**Advances in targeting PD-1/PD-L1 therapy in hematological malignancies**

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**Abstract** PD-1 (Programmed cell death-1) and PD-L1 (Programmed cell death-ligand 1) are important immune checkpoints, and their interactions can mediate immune suppression in the tumor microenvironment. Targeting PD-1 and PD-L1 are immune point inhibitors, which 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 efficacy in malignant melanoma, renal cell carcinoma, non-small cell lung cancer, etc. In addition, for hematological malignancies, studies targeting PD-1 and PD-L1 have also achieved gratifying results. This article briefly reviews the mechanism of action, clinical application of targeting PD-1 and PD-L1, and their applications in hematological malignancies.

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

**INTRODUCTION**

In recent years, tumor immunotherapy has gradually become a hot spot in the field of tumor treatment, and it has shown good prospects in the treatment of cancer[[1](#_ENREF_1" \o "Couzin-Frankel, 2013 #7)], which is also one of the most promising research directions in the tumor treatment. PD-1 (also known as CD279[[2](#_ENREF_2" \o "Ok, 2017 #8)]), is one of the members 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 cell[[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 the function of T cells, 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 anti-tumor effect of the immune system. This article briefly reviews its mechanism of action and its application in hematological malignancies.

**1 The mechanism and overview of PD-1/PD-L1**

**1.1 Structural features**

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

PD-Ls contains PD-L1 and PD-L2. While 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)]. As for structure, they have similar exon organization of the 5′untranslated region, a signal sequence, IgV-like, IgC-like, and transmembrane domains, cytoplasmic exon 1 and 2 with the 3′untranslated region[[11](#_ENREF_11" \o "Latchman, 2001 #118)]. 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 #118)]. PD-L1 can also interact with B7-1, regarding the mechanism of action there are many theories, with some studies suggesting that the cis-PD-L1/B7-1 on APCs disrupts the trans-binding 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 the combination therapy of 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 it has been reported that it has both coinhibitory and costimulatory functions[[13](#_ENREF_13" \o "Patsoukis, 2020 #154)], therefore the design of drugs is mainly focused on PD-1 and PD-L1 targets. PD-L2 can also interact with rejection guiding molecule b (RGMb) to regulate respiratory tolerance[[13](#_ENREF_13" \o "Patsoukis, 2020 #154)].

**1.2 Mechanism**

PD-1 can bind to PD-Ls, when binding to a PD-1 ligand on antigen-presenting cells can shut down self-reactive T cells and induce peripheral tolerance, while binding to a PD-1 ligand on parenchymal cells can maintain tolerance and prevent tissue destruction by inhibit effector T cells[[8](#_ENREF_8" \o "Okazaki, 2006 #13)].

The PD-1 pathway has various mechanisms of action. After the two are combined, the ITIM and ITSM of PD-1 are phosphorylated by Src-family tyrosine kinases and 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 (ZAP70) and protein kinase C-θ (PKC-θ)[[2](#_ENREF_2" \o "Ok, 2017 #8)]. In addition, Francisco and his colleagues demonstrated that PD-L1 can induce and maintain Tregs and enhance immune suppression at the organismal leve[[15](#_ENREF_15" \o "Francisco, 2009 #155)].

**1.3 Clinical application**

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

As for PD-1 inhibitors, Pembrolizumab[[16](#_ENREF_16" \o "Callahan, 2016 #17)] was first approved by the FDA in September 2014 for the treatment of melanoma, NSCLC, etc. 3 months later, Nivolumab was approved for marketing[[16](#_ENREF_16" \o "Callahan, 2016 #17)] and can be used to treat melanoma that does not respond to other drugs. In the same year, MPDL3280A was given a breakthrough therapy for metastatic bladder cancer, and was given a breakthrough therapy for NSCLC in February of the following year. In China, Opdivo (Nivolumab) was first approved for marketing in June 2018, and Keytruda (Pembrolizumab) was approved for marketing in July. After that, several drugs were launched.

As for PD-L1 inhibitors, Atezolizumab was first approved by the FDA for the treatment of bladder cancer, followed by Durvalumab, Avelumab, etc. At present, two PD-L1 inhibitors have been approved for marketing in China. They are Imfinzi (Durvalumab), which was approved in December 2019, and Bavencio (Atezolizumab), which was approved in February 2020.

However, with the progress of drug research, drug resistance has gradually become an urgent problem to be solved. Research shows, 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, migration disorders of T cells, etc. Therefore, combination drugs can use the PD-1/PD-L1 pathway as the cornerstone of the combined checkpoint blockade program, to antagonize additional inhibitory signals, thereby improve immunity efficacy of checkpoint blockade in the treatment of cancer[[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 TLR agonists can promote DC cross-presentation to enhance T cells Anti-tumor response. 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 TIM-3 and Lag-3[[17](#_ENREF_17" \o "Zhuang, 2020 #163)], etc. The above methods 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. Drugs, such as Nivolumab, Pembrolizumab, have conducted relevant clinical trials, and some drugs have been approved for use in the clinical treatment of certain hematological malignancies. According to research, as for hematological malignancies, targeting PD-1/PD-L1 is the most effective for lymphoma, leukemia second, and multiple myeloma is worse. This article will explain its effects in order.

**2.1 Lymphoma**

**2.1.1 Hodgkin lymphoma** **(HL)**

For most Hodgkin lymphoma, cytogenetic studies have shown that the copy number of the gene locus of PD-L1 and PD-L2 is amplified, leading to the up-regulation of the surface expression of PD-L1 and PD-L2[[20](#_ENREF_20" \o "Longley, 2019 #44)]. Therefore, targeting PD-1/PD-L1 has a better therapeutic effect on it.

