**Advances in targeting programmed cell death 1/programmed cell death-ligand 1 therapy for hematological malignancies**

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**Abstract:** Programmed cell death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) are important immune checkpoints, and their interactions can mediate immune suppression in the tumor microenvironment. Targeting PD-1 and PD-L1 are immune checkpoint inhibitors that bind to PD-1 and PD-L1, respectively, to block the signal pathway between the two and increase the immune response. They are widely used in tumor treatment and have good efficacies for malignant melanoma, renal cell carcinoma, and non-small cell lung cancer, among others. In addition, for hematological malignancies, studies targeting PD-1 and PD-L1 have achieved gratifying results. This article briefly reviews the mechanisms of action and clinical and hematological malignancy applications of targeting PD-1 and PD-L1.

**Keywords** PD-1, PD-L1, Mechanism of action, Hematological malignancy

**Introduction**

In recent years, tumor immunotherapy has gradually become a hot spot in the field of tumor treatment and has shown good prospects in cancer treatment[[1](#_ENREF_1" \o "Couzin-Frankel, 2013 #7)], which is also one of the most promising research directions in tumor treatment. Programmed cell death 1 (PD-1; also known as CD279[[2](#_ENREF_2" \o "Ok, 2017 #8)]) is a member of the B7 receptor family. Its ligands are programmed cell death-ligand 1 (PD-L1; also known as CD274) and programmed cell death-ligand 2 (PD-L2; also known as CD273), which are expressed by multiple types of cells[[3](#_ENREF_3" \o "Bachy, 2014 #9)]. Among them, PD-1 and PD-L1 are the most common immune checkpoints, which mainly inhibit stimulation, negatively regulate T-cell functions, and weaken the immune response to tumors. Therefore, targeting PD-1 and PD-L1 can block the combination of PD-1 and PD-L1 to restore the antitumor effect of the immune system. This article briefly reviews its mechanism of action and application in hematological malignancies.

**1 Mechanism and overview of PD-1/PD-L1**

**1.1 Structural features**

PD-1 is a transmembrane protein with 288 amino acids and belongs to the immunoglobulin superfamily. It is present in lymphocytes, natural killer (NK) cells, monocytes, and dendritic cells[[4](#_ENREF_4" \o "Keir, 2008 #10)]. PD-1 contains an Ig variable-type extracellular domain, a transmembrane domain, and a cytoplasmic tail[[5](#_ENREF_5" \o "Zhang, 2004 #11)]. The cytoplasmic tail has an immunoreceptor tyrosine-based inhibitory motif (ITIM)[[6](#_ENREF_6" \o "Ishida, 1992 #12)] and immunoreceptor tyrosine-based switch motif (ITSM). After PD-1 binds to PD-L1, the ITIM and ITSM of PD-1 are phosphorylated by Src family tyrosine kinases[[7](#_ENREF_7" \o "Guntermann, 2002 #116)], thereby inhibiting T-cell activity and proliferation. Thus, PD-1 has dual roles in immunological tolerance: induction and maintenance of peripheral tolerance[[8](#_ENREF_8" \o "Okazaki, 2006 #13)]. PD-1 can also bind to B7-H1 and the crystallizable fragment (Fc) fusion protein to inhibit the production of interleukin-2 (IL-2) in lipopolysaccharide (LPS-stimulated RAW264.7 cells by inhibiting the Janus N-terminal kinase signaling pathway[[9](#_ENREF_9" \o "Cho, 2009 #126)].

Programmed cell death-ligands (PD-Ls) contain PD-L1 and PD-L2. Whereas PD-L1 is constitutively expressed and upregulated in T cells, B cells, macrophages, dendritic cells, endothelial cells, epithelial cells, and muscle cells, PD-L2 is only expressed on the surface of dendritic cells, macrophages, and bone marrow-derived mast cells[[10](#_ENREF_10" \o "Sharpe, 2007 #93)]. Moreover, they have similar exon organizations of the 5′-untranslated region; a signal sequence; IgV-like, IgC-like, and transmembrane domains; and cytoplasmic exons 1 and 2 with the 3′-untranslated region[[11](#_ENREF_11" \o "Latchman, 2001 #15)]. PD-L1 has many functions; when it binds to PD-1, it can inhibit T-cell proliferation and cytokine production[[11](#_ENREF_11" \o "Latchman, 2001 #15)]. PD-L1 can also interact with B7-1. Regarding its mechanism of action, many theories have been proposed, with some studies suggesting that *cis*-PD-L1/B7-1 on antigen-presenting cells (APCs) disrupts the transbinding of PD-1/PD-L1. Through this mechanism, APCs expressing substantial amounts of B7-1 mediate diminished T-cell inhibition via PD-1[[12](#_ENREF_12" \o "Sugiura, 2019 #120)], which provides a relevant basis for combination therapy with B7-1 and PD-L1. The role of the combination of PD-L2 and PD-1 in regulating the differentiation and function of T cells remains to be determined because both coinhibitory and costimulatory functions have been reported[[13](#_ENREF_13" \o "Patsoukis, 2020 #154)]. Therefore, drug designs are mainly focused on PD-1 and PD-L1 targets. PD-L2 can also interact with repulsive guidance molecule b (RGMb) to regulate respiratory tolerance[[13](#_ENREF_13" \o "Patsoukis, 2020 #154)].

**1.2 Mechanisms**

PD-1 can bind to PD-Ls. When binding to a PD-1 ligand on antigen-presenting cells, PD-1 can shut down self-reactive T cells and induce peripheral tolerance. While binding to a PD-1 ligand on parenchymal cells, PD-1 can maintain tolerance and prevent tissue destruction by inhibiting effector T cells[[8](#_ENREF_8" \o "Okazaki, 2006 #13)]. The mechanisms of action of targeting PD-1/PD-L1 are shown in Figure 1.

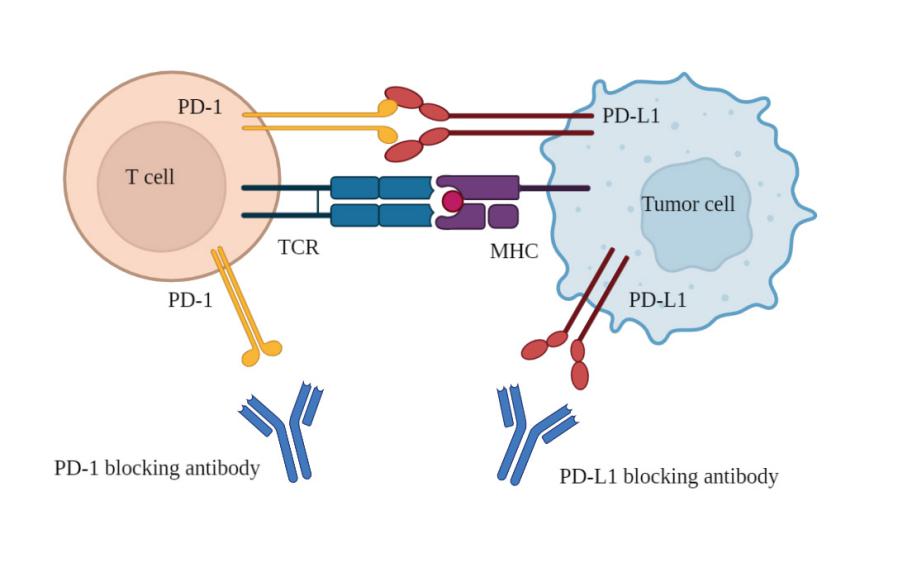


Figure 1. The mechanisms of action of targeting PD-1/PD-L1.

The PD-1 pathway has various mechanisms of action. After the ITIM and ITSM of PD-1 are combined, they are phosphorylated by Src family tyrosine kinases, and Src homology 2 domain-containing phosphatases (SHPs) are further recruited to the phosphorylated tyrosine residue. SHPs can dephosphorylate downstream signaling pathways, thereby blocking cell cycle progression[[14](#_ENREF_14" \o "Saunders, 2010 #122)]. SHPs can also inactivate zeta-chain-associated protein kinase 70 and protein kinase C-θ[[2](#_ENREF_2" \o "Ok, 2017 #8)]. In addition, Francisco and colleagues demonstrated that PD-L1 can induce and maintain Tregs and enhance immune suppression at the organismal level[[15](#_ENREF_15" \o "Francisco, 2009 #155)].

