 inhibitor) treated and higher ORR was observed in PD-L1 positive tumor-associated immune cells (46). Additionally, CDK4/6 ongoing trials should be conducted to explore the efficacy of anti-PD-1/L1 with endocrine therapy. Otherwise, most HR positive BC also expresses the androgen receptor (AR), which could regulate thymic T cell production and T cell cytolytic activity (47). Blockade of AR was associated with increased immune-mediated killing of BC cells, due to the overexpression of cell surface tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptor as well as down-expression of osteoprotegerin (OPG) (48). Further clinical trials in BC should be conducted to evaluate AR blockade or estrogen receptor modulator with anti-PD-1/L1.

#### *Anti-PD-1/L1 with radiotherapy*

Radiotherapy has been commonly adopted in some BC settings with axillary lymph node metastasis, bone metastasis, chest wall lesions, and central nervous system metastasis. Although the main mechanism of radiotherapy is lethal DNA damage, preclinical and clinical studies have shown that radiotherapy combined with immunotherapy would obtain better local and systemic control (49). The DNA damage induced by radiation triggered danger signals which further facilitated DC maturation and release antigens of proinflammatory signals to activate tumor specific T cells (50). Radiotherapy was also associated with T cell recruitment, adaptive loss of MHC, or beta-2 microglobulin (51). In murine models and patients, studies have supported that radiation improved the diversity of the T-cell receptor (TCR) repertoire of intratumoral T cells, and the addition of PD-L1 blockade caused T-cell exhaustion and further facilitated oligoclonal T-cell expansion. This study suggested that the combination of radiation, anti-CTLA4, and anti-PD-L1 would increase the immune response (52). In a BC model, tumor-derived microparticles

(TMPs)-extracellular vesicles might shed from the effect of radiotherapy via inhibition of cytotoxic T lymphocyte activity. In addition, TMP-mediated inhibition of CTL activity was shown to be partly inhibited by blocking the PD-1/L1 axis in response to radiotherapy (8). Baseline T cell functionality is partly impeded in metastatic BC patients with radiotherapy, the addition of PD-1 blockade may improve TGF $\beta$  blockade and radiotherapy response (53). Moreover, the dose and timing of radiotherapy would influence the immunotherapy response, the future study of which is warranted. Radiation with anti-PD-1/L1 has previously been tolerated in metastatic BC (54). Thus, radiation with other immune agents such as TLR3 agonists and fms-related tyrosine kinase 3 ligand, or combined with anti-PD-1/L1 might have synergistic effects in the treatment of BC.

#### **Conclusions**

The monotherapy of immune checkpoint inhibitors, especially PD-1/L1 has been observed to have modest effects in BC compared to other carcinoma, including melanoma and non-small cell lung cancer, partly due to low immunogenicity in BC. However, the minority of patients who responded to PD-1/L1 blockade could benefit from the therapy and experience durable tumor control. Moreover, pre-clinical and early clinical data have all supported continuing study regarding the combination of anti PD-1/L1 with standard-of-care therapy, such as chemotherapy, targeted therapy, endocrine therapy, and radiotherapy.

Among participants receiving anti PD-1/L1 plus chemotherapy, a phase Ib and III trial revealed PFS benefit in the entire cohort and OS benefit in PD-L1 positive metastatic TNBC subgroup, supporting the standard first-line therapy of anti PD-L1 antibody atezolizumab plus nab-paclitaxel in the treatment of PD-L1-positive patients with more than 12 months distant recurrence free interval. The ongoing Keynote 355 clinical trial shall recruit 855 BC patients, which will further address the alternative chemotherapy regimens combined with anti-PD-1/PD-L1. A number of patients will display upregulated expression PD-L1 after chemotherapy, thus a new approach for detecting PD-L1 expression should be developed. For the heavily glycosylation of PD-L1, a new method was developed to detect PD-L1 expression by removing glycan moieties from the cell surface through enzymatic digestion, which significantly improved the binding affinity of anti-PD-L1 antibody, attributing to the guidance of anti-PD-1/

L1 therapy and prolonged durable responses in BC (55-57).

Patients with BC who received anti PD-1/L1 plus targeted therapy have been shown to receive more therapeutic benefit. First-line pertuzumab/trastuzumab/paclitaxel +/- atezolizumab are currently being evaluated in a phase III randomized trial. Anti PD-1/L1 plus T-DM1 has also been associated with prolonged PFS but only in PD-L1 positive group.

For participants receiving anti PD-1/L1 plus endocrine therapy or radiotherapy, several studies have demonstrated comparable benefit with or without anti PD-1/L1, though several strategies had mechanistic bases, especially of AR blockade and radiotherapy with specific dose and timing. Further research with novel biomarkers will assist the development of new personalized therapy for BC patients.

The combination of anti PD-1/L1 with other approaches has been shown to be relatively safe; however, some long-term toxicity existed, which should be noted during clinical treatment.

In conclusion, anti PD-1/L1 combined with therapeutic approaches was safe and effective in BC, especially for atezolizumab plus nab-paclitaxel. Future vast clinical trials should be conducted to provide further evidential support for combination approaches.

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*Ethical Statement:* The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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