**2.1.1.1** **Relapsed/refractory HL** **(rel/ref HL)**

Currently, Nivolumab and Pembrolizumab are approved by FDA for the treatment of advanced r/r HL. And the study found that 70% of r/r HL patients responded to PD-1 inhibitors, and 20% had a complete response[[21](#_ENREF_21" \o "Meti, 2018 #64)].

Regarding Nivolumab, a retrospective study included 53 r/r HL patients from 9 US centers. The overall effective rate of the discoverer was 68%, the 12-month progression-free survival rate was 75%, the overall survival rate was 89%, the complete remission rate was 45%, and the partial remission rate was 23%[[22](#_ENREF_22" \o "Bair, 2019 #134)], indicating that Nivolumab has a good effect on the treatment of HL. Regarding its combination therapy, a trial published on EHA (Abstract: PF431) studied the use of Nivolumab and Brentuximab Vedotin to treat 10 patients who failed the monotherapy of Nivolumab. The median follow-up time was 10.8 (7.4-13) months, the objective response rate of treated patients was 70%, the complete response rate was 30%, and 9 patients (90%) had treatment-related adverse events (AE), of which nausea and peripheral neuropathy were the most common. It shows that the therapeutic effect of Nivolumab + BV is similar to monotherapy, and it is expected to be an effective rescue plan for r/r HL patients who have failed monotherapy with Nivolumab. In addition, a recent study found that, for 59 patients with r/r HL who were treated with Nivolumab and Brentuximab Vedotin after autologous hematopoietic cell transplantation, the 18-month progression-free survival rate and overall survival rate were 95% and 98%[[23](#_ENREF_23" \o "MD, 2020 #95)], indicating that Nivolumab is also expected to be used for the consolidation of autologous hematopoietic cell transplantation.

Pembrolizumab also works well. 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%[[24](#_ENREF_24" \o "Chen, 2016 #164)]. A phase I clinical study found that, after given Pembrolizumab to 31 patients who failed treatment with an anti-CD30 monoclonal antibody, 90% of the patients had tumor shrinkage, with a total effective rate of 65%[[25](#_ENREF_25" \o "Armand, 2016 #165)], showing a satisfactory result. Pembrolizumab can also be combined with other drugs. A phase II study found that, 32 of 34 patients (94%) achieved complete remission after using Pembrolizumab-GVD as a second-line treatment for r/r HL[[26](#_ENREF_26" \o "Moskowitz,  #49)], Which shows that the treatment is better than the stand-alone treatment, and it is an efficient and well-tolerated program.

In addition to the above two drugs, there are many drugs that are effective in the treatment of r/r HL. A study used Sintilimab to treat 96 patients with r/r cHL, and found that as of September 30, 2019, 57.3% of patients completed the treatment. After two years of treatment, the two-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[[27](#_ENREF_27" \o "Su, 2020 #158)]. A clinical study used Camrelizumab combined with Decitabine to treat 51 patients with r/r cHL who had failed to anti-PD-1 therapy. It was found that the median progression-free survival of the combination therapy was significantly longer than that of the previous anti-PD-1 monotherapy. And in patients who achieved complete remission at 24 months, 78% of patients have observed a durable response[[28](#_ENREF_28" \o "Wang, 2021 #106)], indicating that in patients with r/r cHL, the use of Camrelizumab and Decitabine in the third line or above has tolerable and significant anti-tumor activity.

**2.1.1.2 Untreated HL**

With the widespread application of targeting PD-1/PD-L1 in r/r HL, more and more clinical trials are investigating its therapeutic effect in newly-treated HL. In a recent phase II study, it was found that Nivolumab and Brentuximab Vedotin combination therapy in patients older than 60 years old, among the evaluable patients, the best objective response rate was 95%, proving that BV-nivo is effective in untreated elderly HL with comorbidities[[29](#_ENREF_29" \o "Cheson, 2020 #159)]. There are also numerous clinical studies on targeting PD-1/PD-L1 for the treatment of HL.