**1.3 Clinical application**

Immune checkpoint inhibitors have become a key method of cancer treatment, especially targeting PD-1/PD-L1. In recent decades, an increasing number of related drugs have been used to treat malignant tumors.

Among PD-1 inhibitors, pembrolizumab[[16](#_ENREF_16" \o "Callahan, 2016 #17)] was first approved by the Food and Drug Administration (FDA) in September 2014 for the treatment of melanoma, non-small cell lung cancer (NSCLC), and so forth. Three months later, nivolumab was approved for release in the market[[16](#_ENREF_16" \o "Callahan, 2016 #17)] for the treatment of melanomas that are unresponsive to other drugs. In the same year, MPDL3280A was shown to be a breakthrough therapy for metastatic bladder cancer and NSCLC in February of the following year. In China, Opdivo (nivolumab) was first approved for release in the market in June 2018; and Keytruda (pembrolizumab), in July. Thereafter, several drugs have been launched in the market.

Among PD-L1 inhibitors, atezolizumab was first approved by the FDA for the treatment of bladder cancer, followed by durvalumab, avelumab, and so forth. At present, two PD-L1 inhibitors have been approved for release in the market in China, namely Imfinzi (durvalumab) in December 2019 and Bavencio (atezolizumab) in February 2020.

However, with the progress of drug research, drug resistance has gradually become an urgent problem to be solved. Research has shown that the tumor-immune cycle is divided into the following seven steps: the release of cancer antigens, cancer antigen presentation, priming and activation, trafficking of T cells to tumors, infiltration of T cells into tumors, recognition of cancer cells by T cells, and killing of cancer cells. Given that PD-1/PD-L1 blockade is primarily involved in step 7, any abnormalities in the previous steps may lead to drug resistance[[17](#_ENREF_17" \o "Zhuang, 2020 #163)], such as lack of tumor antigen expression, dysbiosis of the normal gut microbiome, and migration disorders of T cells. Therefore, for combination drugs, the PD-1/PD-L1 pathway can be used as the cornerstone of the combined checkpoint blockade program to antagonize additional inhibitory signals and thereby improve the immunity efficacy of checkpoint blockade in cancer treatment[[18](#_ENREF_18" \o "Minn, 2016 #23)]. At present, the most commonly used combination drugs are as follows: Radiotherapy can cause the release of tumor antigens and increase the immunogenicity of tumors[[19](#_ENREF_19" \o "Twyman-Saint Victor, 2015 #133)]. Vaccines, CD40 agonists, and toll-like-receptor agonists can promote dendritic cell (DC) cross-presentation to enhance the anti-tumor response of T cells. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) blockers, CD137 agonists, and inflammatory cytokines such as IL-2 can enhance the initiation and activation of T cells. Block inhibitory immune checkpoint molecules such as T-cell immunoglobulin and mucin domain 3 (TIM-3) and lymphocyte-activation gene 3 (Lag-3)[[17](#_ENREF_17" \o "Zhuang, 2020 #163)] can reduce the drug resistance of targeting PD-1/PD-L1 and enhance the therapeutic effect.

**2 Application of targeting PD-1/PD-L1 in hematological malignancies**

With the progress of drug research, targeting PD-1/PD-L1 has gradually been used in hematological malignancies. Relevant clinical trials have been conducted for drugs such as nivolumab and pembrolizumab, and some drugs have been approved for use in the clinical treatment of certain hematological malignancies. According to research, for hematological malignancies, targeting PD-1/PD-L1 is most effective for lymphoma, followed by leukemia, but least effective for multiple myelomas (MMs). This may be related to the expression levels of PD-L1 in different types of tumors and in the tumor microenvironment.

Several studies have examined the usefulness of PD-L1 expression levels. Immunohistochemistry (IHC) assays have demonstrated that response rate directly correlates with PD-L1 expression level. In addition, patients with high PD-L1 expression levels in tumor-infiltrating immune cells showed better therapeutic responses and clinical outcomes[[20](#_ENREF_20" \o "Diggs, 2017 #166)]. However, the expression levels of PD-L1 on neoplastic cells and in the tumor microenvironment vary between different subtypes, and the prognostic implications of PD-L1 expression remain unclear[[21](#_ENREF_21" \o "Xie, 2019 #167)]. Future studies need to further delineate the mechanisms of PD-L1 expression and explore more possibilities in depth.

In addition, the therapeutic effect of targeting PD-1/PD-L1 may also be related to the tumor microenvironment, in which inflammatory cytokines, especially interferon γ (IFN-γ), are present. Inflammatory cytokines stimulate not only tumor cells that express PD-L1 and PD-L2 but also other types of cells in the tumor microenvironment, such as macrophages, dendritic cells, and stromal cells, that increase the expression level of PD-1 ligand[[22](#_ENREF_22" \o "Boussiotis, 2016 #168)].

Therefore, among hematological malignancies, lymphoma has the best therapeutic response. In particular, the copy numbers of the PD-L1 and PD-L2 gene loci in most patients with Hodgkin lymphoma (HL) are amplified, which leads to the upregulation of PD-L1 and PD-L2 expressions. Therefore, targeting PD-1/PD-L1 has a good therapeutic effect on HL. In non-HL (NHL), targeting PD-1/PD-L1 has a good therapeutic effect on diffuse large B-cell lymphoma (DLBCL). Nearly 20% of DLBCLs not otherwise specified (NOS) have PD-L1 overexpression, and the structural abnormality of the 9p24.1 chromosome is significantly related to PD-L1 expression. Targeting PD-1/PD-L1 also has a good therapeutic effect on NK/T-cell lymphoma (NKTCL). The mRNA levels of PD-L1 and PD-L2 in patients with NKTCL are significantly upregulated. However, patients with mantle cell lymphoma (MCL) have weaker PD-L1 and PD-L2 on the surfaces of B and T cells than healthy individuals, and experiments have shown that, targeting PD-1/PD-L1 is ineffective in these patients. Targeting PD-1/PD-L1 has a weaker therapeutic effect on leukemia than lymphoma. Patients with acute myeloid leukemia (AML) have a significant increase in PD-1 expression on T cells due to the imbalance of the PD-1 pathway and the tumor microenvironment. Targeting PD-1/PD-L1 has the weakest therapeutic effect on MMs. Experiments have shown that in patients with MMs, the expression levels of PD-L1 in plasma cells are different and higher than those in healthy volunteers.

Regarding the specific application of targeting PD-1/PD-L1 to hematological malignancies, this article describes its effects.

**2.1 Lymphoma**

**2.1.1 Hodgkin lymphoma**

For most HLs, cytogenetic studies have shown that the copy numbers of the gene loci of PD-L1 and PD-L2 are amplified, which leads to the upregulation of the surface expressions of PD-L1 and PD-L2[[23](#_ENREF_23" \o "Longley, 2019 #44)]. Therefore, targeting PD-1/PD-L1 has a better therapeutic effect on HLs.

**2.1.1.1** **Relapsed/refractory HL**

Currently, nivolumab and pembrolizumab are approved by the FDA for the treatment of advanced relapsed/refractory (r/r HL). In addition, a previous study found that 70% of patients with r/r HL responded to PD-1 inhibitors, of whom 20% had a complete response[[24](#_ENREF_24" \o "Meti, 2018 #64)].