**Table 1** lists most of the ongoing studies.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| IDX | Disease | Experiment  Title | Status | Intervention  /Treatment | State | Phase |
| 1 | r/r HL | NCT03337919 | Recruiting | Nivolumab | UK | II |
| 2 | HL at relapse/progression risk | NCT03436862 | Recruiting | Nivolumab | US | II |
| 3 | r/r cHL | NCT04091490 | Recruiting | Nivolumab, DHAP | Russia | II |
| 4 | r/r cHL | NCT03681561 | Recruiting | Nivolumab, Ruxolitinib | US | I/II |
| 5 | r/r HL | NCT04981899 | Recruiting | Nivolumab, Ifosfamide, Carboplatin, Etoposide | Russia | I/II |
| 6 | Recurrent HL | NCT03480334 | Recruiting | Nivolumab plus radiotherapy | Germany | II |
| 7 | HL | NCT03495713 | Recruiting | Nivolumab | US | II |
| 8 | r/r cHL | NCT02927769 | Recruiting | Nivolumab, Brentuximab Vedotin, Bendamustine | US | II |
| 9 | r/r cHL | NCT01896999 | Recruiting | Nivolumab, Brentuximab Vedotin, Ipilimumab | US | I/II |
| 10 | r/r HL | NCT03495713 | Recruiting | Nivolumab, Low-dose radiotherapy | US | II |
| 11 | HL | NCT03033914 | Recruiting | Nivolumab, Doxorubicin, Bleomycin, Vinblastine, Dacarbazine | US | I/II |
| 12 | r/r cHL | NCT04938232 | Recruiting | Nivolumab, Ipilimumab | US | II |
| 13 | Early HL | NCT04866654 | Recruiting | Nivolumab | Italy | II |
| 14 | r/r HL | NCT03016871 | Recruiting | Nivolumab, Carboplatin, Etoposide, Ifosfamide | US | II |
| 15 | r/r HL | NCT04134325 | Recruiting | Nivolumab, Pembrolizumab | US | Early I |
| 16 | HL | NCT03233347 | Recruiting | Nivolumab, Brentuximab Vedotin, Dacarbazine, Doxorubicin, Vinblastine | US | II |
| 17 | r/r cHL, anal cancer, AIDS infection, etc. | NCT02408861 | Recruiting | Nivolumab, Ipilimumab | US | I |
| 18 | Early cHL | NCT03712202 | Recruiting | Nivolumab, Bleomycin, Brentuximab Vedotin, Dacarbazine, Doxorubicin, Vinblastine | US | II |
| 19 | New diagnosis cHL | NCT03907488 | Recruiting | Nivolumab, Brentuximab Vedotin, Doxorubicin Hydrochloride, Filgrastim, Pegfilgrastim, Radiation Therapy, Vinblastine Sulfate | US | III |
| 20 | cHL | NCT03200977 | Recruiting | Nivolumab | US |  |
| 21 | cHL | NCT03646123 | Recruiting | Nivolumab, Brentuximab Vedotin, Doxorubicin, Vinblastine, Dacarbazine, G-CSF | US | II |
| 22 | r/r HL, NHL | NCT03015896 | Recruiting | Nivolumab, Lenalidomide | US | I/II |
| 23 | HL, DLBCL | NCT03843294 | Recruiting | Nivolumab, TAA-T cells | US | I |
| 24 | HL, melanoma, lung cancer, etc. | NCT03161613 | Recruiting | Nivolumab | Mexico |  |
| 25 | r/r HL | NCT01703949 | Recruiting | Nivolumab, Brentuximab Vedotin | US | II |
| 26 | HL, NHL, MM | NCT01592370 | Recruiting | Nivolumab, Ipilimumab, Lirilumab, Daratumumab, Pomalidomide, Dexamethasone | US | I/II |
| 27 | HL, PTCL | NCT01716806 | Recruiting | Nivolumab, Brentuximab Vedotin, Bendamustine, Dacarbazine | US | II |
| 28 | cHL, Ewing sarcoma, PEComa, etc. | NCT03190174 | Recruiting | Nivolumab, Nab-Rapamycin | US | I/II |
| 29 | r/r HL | NCT02572167 | Active, not recruiting | Nivolumab, Brentuximab Vedotin | US | I/II |
| 30 | r/r cHL | NCT02940301 | Active, not recruiting | Nivolumab, Ibrutinib | US | II |
| 31 | NIVAHL | NCT03004833 | Active, not recruiting | Nivolumab, Adriamycin, Vinblastine, Dacarbazine | Germany | II |
| 32 | cHL | NCT03580408 | Active, not recruiting | Nivolumab, Vinblastin | Belgium France | II |
| 33 | cHL | NCT02181738 | Active, not recruiting | Nivolumab, Doxorubicin, Vinblastine, Dacarbazine | US | II |
| 34 | cHL, r/r HL | NCT03057795 | Active, not recruiting | Nivolumab, Brentuximab Vedotin | US | II |
| 35 | r/r cHL | NCT03739619 | Active, not recruiting | Nivolumab, Bendamustine， Gemcitabine | US | I/II |
| 36 | Untreated HL | NCT02758717 | Active, not recruiting | Nivolumab, Brentuximab Vedotin | US | II |
| 37 | r/r HL, melanoma, rhabdomyosarcoma, etc. | NCT02304458 | Active, not recruiting | Nivolumab, Ipilimumab | US | I/II |
| 38 | r/r cHL | NCT05039073 | Not yet recruiting | Nivolumab, Brentuximab Vedotin | US | II |
| 39 | Recurrent cHL | NCT04561206 | Not yet recruiting | Nivolumab, Brentuximab Vedotin | US | II |
| 40 | r/r cHL | NCT04838652 | Not yet recruiting | Pembrolizumab plus Chemotherapy (ICE or DHAP) | Germany | II |
| 41 | HL | NCT04510636 | Not yet recruiting | Pembrolizumab, Bendamustine Hydrochloride | Canada | II |
| 42 | r/r cHL | NCT04788043 | Not yet recruiting | Pembrolizumab, Magrolimab | US | II |
| 43 | r/r HL | NCT03179917 | Recruiting | Pembrolizumab, Involved site radiation therapy | US | II |
| 44 | r/r cHL | NCT03776864 | Recruiting | Pembrolizumab, Umbralisib | US | II |
| 45 | HL | NCT03331731 | Recruiting | Pembrolizumab | Australia, New Zealand | II |
| 46 | r/r HL | NCT03618550 | Recruiting | Pembrolizumab, Gemcitabine, Vinorelbine, Liposomal Doxorubicin | US | II |
| 47 | cHL | NCT03407144 | Recruiting | Pembrolizumab, Doxorubicin, Vinblastine, Dacarbazine, Cyclophosphamide, Vincristine, Prednisone/Prednisolone, Bleomycin, Etoposide, Radiotherapy (RT) | US | II |
| 48 | cHL | NCT05008224 | Recruiting | Pembrolizumab, Doxorubicin, Vinblastine, Dacarbazine, Bleomycin, Etoposide, Cyclophosphamide, Vincristine Procarbazine, Prednisone | US, Australia | II |
| 49 | cHL | NCT03331341 | Recruiting | Pembrolizumab, Dacarbazine, Doxorubicin Hydrochloride, Vinblastine | US | II |
| 50 | r/r PMBCL, cHL | NCT04875195 | Recruiting | Pembrolizumab | US, Australia, etc. | II |
| 51 | cHL, malignant melanoma, NSCLC, etc. | NCT03236935 | Recruiting | Pembrolizumab, L-NMMA | US | I |
| 52 | r/r FL, DLBCL, HL | NCT03150329 | Recruiting | Pembrolizumab, Vorinostat | US | I |
| 53 | cHL, NHL, etc. | NCT02981914 | Recruiting | Pembrolizumab | US | Early I |
| 54 | HL, NHL | NCT03598608 | Recruiting | Pembrolizumab, Favezelimab | US | I/II |
| 55 | cHL, r/r cHL, etc. | NCT02595866 | Recruiting | Pembrolizumab | US | I |
| 56 | cHL, melanoma, etc. | NCT02332668 | Recruiting | Pembrolizumab | US, Australia,etc. | I/II |
| 57 | r/r HL, NHL, etc. | NCT03432741 | Recruiting | Pembrolizumab, Belinostat, Carfilzomib, Copanlisib Hydrochloride, Daratumumab, Fludeoxyglucose F-18, Gemcitabine Hydrochloride, Nivolumab, Obinutuzumab, Rituximab, Romidepsin, Saline, Trastuzumab | US | I |
| 58 | HL, FL, CLL, SLL, MCL, etc. | NCT02362035 | Active, not recruiting | Pembrolizumab, ACP-196 | US | I/II |
| 59 | r/r cHL | NCT02684292 | Active, not recruiting | Pembrolizumab, Brentuximab Vedotin |  | III |
| 60 | r/r cHL | NCT02453594 | Active, not recruiting | Pembrolizumab |  | II |
| 61 | DLBCL, HL, PTCL | NCT02362997 | Active, not recruiting | Pembrolizumab | US | II |
| 62 | cHL | NCT03226249 | Active, not recruiting | Pembrolizumab, Dacarbazine, Doxorubicin Hydrochloride, Fludeoxyglucose F-18, Vinblastine Sulfate | US | II |
| 63 | r/r HL | NCT03077828 | Active, not recruiting | Pembrolizumab, Carboplatin， Etoposide, Ifosfamide | US |  |
| 64 | cHL | NCT04044222 | Recruiting | Sintilimab, Carboplatin, Etoposide, Ifosfamide, Placebo | China | III |
| 65 | r/r cHL | NCT04510610 | Recruiting | Camrelizumab, Decitabine | China | II/III |
| 66 | cHL | NCT04067037 | Recruiting | Camrelizumab, Epirubicin, Vincristine, Dacarbazine | China | II |
| 67 | r/r HL | NCT04239170 | Recruiting | Camrelizumab(SHR-1210) | China | II |
| 68 | r/r cHL | NCT04233294 | Recruiting | Camrelizumab, Chidamide, Decitabine | China | II |
| 69 | r/r cHL | NCT04342936 | Recruiting | Camrelizumab, Investigator's choice of Chemotherapy | China | III |
| 70 | cHL | NCT04514081 | Recruiting | Camrelizumab, Chidamide, Decitabine | China | II |

**2.1.2** **Non-Hodgkin's lymphoma** **(NHL)**

NHL is divided into B-cell lymphoma, T-cell lymphoma and NK/T-cell lymphoma. B-cell lymphoma includes diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL), etc. This article will elaborate on them in turn.

**2.1.2.1** **Diffuse large B-cell lymphoma** **(DLBCL)**

In DLBCL, PD-L1 can be expressed by B cells in DLBCL tumors, and non-malignant cells (such as macrophages) from its immune microenvironment[[30](#_ENREF_30" \o "Laurent, 2015 #136)]. According to reports, nearly 20% of DLBCL NOS have genetic abnormalities and chromosomal changes, leading to PD-L1 overexpression[[31](#_ENREF_31" \o "Georgiou, 2016 #51)]. Among which, the structural abnormality of 9p24.1 chromosome is significantly related to the expression of PD-L1 in DLBCL[[32](#_ENREF_32" \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, a phase I study found that the use of Nivolumab alone to treat 81 patients with lymphoma and myeloma (11 cases of DLBCL) has an effective rate of 36%[[33](#_ENREF_33" \o "Lesokhin, 2016 #100)]. Nivolumab can also be used in combination therapy. The combined use of Nivolumab and Ipilimumab to treat 65 cases of hematological malignancies (10 cases of DLBCL), found that only 3 cases responded[[34](#_ENREF_34" \o "Ansell, 2016 #156)], the effect was not good. Recently, a study (NCT03305445) of 6 DLBCL patients treated with Nivolumab and Ipilimumab after conventional treatment and before immunotransplantation, found that 3 (50%) of the patients had benefited from immunotransplantation and were well tolerated, the effect of this method is acceptable. Regarding the treatment of Pembrolizumab, a trial evaluated Pembrolizumab combined with R-CHOP in the treatment of 30 untreated DLBCL patients, found comparable toxicity to standard R-CHOP, but there were 2 cases of grade 3 immune-related adverse events. The overall response rate and complete response rate were 90% and 77%, and the 2-year progression-free survival rate was 83%[[35](#_ENREF_35" \o "Smith, 2020 #138)], which was better than using it alone. Several later studies were conducted to explore the effect of Pembrolizumab combined with other drug treatments.