A retrospective study included 53 patients with r/r HL from nine US centers who were treated with nivolumab. The overall efficacy rate obtained by the discoverer was 68%; 12-month progression-free survival rate, 75%; overall survival rate, 89%; complete remission rate, 45%; and partial remission rate, 23%[[25](#_ENREF_25" \o "Bair, 2019 #134)], indicating that nivolumab has a good treatment effect on HL. A clinical trial published by the European Hematology Association (Abstract: PF431) studied the use of nivolumab and brentuximab vedotin (BV) as combination therapy for the treatment of 10 patients after failure of nivolumab monotherapy. The median follow-up time was 10.8 months (range, 7.4–13 months). The objective response rate of the treated patients was 70%, the complete response rate was 30%, and nine patients (90%) had treatment-related adverse events (AEs), of which nausea and peripheral neuropathy were the most common. This shows that the therapeutic effect of nivolumab + BV is similar to that of monotherapy. Thus, nivolumab + BV is expected to be an effective rescue plan for patients with r/r HL who have failed to respond to nivolumab monotherapy. In addition, a recent study found that for 59 patients with r/r HL treated with nivolumab and BV after autologous hematopoietic cell transplantation, the 18-month progression-free and overall survival rates were 95% and 98%[[26](#_ENREF_26" \o "MD, 2020 #95)], respectively, indicating that nivolumab is also expected to be used for the consolidation of autologous hematopoietic cell transplantation.

Pembrolizumab therapy is also effective. A multi-cohort phase II study found that pembrolizumab has clinical activity in patients with r/r HL, with an objective response rate of 65–72% and a complete response rate of 22%[[27](#_ENREF_27" \o "Chen, 2016 #164)]. A phase I clinical study found that after treatment with pembrolizumab, of 31 patients who failed treatment with an anti-CD30 monoclonal antibody, 90% had tumor shrinkage, with a total efficacy rate of 65%[[28](#_ENREF_28" \o "Armand, 2016 #165)], showing a satisfactory result. Pembrolizumab can also be combined with other drugs. A phase II study found that 32 (94%) of 34 patients achieved complete remission after using pembrolizumab-GVD (gemcitabine, vinorelbine, and liposomal doxorubicin) as a second-line treatment for r/r HL[[29](#_ENREF_29" \o "Moskowitz,  #49)]. This shows that the treatment is better than the standalone treatment and is an efficient and well-tolerated program.

In addition to the two above-mentioned drugs, many drugs are effective for the treatment of r/r HL. A study used sintilimab to treat 96 patients with r/r cHL and showed that as of September 30, 2019, 57.3% of patients completed the treatment. After 2 years of treatment, the 2-year overall survival rate was 96.3%. The long-term follow-up results showed that in addition to the high response rate, sintilimab also showed long-lasting efficacy and good long-term safety[[30](#_ENREF_30" \o "Su, 2020 #158)]. A clinical study used camrelizumab combined with decitabine to treat 51 patients with r/r cHL who failed treatment with anti-PD-1 therapy. The median progression-free survival time with the combination therapy was significantly longer than that with the previous anti-PD-1 monotherapy. In patients who achieved complete remission at 24 months, 78% observed a durable response[[31](#_ENREF_31" \o "Wang, 2021 #106)], indicating that in patients with r/r cHL, the use of camrelizumab and decitabine as third-line therapy or beyond has tolerable and significant antitumor activity.

**2.1.1.2 Untreated HL**

With the widespread application of targeting PD-1/PD-L1 in r/r HL, an increasing number of clinical trials have investigated its therapeutic effect on newly treated HL. In a recent phase II study, nivolumab and BV combination therapy in patients older than 60 years among the evaluable patients, the best objective response rate was 95%, proving that BV-nivo is effective for elderly patients with untreated HL who have comorbidities[[32](#_ENREF_32" \o "Cheson, 2020 #159)].

**2.1.2** **Non-Hodgkin lymphoma**

NHL is divided into B-, T-, and NK/T-cell lymphomas. B-cell lymphomas include DLBCL, follicular lymphoma (FL), and MCL. This article elaborates on these.

**2.1.2.1** **Diffuse large B-cell lymphoma**

In DLBCLs, PD-L1 can be expressed by B cells in DLBCL tumors and non-malignant cells (e.g., macrophages) from its immune microenvironment[[33](#_ENREF_33" \o "Laurent, 2015 #136)]. According to reports, nearly 20% of DLBCL NOS have genetic abnormalities and chromosomal changes, which lead to PD-L1 overexpression[[34](#_ENREF_34" \o "Georgiou, 2016 #51)]. Among these abnormalities, the structural abnormality of the 9p24.1 chromosome is significantly related to the expression of PD-L1 in DLBCL[[35](#_ENREF_35" \o "Kiyasu, 2015 #137)].

For the treatment of DLBCL, preliminary trials have shown that PD-1 inhibitors have limited effects on DLBCL. Nivolumab can be used alone, as a phase I study found that the use of nivolumab alone in the treatment of 81 patients with lymphoma and myeloma (11 cases of DLBCL) had an efficacy rate of 36%[[36](#_ENREF_36" \o "Lesokhin, 2016 #42)]. Nivolumab can also be used in combination therapies. In the combined use of nivolumab and ipilimumab in the treatment of 65 cases of hematological malignancies (10 cases of DLBCL), only three cases responded[[37](#_ENREF_37" \o "Ansell, 2016 #156)], indicating a poor treatment effect. Recently, a study (NCT03305445) that included six patients with DLBCL treated with nivolumab and ipilimumab after conventional treatment and before stem cell transplantation showed that three (50%) of the patients benefited from and well tolerated the transplantation, indicating an acceptable effect. A clinical trial evaluated pembrolizumab combined with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in the treatment of 30 patients with untreated DLBCL and revealed that the therapy had comparable toxicity with the standard R-CHOP therapy, but two patients developed grade 3 immune-related AEs. The overall and complete response rates were 90% and 77%, respectively, and the 2-year progression-free survival rate was 83%[[38](#_ENREF_38" \o "Smith, 2020 #138)], which was better than pembrolizumab monotherapy. Several later studies were conducted to examine the effect of pembrolizumab combined with other drug treatments.

In addition to the two abovementioned drugs, many other drugs have been studied for the treatment of DLBCL. A study of zanubrutinib in combination with tislelizumab in 69 patients with B-cell malignancies (including 27 with DLBCL) showed an objective remission rate of 37% in patients with DLBCL, of whom four (14.8%) had a complete remission and six (22.2%) had a partial remission[[39](#_ENREF_39" \o "Tam, 2019 #113)]. In germinal center B-cell-like (GCB) and non-GCB (NGCB) DLBCLs, the objective remission rates were 33.3% and 40%, respectively, indicating a poor therapeutic effect. A clinical trial of atezolizumab combined with R-CHOP in the treatment of 42 patients with untreated DLBCL showed that 31 patients (77.5%) achieved complete remission and four (10%) achieved partial remission according to an independent review committee[[40](#_ENREF_40" \o "Younes, 2019 #115)], which indicate a promising effect.

In some special types of DLBCL, targeting PD-1/PD-L1 has a better curative effect. In primary central nervous system lymphoma (PCNSL), owing to the changes in chromosome 9p24.1[[41](#_ENREF_41" \o "Chapuy, 2016 #139)], the PD-L1 expression level is increased, so targeted therapy drugs have a better effect. A clinical trial that used nivolumab to treat four patients with r/r PCNSL and one patient with relapsed primary testicular lymphoma (PTL) revealed that all five patients had objective responses, including complete remission in four patients and partial remission in one patient[[42](#_ENREF_42" \o "Reddy, 2017 #73)], indicating that the treatment has high efficacy, had a long-lasting curative effect, and can improve central symptoms at the same time. However, a phase II trial of nivolumab for r/r PCNSL or r/r PTL showed that the objective response rate assessed by blinded independent central review (BICR) was 6.4%, and the progression-free survival period was 1.41 months[[43](#_ENREF_43" \o "Nayak, 2017 #140)], indicating that the efficacy of targeting PD1/PD-L1 in PCNSL must be confirmed by more prospective clinical studies. An ongoing phase II clinical trial of nivolumab and ibrutinib for r/r PCNSL is currently recruiting patients[[44](#_ENREF_44" \o "Westin, 2019 #141)].

Primary mediastinal large B cell lymphoma (PMBCL) is similar to PCNSL because of the chromosome changes that lead to the overexpression of PD-L1; thus, the application of targeted drugs has a better effect. According to a report, the objective response rate of the first batch of 19 patients in the PMBCL cohort was 41%[[45](#_ENREF_45" \o "Chang, 2018 #66)]. The National Comprehensive Cancer Network guidelines recommend pembrolizumab for r/r PMBL. A phase II trial of pembrolizumab in the treatment of 53 patients with r/r PMBL showed an objective response rate of 45% and a complete response rate of 21%[[46](#_ENREF_46" \o "Armand, 2019 #74)], indicating effective outcomes. A clinical trial of nivolumab combined with BV in the treatment of 30 patients with r/r PMBL showed that at a median follow-up of 11.1 months, the objective response rate was 73%, the complete response rate assessed by each investigator was 37%, and the remission rate was 70%[[47](#_ENREF_47" \o "Zinzani, 2019 #110)], which is better than the treatment alone.

The overexpression of PD-L1 in Epstein-Barr virus (EBV)-associated lymphoma[[48](#_ENREF_48" \o "Lin, 2020 #75)] is thought to be mediated by the latent membrane protein 1 (LMP1) encoded by EBV[[49](#_ENREF_49" \o "Garon, 2015 #77)], which makes it sensitive to PD-1 blockade. An experiment was conducted to study the effect of PD-1 blockade on the antitumor immunity of lymphoma cells and revealed that PD-1 blockade exerted a highly effective role in EBV+ DLBCL[[50](#_ENREF_50" \o "Quan, 2015 #142)], stronger than that of EBV− DLBCL, indicating that targeting PD-1/PD-L1 will have a better effect on DLBCL. We look forward to conducting more clinical trials to verify the efficacy of the drug in the future.

**2.1.2.2** **Follicular lymphoma**

Unlike DLBCL, most FL tumor cells do not express PD-L1 or PD-L2[[33](#_ENREF_33" \o "Laurent, 2015 #136)], but the immune infiltrates expressed PD-L1 and PD-L2 at normal levels and overexpressed PD-1.[[33](#_ENREF_33" \o "Laurent, 2015 #136)]. Cells expressing PD-1 include not only cells derived from tumor-infiltrating lymphocytes (TILs) but also follicular helper T cells from lymphoma follicles or residual germinal centers[[51](#_ENREF_51" \o "Wahlin, 2010 #54)]. In addition, PD-1+ TILs in FL and DLBCL positively correlate with prognosis, and the presence of PD-1+ TILs in lymphoid tumors may indicate the source of the cells[[52](#_ENREF_52" \o "Kieser, 1997 #143)].

Regarding the treatment of FL, a phase I study of nivolumab for the treatment of r/r hematological malignancies (including 10 patients with recurrent FL) showed an objective remission rate of 40%[[36](#_ENREF_36" \o "Lesokhin, 2016 #42)]. A phase II clinical trial found that the use of nivolumab as the first-line treatment for immune initiation, followed by treatment with nivolumab and rituximab, in 39 patients with FL at a median follow-up time of 17.5 months achieved an overall response rate of 92%, a remission rate of 54%, and a median remission time of 5 months. In 25 evaluable patients, the 12-month progression-free and overall survival rates were 72% and 96%[[53](#_ENREF_53" \o "Alrawashdh, 2021 #161)], respectively, indicating that the effect of the regimen is better than that of nivolumab alone. A phase II clinical trial demonstrated that pidilizumab combined with rituximab in the treatment of 30 patients with relapsed FL had a total efficacy rate of 66%, with 52% of the patients achieving complete remission and 14% achieving partial remission[[54](#_ENREF_54" \o "Westin, 2014 #101)], indicating a good overall effect.

**2.1.2.3** **Mantle cell lymphoma**

On the basis of experiment results, PD-L1 and PD-L2 expressions on the surface of B and T cells in patients with MCL are weaker than those in healthy individuals[[55](#_ENREF_55" \o "Karolova, 2020 #78)]. Therefore, these results show that targeting PD-1/PD-L1 is not effective for the treatment of MCL and should not be used as a related drug target.

**2.1.2.4** **T-cell lymphoma**

Studies have shown that TCL overexpresses PD-1[[56](#_ENREF_56" \o "Vranic, 2016 #144)] according to the severity of the disease, so targeting PD-1/PD-L1 has a certain therapeutic effect on TCL. Targeting PD-1/PD-L1 is mostly used for r/r peripheral T-cell lymphoma (PTCL). A phase I clinical study used nivolumab to treat 23 patients with r/r TCL (of whom five had PTCL) and showed that the partial response rate of the patients with PTCL was 40%[[36](#_ENREF_36" \o "Lesokhin, 2016 #42)]. A clinical trial (NCT03075553) used nivolumab in the treatment of 12 patients with r/r PTCL and showed that the response rate of participants who achieved complete or partial remission was 33.3%, proving that nivolumab is effective for the treatment of PTCL. Pembrolizumab combined with romidepsin has been approved by the FDA for the treatment of r/r PTCL. It has been applied in the treatment of r/r PTCL in a phase I/II clinical study (NCT03278782) with 15 evaluable patients, with an objective response rate of 44% and a complete remission rate of 20%.

Regarding untreated T-cell lymphoma, a previous study showed a significant increase in PD-1 expression in peripheral CD4+ and CD8+ T cells. After treatment, the decline in PD-1 expression level was similar to that in healthy people, so we can infer that targeting PD-1/PD-L1 also has a good effect on T-cell lymphoma. Few clinical trials have been conducted on the treatment of untreated T-cell lymphoma, and targeting PD-1/PD-L1 is expected to have more applications in the future.

**2.1.2.5** **NK/T cell lymphoma**

The mRNA expression levels of PD-L1 and PD-L2 in extranodal NKTCL (ENKTCL) were significantly upregulated, and studies have found that PD-L1 protein is expressed in tumor cells in patients with ENKTCL[[57](#_ENREF_57" \o "Han, 2014 #81)]. Moreover, the expression level of soluble PD-L1 after treatment is a useful biomarker for monitoring patients with minimal residual disease[[58](#_ENREF_58" \o "Wang, 2016 #82)].

Targeting PD-1/PD-L1 for the treatment of r/r ENKTCL has a good effect. Nivolumab therapy has been proven to be effective for ENKTCL[[59](#_ENREF_59" \o "Chan, 2018 #145)]. A clinical trial of nivolumab in the treatment of three cases of r/r ENKTCL demonstrated a complete response in two patients and a partial response in one patient. Targeting PD-1 has also been proven to be effective for r/r ENKTCL for which treatment with l-asparaginase had failed[[60](#_ENREF_60" \o "Kwong, 2017 #103)]. In a retrospective case report, seven patients with r/r NKTCL achieved an objective response rate of 100% after seven treatment cycles[[60](#_ENREF_60" \o "Kwong, 2017 #103)]. The therapeutic effects of other drugs subjected to clinical trials were not as good as those of nivolumab and pembrolizumab. In a phase II trial, avelumab achieved a complete remission rate of 24% and an overall response rate of 38% in the treatment of 21 patients with r/r ENKTCL[[61](#_ENREF_61" \o "Kim, 2020 #146)]. A clinical trial (NCT03228836) of IBI308 in the treatment of 28 patients with r/r ENKTCL revealed a progression-free survival period of 30 months.

A study showed that the use of targeting PD-1 and pegaspargase, gemcitabine, and oxaliplatin (P-GEMOX) as a combination therapy for the treatment of nine patients with advanced ENKTCL achieved significant remission in eight patients, including complete remission in seven and partial remission in one[[62](#_ENREF_62" \o "Cai, 2021 #108)]. A clinical trial of sintilimab combined with chidamide in the treatment of 41 patients with r/r ENKTCL revealed an objective response rate of 58.3%, a complete response rate of 44.4%, and a partial response rate of 13.9%[[63](#_ENREF_63" \o "Gao, 2020 #109)]. These results show that sintilimab also has a beneficial effect in combination therapies.

**2.2 Leukemia**

**2.2.1 Acute myeloid leukemia**

Most patients with AML can achieve complete remission after conventional chemotherapy, and allogeneic hematopoietic stem cell transplantation is the only treatment option for AML[[64](#_ENREF_64" \o "Wang, 2020 #24)]. In recent years, the development of targeting PD-1/PD-L1 has also made significant achievements in the treatment of AML.