In addition to the above two drugs, there are also many drugs that 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), found an objective remission rate of 37% in DLBCL patients, with 4 (14.8%) in complete remission and 6 (22.2%) in partial remission[[36](#_ENREF_36" \o "Tam, 2019 #113)]. And in germinal center B-cell-like (GCB) DLBCL and non-germinal center B-cell-like (NGCB) DLBCL, the objective remission rates were 33.3% and 40%, which did not show a good therapeutic effect. A trial study of Atezolizumab combined with R-CHOP (R-CHOP-atezo) in the treatment of 42 patients with untreated DLBCL, found that 31 (77.5%) achieved complete remission and 4 (10%) achieved partial remission through IRC[[37](#_ENREF_37" \o "Younes, 2019 #115)], which has a promising effect.

In DLBCL, targeting PD-1/PD-L1 has better curative effect on some special types. In primary central nervous system lymphoma (PCNSL), due to the change of chromosome 9p24.1[[38](#_ENREF_38" \o "Chapuy, 2016 #139)], it shows increased expression of PD-L1, so targeted therapy drugs have a better effect. A clinical trial using Nivolumab to treat 4 patients with r/r PCNSL and 1 patient with relapsed primary testicular lymphoma (PTL), found that all 5 patients had objective responses, including 4 complete remissions and 1 partial remission[[39](#_ENREF_39" \o "Reddy, 2017 #73)], indicating that the treatment has high efficiency, long-lasting curative effect, and can improve central symptoms at the same time. However, a phase II trial by studying Nivolumab for r/r PCNSL or r/r PTL, found that the objective response rate assessed by BICR was 6.4%, and the progression-free survival period was 1.41 months[[40](#_ENREF_40" \o "Nayak, 2017 #140)], indicating the efficacy of targeting PD1/PD-L1 in PCNSL needs to be confirmed by more prospective clinical studies. Regarding combination therapy, a phase II clinical trial of Nivolumab and Ibrutinib for r/r PCNSL is recruiting patients[[41](#_ENREF_41" \o "Westin, 2019 #141)].

Primary mediastinal large B cell lymphoma (PMBCL) is similar to PCNSL, both because of the chromosome changes lead to the overexpression of PD-L1, the application of targeted drugs has a better effect. According to reports, the objective response rate of the first batch of 19 patients in the PMBCL cohort was 41%[[42](#_ENREF_42" \o "Chang, 2018 #66)]. The NCCN guidelines recommend Pembrolizumab for r/r PMBL. A phase II trial using Pembrolizumab to treat 53 r/r PMBL patients, found that the objective response rate was 45%, and the complete response rate was 21%[[43](#_ENREF_43" \o "Armand, 2019 #74)], showing an effective outcome. And a clinical trial using Nivolumab combined with BV to treat 30 r/r PMBL patients, found that at a median follow-up of 11.1 months, the objective response rate was 73%, the complete response rate for each investigator was 37%, and the remission rate is 70% [[44](#_ENREF_44" \o "Zinzani, 2019 #110)], which is better than treatment alone.

The overexpression of PD-L1 in EBV-associated lymphoma[[45](#_ENREF_45" \o "Lin, 2020 #75)] is thought to be mediated by the latent membrane protein 1 (LMP1) encoded by EBV[[46](#_ENREF_46" \o "Garon, 2015 #77)], which makes it sensitive to PD-1 blockade. An experiment studied the effect of PD-1 blockade on the anti-tumor immunity of lymphoma cells, and found that PD-1 blockade exerted a highly effective role in EBV+ DLBCL[[47](#_ENREF_47" \o "Quan, 2015 #142)], stronger than EBV- DLBCL, indicating that targeting PD-1/PD-L1 will have a better effect on it. With regard to its clinical trials, we look forward to carrying out more clinical trials to verify the efficacy of the drug in the future.

**Table 2** lists the clinical trials currently underway.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| IDX | Disease | Experiment Title | Status | Intervention  /Treatment | State | Phase |
| 1 | DLBCL | NCT03305445 | Recruiting | Nivolumab, Ipilimumab | US | I/II |
| 2 | DLBCL, HL | NCT03843294 | Recruiting | Nivolumab, TAA-T cells | US | I |
| 3 | DLBCL, CNS lymphoma | NCT04609046 | Recruiting | Nivoluma, BLenalidomide, Methotrexate, Rituximab | US | I |
| 4 | DLBCL | NCT03704714 | Recruiting | Nivolumab, Cyclophosphamide, Doxorubicin Hydrochloride, Prednisone, Quality-of-Life Assessment, Rituximab, Vincristine Sulfate | US | I/II |
| 5 | r/r DLBCL | NCT03038672 | Recruiting | Nivolumab, Varlilumab | US | II |
| 6 | RS, DLBCL, r/r DLBCL | NCT03892044 | Recruiting | Nivolumab, Duvelisib | US | I |
| 7 | r/r HL, NHL（including DLBCL) | NCT03015896 | Recruiting | Nivolumab, Lenalidomide | US | I/II |
| 8 | r/r Hematological malignancies(including DLBCL） | NCT04205409 | Recruiting | Nivolumab | US | II |
| 9 | Richter transforms or transforms indolent non-Hodgkin's lymphoma (including DLBCL) | NCT03884998 | Recruiting | Nivolumab, Copanlisib | US | I |
| 10 | r/r DLBCL | NCT04920617 | Recruiting | Pembrolizumab, DPX-Survivac, CPA | US | II |
| 11 | DLBCL | NCT03990961 | Recruiting | Pembrolizumab | US | II |
| 12 | r/r DLBCL, FL | NCT03401853 | Recruiting | Pembrolizumab, Rituximab, Obinutuzumab | US | II |
| 13 | r/r FL, DLBCL, HL | NCT03150329 | Recruiting | Pembrolizumab, Vorinostat | US | I |
| 14 | Recurrent FL, DLBCL | NCT02446457 | Recruiting | Pembrolizumab, Lenalidomide, Rituximab | US | II |
| 15 | DLBCL | NCT03340766 | Active, not recruiting | Pembrolizumab, Blinatumomab | US | I |
| 16 | r/r DLBCL | NCT03309878 | Active, not recruiting | Pembrolizumab, Mogamulizumab | US | I/II |
| 17 | DLBCL, GZL, PCNSL | NCT03255018 | Active, not recruiting | Pembrolizumab | US | II |
| 18 | DLBCL, HL, PTCL | NCT02362997 | Active, not recruiting | Pembrolizumab | US | II |
| 19 | DLBCL | NCT03349450 | Active, not recruiting | Pembrolizumab, DPX-Survivac, Cyclophosphamide | Canada | II |
| 20 | r/r PCNSL | NCT04845139 | Recruiting | Nivolumab | US |  |
| 21 | PCNSL | NCT04401774 | Recruiting | Nivolumab | US | II |
| 22 | r/r PCNSL | NCT03770416 | Recruiting | Nivolumab, Ibrutinib | US | II |
| 23 | PCNSL | NCT04022980 | Recruiting | Nivolumab | US | I |
| 24 | PCNSL | NCT04421560 | Recruiting | Pembrolizumab, Ibrutinib, Rituximab | US | I/II |
| 25 | r/r PCNSL, PTL | NCT02857426 | Active, not recruiting | Nivolumab | US | II |
| 26 | Recurrent  PCNSL | NCT02779101 | Unknown | Pembrolizumab | Austria | II |
| 27 | PMBCL | NCT04745949 | Recruiting | Nivolumab, Brentuximab Vedotin, Cyclophosphamide, Doxorubicin, Prednisone, Rituximab | US | II |
| 28 | PMBCL | NCT04759586 | Recruiting | Nivolumab, Cyclophosphamide, Doxorubicin Hydrochloride, Etoposide Phosphate, Filgrastim, Pegfilgrastim, Prednisolone, Prednisone, Radiation Therapy, Rituximab, Rituximab and Hyaluronidase Human, Vincristine Sulfate | US | III |
| 29 | NHL（including PMBCL） | NCT03749018 | Recruiting | Nivolumab, Cyclophosphamide, Doxorubicin Hydrochloride, Etoposide, Prednisone, Rituximab, Vincristine Sulfate | US | II |
| 30 | r/r PMBCL, cHL | NCT04875195 | Recruiting | Pembrolizumab | US, Italy, etc. | II |
| 31 | PCNSL | NCT04961515 | Recruiting | Sintilimab, Orelabrutinib | China | I/II |
| 32 | r/r PMBCL, EBC+ DLBCL | NCT04705129 | Recruiting | Tislelizumab, Zanubrutinib | China | II |
| 33 | DLBCL, CLL, NSCLC, etc. | NCT04282018 | Recruiting | Tislelizumab, BGB-10188, Zanubrutinib | Australia | I/II |
| 34 | r/r DLBCL | NCT04799314 | Recruiting | Tislelizumab | China | III |
| 35 | DLBCL | NCT04789434 | Recruiting | Tislelizumab | China | III |
| 36 | PCNSL | NCT04899427 | Recruiting | Tislelizumab Orelabrutinib, Sintilimab | China | II |
| 37 | Refractory DLBCL | NCT02926833 | Active, not recruiting | Atezolizumab, KTE-C19, Cyclophosphamide, Fludarabine | US | I/II |
| 38 | r/r DLBCL | NCT03422523 | Active, not recruiting | Atezolizumab, Rituximab, Gemcitabine, Oxaliplatin | UK | II |
| 39 | Refractory DLBCL | NCT03321643 | Recruiting | Atezolizumab, Gemcitabine, Oxaliplatin, Rituximab | US | I |
| 40 | DLBCL, NHL | NCT03463057 | Recruiting | Atezolizumab | Belgium, Netherlands | II |

**2.1.2.2** **Follicular lymphoma (FL)**

Unlike DLBCL, most FL tumor cells do not express PD-L1 or PD-L2[[30](#_ENREF_30" \o "Laurent, 2015 #136)], but PD-1 expressing cells are abundant in ME of FL[[30](#_ENREF_30" \o "Laurent, 2015 #136)]. Cells expressing PD-1 include not only cells derived from TILs, but also follicular helper T cells (TFH) from lymphoma follicles or residual germinal centers[[48](#_ENREF_48" \o "Wahlin, 2010 #54)]. In addition, PD-1+ TILs in FL and DLBCL are positively correlated with prognosis, and the presence of PD-1+ TILs in lymphoid tumors may indicate the source of cells[[49](#_ENREF_49" \o "Kieser, 1997 #143)].