Studies have shown that the PD-1 pathway is abnormally expressed in AML. Mouse leukemia cell C1498 expresses low levels of PD-L1 when cultured in vitro but expresses elevated PD-L1 levels when cultured in vivo, which suggests that the PD-L1 expressions in leukemia cells benefit from the tumor microenvironment[[65](#_ENREF_65" \o "Zhang, 2009 #25)]. Clinical data also support the dysregulation of the PD-1 pathway in AML. Compared with healthy people, patients with AML have significantly higher PD-1 expression levels on T cells[[66](#_ENREF_66" \o "MD, 2016 #157)]. In addition to the PD-1 pathway, CTLA-4 and TIM-3[[2](#_ENREF_2" \o "Ok, 2017 #8)] are also involved in the pathogenesis of AML.

Clinical trials are ongoing to determine the effectiveness of targeting PD-1/PD-L1 for the treatment of AML, and its individual and combination treatments have shown positive results. A clinical trial showed that the use of nivolumab monotherapy as maintenance treatment in 14 patients with AML (not eligible for transplantation) achieved 6- and 12-month complete remission rates of 79% and 71%, respectively[[67](#_ENREF_67" \o "Kadia, 2018 #147)]. A phase II clinical study showed that the objective remission rate of nivolumab combined with azacytidine in the treatment of r/r AML was 33%[[68](#_ENREF_68" \o "Daver, 2019 #148)]. A clinical trial (NCT02464657) of idarubicin and cytarabine with nivolumab for the treatment of myelodysplastic syndrome and AML showed a relapse-free survival time of 18.54 months (range, 8.20–23.22 months) and an overall survival time of 18.54 months (range, 10.81–28.81 months).

A clinical trial (NCT02708641) of pembrolizumab in the treatment of 12 patients with AML showed a relapse time of 12.14 months. A clinical trial (NCT02996474) of pembrolizumab combined with decitabine in the treatment of 10 patients with r/r AML demonstrated that the regimen was feasible for all 10 people, indicating that the combined drug effect was better.

**2.2.2** **Acute lymphocytic leukemia**

Little is known about the role of targeting PD-1/PD-L1 in acute lymphocytic leukemia (ALL), and only a few relevant clinical trials have been conducted. Currently, a clinical trial (NCT02879695) of nivolumab and blinatumomab or nivolumab and ipilimumab in the treatment of patients with B-cell acute lymphoblastic leukemia is recruiting participants. A clinical trial (NCT04546399) of nivolumab combined with blinatumomab for the treatment of relapsed B-cell acute lymphoblastic leukemia is also recruiting participants. A phase I trial (NCT02819804) of nivolumab combined with dasatinib in the treatment of patients with ALL[[69](#_ENREF_69" \o "Man, 2017 #90)] was terminated because its efficacy could not be evaluated and analyzed. Another clinical trial (NCT03160079) of pembrolizumab combined with blinatumomab for the treatment of adult r/r B-cell acute lymphoblastic leukemia is also currently recruiting participants, and more related trials can be expected in the future.

**2.2.3** **Chronic myeloid leukemia**

Studies have shown that in chronic myeloid leukemia (CML), PD-L1 expression is upregulated in bone marrow cells, and PD-1 is present on T cells[[70](#_ENREF_70" \o "Christiansson, 2013 #149)]. However, little is known about the effectiveness of targeting PD-1/PD-L1 for CML. Some scholars have shown that the use of antigen-pulsed autologous dendritic cells or direct application of in vitro transcribed RNA encoding leukemia-related antigens combined with targeting PD-1 may help obtain a stronger immune response and better clinical results[[71](#_ENREF_71" \o "Held, 2013 #91)].

A clinical trial (NCT02011945) of nivolumab combined with dasatinib in the treatment of 16 patients with CML showed no incidence of dose-limiting toxicity. A clinical trial (NCT03516279) of pembrolizumab, dasatinib, and imatinib mesylate or nilotinib for the treatment of CML is currently conducting recruitment, and more related trials are expected in the future.

**2.2.4 Chronic lymphocytic leukemia**

Ramsay[[72](#_ENREF_72" \o "Ramsay, 2012 #33)] confirmed that the expression of PD-1 on CD3+ cells in patients with chronic lymphocytic leukemia (CLL) was significantly higher than that in healthy individuals. PD-1 expression was found to be a feature of CD4+ and CD8+ T-cell exhaustion in CLL, which inhibits CD4+ and CD8+ T cells from producing certain cytokines (IFN-γ and tumor necrosis factor [TNF])[[73](#_ENREF_73" \o "Riches, 2013 #34)].

However, the efficacy rate of targeting PD-1/PD-L1 for CLL is low. A phase II study (NCT02332980) reported that pembrolizumab was ineffective for CLL but effective for Richter's syndrome (RS) because patients with RS have higher PD-L1 expression levels and low T-cell receptor clonality[[74](#_ENREF_74" \o "Wang, 2018 #160)]. Currently, two trials (NCT03153202 and NCT03514017) of pembrolizumab combined with ibrutinib in the treatment of patients with CLL are conducting recruitment. However, no clinical trial (NCT04781855) of the combination of ipilimumab, ibrutinib, and nivolumab for the treatment of CLL has yet been conducted. A clinical trial (NCT03884998) of copanlisib combined with nivolumab in the treatment of patients with NHL in CLL is currently recruiting. Research on immunotherapy for patients with CLL is still ongoing, and more data to guide treatment needs must be confirmed through further research[[75](#_ENREF_75" \o "Yinjuan, 2020 #150)].

**2.3** **Multiple myeloma**

Studies have shown that the expression level of PD-L1 in plasma cells is different. Its expression level in patients with MM was higher than those in healthy volunteers and patients with monoclonal gammopathy of undetermined significance. In r/r MM, the expression level of PD-L1 is significantly increased[[76](#_ENREF_76" \o "Tamura, 2020 #151)]. Similar to that in CHL, the protein expression level of PD-L1 in myeloma cells is related to the increase in the PD-L1 copy number. Studies have shown that targeting PD-1 can improve survival in myeloma mouse models[[77](#_ENREF_77" \o "Hallett, 2011 #41)]. Unlike PD-L1, PD-L2 is not expressed in myeloma cells[[78](#_ENREF_78" \o "Görgün, 2015 #40)].

In a phase I study, 27 patients with r/r MM were treated with nivolumab, with a median follow-up time of 65.6 weeks, and 17 patients (63%) had the best remission rate[[36](#_ENREF_36" \o "Lesokhin, 2016 #42)]. A phase II study (NCT02612779) used nivolumab combined with elotuzumab in the treatment of six patients with MM and showed a progression-free survival time of 16.7 months and an objective remission rate of 51.5%, which were not better than those with monotherapy. Some clinical trials are also underway, such as that of nivolumab combined with melphalan for the treatment of MM (NCT03292263) and nivolumab, carfilzomib, dexamethasone, and pelareorep combined with r/r MM (NCT03605719).

A phase I study showed 20 patients (50%) experienced remission of r/r MM after treatment with pembrolizumab combined with lenalidomide and low-dose dexamethasone[[79](#_ENREF_79" \o "Mateos, 2016 #152)]. At present, this treatment method is not mentioned in the treatment guidelines for MM, and only a few related clinical trials have been conducted. Thus, more research and exploration are needed in the future.

**3 Adverse reactions**

Although targeting PD-1/PD-L1 has remarkable efficacy, it also induces immune-related AEs (irAEs). In principle, all checkpoint inhibitors can potentially induce irAEs in any organ, which can occur late after therapy initiation but possibly also after therapy cessation[[80](#_ENREF_80" \o "Zimmer, 2016 #169)]. As for targeting PD-1/PD-L1, related irAEs can involve the skin, gastrointestinal tract, liver, and endocrine system and other organ systems[[81](#_ENREF_81" \o "Hofmann, 2016 #176)].

irAEs occur for many reasons, which may be related to the increase in cytokine production[[82](#_ENREF_82" \o "Oyanagi, 2019 #171)]. However, the types of specific cytokines and their exact roles in the development of irAEs remain unclear, requiring further research. irAEs may also be caused by the cross reaction of T cells and similar antigens on healthy cells[[83](#_ENREF_83" \o "Yoest, 2017 #173)]. When treating two patients with fatal fulminant myocarditis and rhabdomyolysis, Johnson et al. examined the cross-reactivity theory of the etiology of irAEs and found that one or more targets of each patient's anti-tumor immune response were the same as or similar to the antigens normally expressed in the skeletal muscle and myocardium[[84](#_ENREF_84" \o "Johnson, 2016 #174)].

Most observed irAEs were successfully treated with systemic corticosteroids, but this was not always the case[[83](#_ENREF_83" \o "Yoest, 2017 #173)]. Hofmann et al. retrospectively reviewed cases with irAEs due to nivolumab or pembrolizumab treatment and found that some of these events resolved without treatment, improved with corticosteroid or other treatments, or were not resolved[[81](#_ENREF_81" \o "Hofmann, 2016 #176)]. In addition, Horvat et al. recommended that the threshold for starting systemic corticosteroids should be low, and if the symptoms do not improve, the threshold for upgrading the treatment to anti-TNF-α drugs should be considered within 1 week after treatment with high-dose corticosteroids[[85](#_ENREF_85" \o "Horvat, 2015 #177)].

**4 Conclusions**

In summary, targeting PD-1 and PD-L1 can block the combination of PD-1 and PD-L1 to enhance the immune response. It has many applications in tumors and is used in clinical immunotherapy for various tumors, with satisfactory therapeutic effects. In addition, with the gradual advancement of research and the increase in technical level, the therapeutic range of targeting PD-1/PD-L1 in tumors has gradually widened, and the remission rate of the disease has gradually increased. However, this treatment method still faces problems such as high drug development costs, instability, potential side effects, and a lack of standardized PD-1 detection procedures. We believe that with the advancement of research and the improvement of the technical level, these issues will be solved or improved. Targeting PD-1/PD-L1 will achieve greater breakthroughs and exert greater value in clinical research and antitumor therapy in the future.

**Abbreviations**

AE: adverse events

ALL: acute lymphocytic leukemia

AML: acute myeloid leukemia

APCs: antigen presenting cells

BICR: blinded independent central review

BV: brentuximab vedotin

CLL: chronic lymphocytic leukemia

CML: chronic myeloid leukemia

CTLA-4: Cytotoxic-T-lymphocyte-antigen-4

DC: dendritic cell

DLBCL: diffuse large B-cell lymphoma

EBV: Epstein-Barr virus

EHA: The European Hematology Association

ENKTCL: extranodal NK/T cell lymphoma

Fc: crystallizable fragment

FDA: Food and Drug Administration

FL: follicular lymphoma

GCB: germinal center B-cell-like

GVD: gemcitabine, vinorelbine, liposomal doxorubicin

HL: Hodgkin lymphoma

IFN γ: interferon γ

IHC: immunohistochemistry

IL-2: interleukin-2

irAEs: immune-related adverse events

IRC: independent review committee

ITIM: immunoreceptor tyrosine-based inhibitory motif

ITSM: immunoreceptor tyrosine-based switch motif

JNK: Janus N-terminal Kinase

Lag-3: lymphocyte-activation gene 3

LMP1: latent membrane protein 1

LPS: lipopolysaccharide

MCL: mantle cell lymphoma

MDS: myelodysplastic syndromes

MGUS: monoclonal gammopathy of undetermined significance

MM: multiple myeloma

MRD: minimal residual disease

NCCN: National Comprehensive Cancer Network

NGCB: non-germinal center B-cell-like

NHL: non-Hodgkin's lymphoma

NK: natural killer

NKTCL: NK/T cell lymphoma

NOS: not otherwise specified

NSCLC: non-small cell lung cancer

PCNSL: primary central nervous system lymphoma

PD-1: programmed cell death-1

PD-L1: programmed cell death-ligand 2

PD-L2: programmed cell death-ligand 1

PD-Ls: programmed cell death-ligands

P-GEMOX: pegaspargase, gemcitabine, oxaliplatin

PKC-θ: protein kinase C-θ

PMBCL: primary mediastinal large B cell lymphoma

PTCL: peripheral T cell lymphoma

PTL: primary testicular lymphoma

r/r HL: relapsed/refractory HL

R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone

RGMb: rejection guiding molecule b

RS: Richter’s syndrome

SHPs: Src homology 2 domain-containing phosphatases

TCL: T cell lymphoma

TCR: T-cell receptor

TFH: follicular helper T cells

TILs: tumor-infiltrating lymphocytes

TIM-3: T cell immunoglobulin and mucin-domain containing-3

TLR: Toll-like-receptor

TNF: tumor necrosis factor

ZAP70: zeta-chain-associated protein kinase 70

**Declarations**

**Competing interests:** All authors declare no conflicts of interest.

**Author contributions:** Liang Wang designed the study. Wanying Zhao and Yuanzheng Liang collected all the literatures and analyzed the data. Wanying Zhao wrote the paper. All authors revised the paper and approved the publication of this paper.

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**References：**

[1] Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy [J]. Science, 2013, 342(6165): 1432-1433.

[2] Ok C Y, Young K H. Checkpoint inhibitors in hematological malignancies [J]. Journal of Hematology & Oncology, 2017, 10(1): 103.

[3] Bachy E, Coiffier B. Anti-PD1 antibody: a new approach to treatment of lymphomas [J]. Lancet Oncology, 2014, 15(1): 7-8.

[4] Keir M E, Butte M J, Freeman G J, et al. PD-1 and its ligands in tolerance and immunity [J]. Annual Review of Immunology, 2008, 26(1): 677-704.

[5] Zhang X, Schwartz J-C D, Guo X, et al. Structural and Functional Analysis of the Costimulatory Receptor Programmed Death-1 [J]. Immunity, 2004, 20(3): 337-347.

[6] Ishida Y, Agata Y, Shibahara K, et al. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death [J]. The EMBO Journal, 1992, 11(11): 3887-3895.

[7] Guntermann C, Alexander D R. CTLA-4 Suppresses Proximal TCR Signaling in Resting Human CD4+ T Cells by Inhibiting ZAP-70 Tyr319 Phosphorylation: A Potential Role for Tyrosine Phosphatases [J]. Journal of Immunology, 2002, 168(9): 4420-4429.

[8] Okazaki T, Honjo T. The PD-1-PD-L pathway in immunological tolerance [J]. Trends in Immunology, 2006, 27(4): 195-201.

[9] Cho H-Y, Choi E-K, Lee S-W, et al. Programmed death-1 receptor negatively regulates LPS-mediated IL-12 production and differentiation of murine macrophage RAW264.7 cells [J]. Immunology Letters, 2009, 127(1): 39-47.

[10] Sharpe A H, Wherry E J, Ahmed R, et al. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection [J]. Nature Immunology, 2007, 8(3): 239-245.

[11] Latchman Y, Wood C R, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation [J]. Nature Immunology, 2001, 2(3): 261-268.

[12] Sugiura D, Maruhashi T, Okazaki I-M, et al. Restriction of PD-1 function by cis -PD-L1/CD80 interactions is required for optimal T cell responses [J]. Science, 2019, 364(6440): 558-566.

[13] Patsoukis N, Wang Q, Strauss L, et al. Revisiting the PD-1 pathway [J]. Science Advances, 2020, 6(38): eabd2712.

[14] Saunders P A, Hendrycks V R, Lidinsky W A, et al. PD-L2:PD-1 involvement in T cell proliferation, cytokine production, and integrin-mediated adhesion [J]. European Journal of Immunology, 2010, 35(12): 3561-3569.

[15] Francisco L M, Salinas V H, Brown K E, et al. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells [J]. Journal of Experimental Medicine, 2009, 206(13): 3015-3029.

[16] Callahan M K, Postow M A, Wolchok J D. Targeting T Cell Co-receptors for Cancer Therapy [J]. Immunity, 2016, 44(5): 1069-1078.

[17] Zhuang Y, Liu C, Liu J, et al. Resistance mechanism of PD-1/PD-L1 blockade in the cancer-immunity cycle [J]. OncoTargets and therapy, 2020, 13: 83-94.