Regarding the treatment of FL, a phase I study of Nivolumab in the treatment of r/r hematological malignancies (including 10 with recurrent FL), the result showed that the objective remission rate was 40%[[33](#_ENREF_33" \o "Lesokhin, 2016 #100)]. And a phase II clinical trial found that the use of Nivolumab as the first-line treatment for 39 patients with FL for immune initiation, followed by treatment with Nivolumab and Rituximab, the median follow-up time was 17.5 months, the overall response rate was 92%, the remission rate was 54%, and the median remission time was 5 months. Among the 25 evaluable patients, the 12-month progression-free survival rate and overall survival rate were 72% and 96%[[50](#_ENREF_50" \o "Alrawashdh, 2021 #161)], indicating that the effect of this program is better than that of Nivolumab alone. A phase II clinical trial found that Pidilizumab combined with Rituximab in the treatment of 30 patients with relapsed FL has a total effective rate of 66%, of which 52% can achieve complete remission and 14% can achieve partial remission[[51](#_ENREF_51" \o "Westin, 2014 #101)], the overall effect is good.

**Table 3** lists the clinical trials currently underway.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| IDX | Disease | Experiment  Title | Status | Intervention  /Treatment | State | Phase |
| 1 | FL | NCT03245021 | Recruiting | Nivolumab, Rituximab | Australia | I |
| 2 | FL | NCT03121677 | Recruiting | Nivolumab, Personalized tumor vaccine, Poly ICLC, Rituximab | US | I |
| 3 | Richter syndrome or transforming FL | NCT03892044 | Recruiting | Nivolumab, Duvelisib | US | I |
| 4 | r/r Blood system diseases (including FL) | NCT04205409 | Recruiting | Nivolumab | US | II |
| 5 | r/r HL, NHL (including FL) | NCT03015896 | Recruiting | Nivolumab, Lenalidomide | US | I/II |
| 6 | r/r FL | NCT02038946 | Active, not recruiting | Nivolumab | US | II |
| 7 | FL | NCT03361852 | Not yet recruiting | Pembrolizumab, Rituximab, Neo Vax | US | I |
| 8 | Recurrent FL, DLBCL | NCT02446457 | Recruiting | Pembrolizumab, Lenalidomide, Rituximab | US | II |
| 9 | r/r FL, DLBCL | NCT03401853 | Recruiting | Pembrolizumab, Rituximab, Obinutuzumab | US | II |
| 10 | r/r FL, DLBCL, HL | NCT03150329 | Recruiting | Pembrolizumab, Vorinostat | US | I |
| 11 | FL, indolent B-cell NHL, MZL | NCT03498612 | Recruiting | Pembrolizumab | US | II |
| 12 | r/r CLL, NHL(including FL) | NCT02332980 | Active, not recruiting | Pembrolizumab, Ibrutinib, Idelalisib | US | II |
| 13 | FL, CLL, SLL, MCL, etc. | NCT02362035 | Active, not recruiting | Pembrolizumab, ACP-196 | US | I/II |

**2.1.2.3** **Mantle cell lymphoma** **(MCL)**

According to experiments, the PD-L1 and PD-L2 on the surface of B and T cells in mantle cell lymphoma patients are weaker than those of healthy individuals[[52](#_ENREF_52" \o "Karolova, 2020 #78)]. Therefore, according to the results, it is shown that targeting PD-1/PD-L1 is not effective in the treatment of MCL, and it is not used as its related drug target.

**2.1.2.4** **T cell lymphoma (TCL)**

Studies have shown that TCL overexpresses PD-1[[53](#_ENREF_53" \o "Vranic, 2016 #144)], and its expression level is related 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 PTCL (peripheral T cell lymphoma). A phase I clinical study used Nivolumab to treat 23 patients with r/r TCL (5 of which were PTCL), found that the partial response rate of PTCL patients was 40% [[33](#_ENREF_33" \o "Lesokhin, 2016 #100)]. A trial (NCT03075553) used Nivolumab to treat 12 patients with r/r PTCL, and found that the response rate of participants who achieved complete or partial remission was 33.3%, proving that Nivolumab is effective in its treatment. Regarding Pembrolizumab, Pembrolizumab combined with Romidepsin has been approved by the FDA for the treatment of r/r PTCL. And has been applied to treat r/r PTCL in a phase I/II clinical study (NCT03278782), a total of 15 patients can be evaluated, with an objective response rate was 44% and the complete remission rate was 20%.

Regarding untreated T cell lymphoma, previous study found that the expression of PD-1 in peripheral CD4+ and CD8+ T cells was significantly increased. And after treatment, the PD-1 decline was similar to that of healthy people, so targeting PD-1/PD-L1 also has a good effect on it. There are not many clinical trials on the treatment of untreated T cell lymphoma, and it is expected that targeting PD-1/PD-L1 will have more applications in the future.

**Table 4** lists the clinical trials currently underway.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| IDX | Disease | Experiment  Title | Status | Intervention  /Treatment | State | Phase |
| 1 | PTCL | NCT03586999 | Active, not recruiting | Nivolumab, EPOCH | US | I/II |
| 2 | r/r PTCL | NCT03927105 | Active, not recruiting | Nivolumab, Cabiralizumab | US | II |
| 3 | HL, DLBLC, PTCL | NCT02362997 | Active, not recruiting | Pembrolizumab | US | II |
| 4 | PTCL | NCT01716806 | Recruiting | Nivolumab, Brentuximab Vedotin, Bendamustine, Dacarbazine | US | II |
| 5 | CTCL | NCT03385226 | Recruiting | Pembrolizumab, Radiotherapy | US | II |
| 6 | r/r NHL(IncludingTCL) | NCT03210662 | Recruiting | Pembrolizumab, Radiotherapy | US | II |
| 7 | r/r CTCL | NCT04118868 | Not yet recruiting | Pembrolizumab administered using the Sofusa® DoseConnect™ |  | I |
| 8 | PTCL, CTCL | NCT03240211 | Not yet recruiting | Pembrolizumab, Pralatrexate, Decitabine |  | I |
| 9 | PTCL | NCT04795869 | Not yet recruiting | Pembrolizumab, Brentuximab Vedotin | US | II |