[18] Minn A J, Wherry E J. Combination Cancer Therapies with Immune Checkpoint Blockade: Convergence on Interferon Signaling [J]. Cell, 2016, 165(2): 272-275.

[19] Twyman-Saint Victor C, Rech A J, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer [J]. Nature, 2015, 520(7547): 373-377.

[20] Diggs L P, Hsueh E C. Utility of PD-L1 immunohistochemistry assays for predicting PD-1/PD-L1 inhibitor response [J]. Biomarker Research, 2017, 5(1): 12.

[21] Xie M, Huang X, Ye X, et al. Prognostic and clinicopathological significance of PD-1/PD-L1 expression in the tumor microenvironment and neoplastic cells for lymphoma - ScienceDirect [J]. International Immunopharmacology, 2019, 77: 105999.

[22] Boussiontis V A. Molecular and Biochemical Aspects of the PD-1 Checkpoint Pathway [J]. New England Journal of Medicine, 2016, 375(18): 1767-1778.

[23] Longley J, Johnson P W M. Options for first line therapy of Hodgkin lymphoma [J]. Hematological Oncology, 2019, 37 Suppl 1(Suppl Suppl 1): 82-86.

[24] Meti N, Esfahani K, Johnson N A. The Role of Immune Checkpoint Inhibitors in Classical Hodgkin Lymphoma [J]. Cancers (Basel), 2018, 10(6): 204.

[25] Bair S M, Strelec L E, Feldman T A, et al. Outcomes and Toxicities of Programmed Death‐1 (PD‐1) Inhibitors in Hodgkin Lymphoma Patients in the United States: A Real‐World, Multicenter Retrospective Analysis [J]. The oncologist, 2019, 24(7): 955-962.

[26] Md A F H, Phd L C, Md Y N, et al. Consolidation with Nivolumab and Brentuximab Vedotin after Autologous Hematopoietic Cell Transplantation in Patients with High-Risk Hodgkin Lymphoma [J]. Blood, 2020, 136(Supplement 1): 19-20.

[27] Chen R W, Zinzani P L, Fanale M A, et al. Pembrolizumab for relapsed/refractory classical Hodgkin lymphoma (R/R cHL): phase 2 KEYNOTE-087 study [J]. Journal of Clinical Oncology, 2016, 34(15\_suppl): 7555.

[28] Armand P, Shipp M A, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure [J]. Journal of Clinical Oncology, 2016, 34(31): 3733.

[29] Moskowitz A J, Shah G, Sch Der H, et al. Phase II Study of Pembrolizumab Plus GVD As Second-Line Therapy for Relapsed or Refractory Classical Hodgkin Lymphoma [J]. Blood 2020, 136(Supplement 1): 17–18.

[30] Su H, Song Y, Jiang W, et al. Sintilimab for relapsed/refractory classical Hodgkin’s lymphoma: Long-term follow-up on the multicenter, single-arm phase II ORIENT-1 study [J]. American Society of Clinical Oncology, 2020, 38(15\_suppl): 8034.

[31] Wang C, Liu Y, Dong L, et al. Efficacy of Decitabine plus Anti-PD-1 Camrelizumab in Patients with Hodgkin Lymphoma Who Progressed or Relapsed after PD-1 Blockade Monotherapy [J]. Clinical Cancer Research, 2021, 27(10): 2782-2791.

[32] Cheson B D, Bartlett N L, Laplant B, et al. Phase II, multicenter trial of nivolumab (Nivo) and brentuximab vedotin (BV) in patients (Pts) with untreated Hodgkin lymphoma (HL) over the age of 60 years or unable to receive standard ABVD chemotherapy: Results of a study of Academic and Community Cancer Research United (ACCRU) RU051505I [J]. Journal of Clinical Oncology 2020, 38(15\_suppl): 8014.

[33] Laurent C, Charmpi K, Ggavelle P, et al. Several immune escape patterns in non-Hodgkin's lymphomas [J]. Oncoimmunology, 2015, 4(8): e1026530.

[34] Georgiou K, Chen L, Berglund M, et al. Genetic basis of PD-L1 overexpression in diffuse large B-cell lymphomas [J]. Blood, 2016, 127(24): 3026-3034.

[35] Kiyasu J, Miyoshi H, Hirata A, et al. Expression of programmed cell death ligand 1 is associated with poor overall survival in patients with diffuse large B-cell lymphoma [J]. Blood, The Journal of the American Society of Hematology, 2015, 126(19): 2193-2201.

[36] Lesokhin A M, Ansell S M, Armand P, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study [J]. Journal of Clinical Oncology, 2016, 34(23): 2698-2704.

[37] Ansell S, Gutierrez M E, Shipp M A, et al. A phase 1 study of nivolumab in combination with ipilimumab for relapsed or refractory hematologic malignancies (CheckMate 039) [J]. Blood, 2016, 128(22): 183.

[38] Smith S D, Till B G, Shadman M S, et al. Pembrolizumab with R‐CHOP in previously untreated diffuse large B‐cell lymphoma: potential for biomarker driven therapy [J]. British journal of haematology, 2020, 189(6): 1119-1126.

[39] Tam C S, Cull G, Opat S, et al. An Update on Safety and Preliminary Efficacy of Highly Specific Bruton Tyrosine Kinase (BTK) Inhibitor Zanubrutinib in Combination with PD-1 Inhibitor Tislelizumab in Patients with Previously Treated B-Cell Lymphoid Malignancies [J]. Blood, 2019, 134 (Supplement\_1): 1594.

[40] Younes A, Burke J M, Cheson B D, et al. Sharman; Safety and Efficacy of Atezolizumab in Combination with Rituximab Plus CHOP in Previously Untreated Patients with Diffuse Large B-Cell Lymphoma (DLBCL): Updated Analysis of a Phase I/II Study [J]. Blood, 2019, 134(Supplement\_1): 2874.

[41] Chapuy B, Roemer M G M, Stewart C, et al. Targetable genetic features of primary testicular and primary central nervous system lymphomas [J]. Blood, The Journal of the American Society of Hematology, 2016, 127(7): 869-881.

[42] Reddy N M, Thieblemont C. Thieblemont C Maintenance therapy following induction chemoimmunotherapy in patients with diffuse large B-cell lymphoma: current perspective [J]. Ann Oncol, 2017, 28(11): 2680–2690.

[43] Nayak L, Iwamoto F, Ferreri A, et al. CHECKMATE 647: A PHASE 2, OPEN‐LABEL STUDY OF NIVOLUMAB IN RELAPSED/REFRACTORY PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA OR RELAPSED/REFRACTORY PRIMARY TESTICULAR LYMPHOMA [J]. Hematological Oncology, 2017, 35(S2): 420-421.

[44] Westin J R, Fowler N H, Nastoupil L J, et al. A Phase II Trial of Nivolumab and Ibrutinib for Patients with Relapsed or Refractory Central Nervous System Lymphoma [J]. Blood, 2019, 134(Supplement\_1): 4086.

[45] Chang A, Schlafer D, Flowers C R, et al. Investigational PD-1 inhibitors in HL and NHL and biomarkers for predictors of response and outcome [J]. Expert Opin Investig Drugs, 2018, 27(1): 55-70.

[46] Armand P, Rodig S, Melnichenko V, et al. Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma [J]. J Clin Oncol, 2019, 37(34): 3291–3299.

[47] Zinzani P L, Santoro A, Gritti G, et al. Nivolumab Combined With Brentuximab Vedotin for Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma: Efficacy and Safety From the Phase II CheckMate 436 Study [J]. Journal of Clinical Oncology, 2019, 37(33): 3081-3089.

[48] Lin N, Song Y, Zhu J. Immune checkpoint inhibitors in malignant lymphoma: Advances and perspectives [J]. Chin J Cancer Res, 2020, 32(3): 303-318.

[49] Garon E B, Rizvi N A, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer [J]. N Engl J Med, 2015, 372(21): 2018-2028.

[50] Quan L, Chen X, Liu A, et al. PD-1 blockade can restore functions of T-cells in Epstein-Barr virus-positive diffuse large B-cell lymphoma in vitro [J]. PloS one, 2015, 10(9): e0136476.

[51] Wahlin B E, Aggarwal M, Montes-Moreno S, et al. A unifying microenvironment model in follicular lymphoma: outcome is predicted by programmed death-1--positive, regulatory, cytotoxic, and helper T cells and macrophages [J]. Clinical Cancer Research, 2010, 16(2): 637-650.

[52] Kieser A, Kilger E, Gires O, et al. Epstein–Barr virus latent membrane protein‐1 triggers AP‐1 activity via the c‐Jun N‐terminal kinase cascade [J]. The EMBO journal, 1997, 16(21): 6478-6485.

[53] Alrawashdh N, Mcbride A, Persky D O, et al. Survival trends in chronic lymphocytic leukemia in the era of oral targeted therapies in the United States: SEER database analyses (1985 to 2017) [J]. 2021, 39(15\_suppl): 7524.

[54] Westin J R, Chu F, Zhang M, et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial [J]. Lancet Oncology, 2014, 15(1): 69-77.

[55] Karolova J, Radek M, Helman K, et al. PD-1, PD-L1 and PD-L2 Expression in Mantle Cell Lymphoma and Healthy Population [J]. Folia Biologica, 2020, 66(4): 117-122.

[56] Vranic S, Ghosh N, Kimbrough J, et al. PD-L1 status in refractory lymphomas [J]. PloS one, 2016, 11(11): e0166266.

[57] Han L, Liu F, Li R, et al. Role of programmed death ligands in effective T-cell interactions in extranodal natural killer/T-cell lymphoma [J]. Oncology letters, 2014, 8(4): 1461-1469.

[58] Wang H, Wang L, Liu W-J. High post-treatment serum levels of soluble programmed cell death ligand 1 predict early relapse and poor prognosis in extranodal NK/T cell lymphoma patients [J]. Oncotarget, 2016, 7(22): 33035-33045.

[59] Chan T S Y, Li J, Loong F, et al. PD1 blockade with low-dose nivolumab in NK/T cell lymphoma failing L-asparaginase: efficacy and safety [J]. Annals of hematology, 2018, 97(1): 193-196.

[60] Kwong Y L, Chan T S Y, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase [J]. Blood, 2017, 129(17): 2437-2442.

[61] Kim S J, Lim J Q, Laurensia Y, et al. Avelumab for the treatment of relapsed or refractory extranodal NK/T-cell lymphoma: an open-label phase 2 study [J]. Blood, 2020, 136(24): 2754-63.

[62] Cai J, Liu P, Huang H, et al. Combination of anti-PD-1 antibody with P-GEMOX as apotentially effective immunochemotherapy for advancednatural killer/T cell lymphoma [J]. Signal Transduction and Targeted Therapy, 2021, 5(1): 289.

[63] Gao Y, Huang H, Wang X, et al. Anti-PD-1 Antibody (Sintilimab) Plus Histone Deacetylase Inhibitor (Chidamide) for the Treatment of Refractory or Relapsed Extranodal Natural Killer/T Cell Lymphoma, Nasal Type (r/r-ENKTL): Preliminary Results from a Prospective, Multicenter, Single-Arm, Phase Ib/II Trial (SCENT) [J]. Blood, 2020, 136(Supplement 1): 39–40.

[64] Wang J S. Progress and Trend of CAR-T and PD-1 Blockade in the Treatment of Acute Myeloid Leukemia--Review [J]. Zhongguo shi yan xue ye xue za zhi, 2020, 28(3): 1069-1074.

[65] Zhang L, GAJEWSKI T F, KLINE J. PD-1/PD-L1 interactions inhibit antitumor immune responses in a murine acute myeloid leukemia model [J]. Blood, 2009, 114(8): 1545-1552.

[66] Md N D, Phd S B, Md G G-M, et al. Defining the immune checkpoint landscape in patients (pts) with acute myeloid leukemia (AML) [J]. Blood, 2016, 128(22): 2900.

[67] Kadia T M, Cortes J E, Ghorab A, et al. Nivolumab (Nivo) maintenance (maint) in high-risk (HR) acute myeloid leukemia (AML) patients [J]. Journal of Clinical Oncology, 2018, 36(15\_suppl): 7014.

[68] Daver N, Garcia-Manero G, Basu S, et al. Efficacy, safety, and biomarkers of response to azacitidine and nivolumab in relapsed/refractory acute myeloid leukemia: a nonrandomized, open-label, phase II study [J]. Cancer discovery, 2019, 9(3): 370-383.

[69] Man L M, Morris A L, Keng M. New Therapeutic Strategies in Acute Lymphocytic Leukemia [J]. Current Hematologic Malignancy Reports, 2017, 12(3): 197-206.

[70] Christiansson L, S Dderlund S, Svensson E, et al. Loskog ASI Increased Level of Myeloid-Derived Suppressor Cells, Programmed Death Receptor Ligand 1/Programmed Death Receptor 1, and Soluble CD25 in Sokal High Risk Chronic Myeloid Leukemia [J]. PLoS One, 2013, 8(1): e55818.

[71] Held S A E, Heine A, Mayer K T, et al. Advances in Immunotherapy of Chronic Myeloid Leukemia CML [J]. Curr Cancer Drug Targets, 2013, 13(7): 768-774.

[72] Ramsay A G, Clear A J, Fatah R, et al. Multiple inhibitory ligands induce impaired T-cell immunologic synapse function in chronic lymphocytic leukemia that can be blocked with lenalidomide: establishing a reversible immune evasion mechanism in human cancer [J]. Blood, 2012, 120(7): 1412-1421.

[73] Riches J C, Davies J K, Mcclananan F, et al. T cells from CLL patients exhibit features of T-cell exhaustion but retain capacity for cytokine production [J]. Blood, 2013, 121(9): 1612-1621.

[74] Wang Y, Sinha S, Dong H, et al. Distinct immune signatures in chronic lymphocytic leukemia (CLL) and Richter’s syndrome (RS) [J]. Journal of Clinical Oncology, 2018, 36(15\_suppl): 7524.

[75] Yinjuan M, Yaozhu P. Research update on PD-1/PD-L1 pathway in hematological diseases [J]. Journal of Modern Oncology, 2020, 28(16): 2905-2909.

[76] Tamura H, Ishibashi M, Sunakawa-Kii M, et al. PD-L1–PD-1 pathway in the pathophysiology of multiple myeloma [J]. Cancers, 2020, 12(4): 924.

[77] Hallett W H D, Jing W, Drobyski W R, et al. Immunosuppressive Effects of Multiple Myeloma Are Overcome by PD-L1 Blockade - ScienceDirect [J]. Biology of Blood and Marrow Transplantation, 2011, 17(8): 1133-1145.

[78] G RG N G, Samur M K, Cowens K B, et al. Lenalidomide Enhances Immune Checkpoint Blockade-Induced Immune Response in Multiple Myeloma [J]. Clinical Cancer Research, 2015, 21(20): 4607-4618.

[79] Mateos M-V, Orlowski R, Siegel D, et al. Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma: final efficacy and safety analysis [J]. J Clin Oncol, 2016, 34(suppl 15): 8010a.

[80] Zimmer L, Goldinger S M, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy [J]. European Journal of Cancer, 2016, 60: 210-225.

[81] Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy [J]. European Journal of Cancer, 2016, 60: 190-209.

[82] Oyanagi J, Koh Y, Sato K, et al. Predictive value of serum protein levels in patients with advanced non-small cell lung cancer treated with nivolumab [J]. Lung Cancer, 2019, 132: 107-113.

[83] Yoest J M. Clinical features, predictive correlates, and pathophysiology of immune-related adverse events in immune checkpoint inhibitor treatments in cancer: a short review [J]. ImmunoTargets and therapy, 2017, 6: 73-82.

[84] Johnson D B, Balko J M, Compton M L, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade [J]. New England Journal of Medicine, 2016, 375(18): 1749-1755.

[85] Horvat T Z, Adel N G, Dang T-O, et al. Immune-Related Adverse Events, Need for Systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients With Melanoma Treated With Ipilimumab at Memorial Sloan Kettering Cancer Center [J]. Journal of Clinical Oncology, 2015, 33(28): 3193-3198.