**2.1.2.5** **NK/T cell lymphoma (NKTCL)**

The levels of PD-L1 and PD-L2 mRNA in extranodal NK/T cell lymphoma (ENKTCL) were significantly up-regulated, and studies have found that PD-L1 protein is expressed in tumor cells of ENKL patients[[54](#_ENREF_54" \o "Han, 2014 #81)]. What's more, the level of sPD-L1 after treatment is a useful biomarker for monitoring patients with minimal residual disease (MRD)[[55](#_ENREF_55" \o "Wang, 2016 #82)].

Targeting PD-1/PD-L1 to treat r/r ENKTCL has a good effect. Nivolumab has been proven to be effective against ENKTCL[[56](#_ENREF_56" \o "Chan, 2018 #145)]. A trial studied Nivolumab in the treatment of 3 cases of r/r ENKTCL, and found 2 complete responses and 1 partial response. Targeting PD-1 has also been proven to be very effective for r/r ENKTCL that has failed treatment with L-asparaginase[[57](#_ENREF_57" \o "Kwong, 2017 #103)], a retrospective case found in the treatment of 7 patients with r/r NK/T cell lymphoma, after 7 treatment cycles, the objective response rate was 100%[[57](#_ENREF_57" \o "Kwong, 2017 #103)]. In addition to the above drugs, there are other drugs that also have undergone clinical trials, but the therapeutic effects are not as good as Nivolumab and Pembrolizumab. A phase II trial used Avelumab to treat 21 patients with r/r ENKTCL, and the complete remission rate was 24%, the overall response rate was 38%[[58](#_ENREF_58" \o "Kim, 2020 #146)]. There is also a clinical trial (NCT03228836) by studying IBI308 to treat 28 r/r ENKTCL and found that the progression-free survival period is 30 months.

In terms of combination therapy, a study found that the use of targeting PD-1 and P-GEMOX (Pegaspargase, Gemcitabine, Oxaliplatin) in the treatment of 9 patients with advanced ENKTCL, 8 patients showed significant remission, including 7 Complete remissions and 1 partial remission[[59](#_ENREF_59" \o "Cai, 2021 #108)]. A clinical trial by studying Sintilimab combined with Chidamide in the treatment of 41 r/r ENKTCL, found that the objective response rate was 58.3%, the complete response rate was 44.4%, and the partial response rate was 13.9%[[60](#_ENREF_60" \o "Gao, 2020 #109)]. It shows that it also has a beneficial effect in combination therapy. **Table 5** lists the currently ongoing clinical trials.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| IDX | Disease | Experiment  Title | Status | Intervention  /Treatment | State | Phase |
| 1 | TNKL | NCT03728972 | Not yet recruiting | Pembrolizumab | US | II |
| 2 | r/r TNKL | NCT03107962 | Unknown | Pembrolizumab | China | II |
| 3 | TNKL | NCT03021057 | Unknown | Pembrolizumab | China (Hong Kong) | II |
| 4 | r/r TNKL | NCT03598998 | Recruiting | Pembrolizumab, Pralatrexate | US | I/II |
| 5 | TNKL | NCT04417166 | Not yet recruiting | Pembrolizumab, Field Radiation Therapy | China | II |
| 6 | r/r TNKL | NCT04231370 | Recruiting | Sintilimab, Lenalidomide | China | II |
| 7 | r/r TNKL | NCT04279379 | Recruiting | Sintilimab, Decitabine | China | II |
| 8 | TNKL | NCT04127227 | Recruiting | Sintilimab, Pegaspargase, Gemcitabine, oxaliplatin | China | II |
| 9 | TNKL | NCT03936452 | Recruiting | Sintilimab | China | II |

**2.2 Leukemia**

**2.2.1 Acute myeloid leukemia (AML)**

Most AML can achieve complete remission after conventional chemotherapy, and allogeneic hematopoietic stem cell transplantation is the only way to treat AML[[61](#_ENREF_61" \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 PD-L1 low when cultured in vitro, but expresses PD-L1 elevated when cultured in vivo, suggesting the expression of PD-L1 in leukemia cells benefit from the tumor microenvironment[[62](#_ENREF_62" \o "Zhang, 2009 #25)]. Clinical data also supports the dysregulation of the PD-1 pathway in AML. Compared with healthy people, the expression of PD-1 on T cells in AML patients is significantly higher[[63](#_ENREF_63" \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.

In the treatment of AML, targeting PD-1/PD-L1 is undergoing clinical trials, and its individual treatments and combination treatments have had positive results. A clinical trial found that the use of Nivolumab alone for maintenance treatment of 14 AML patients (not eligible for transplantation), the 6-month and 12-month CRd rates were 79% and 71%[[64](#_ENREF_64" \o "Kadia, 2018 #147)]. A phase II clinical study found that the objective remission rate of Nivolumab combined with Azacytidine in the treatment of r/r AML was 33%[[65](#_ENREF_65" \o "Daver, 2019 #148)]. A trial (NCT02464657) studied Idarubicin, Cytarabine combined with Nivolumab in the treatment of MDS and AML, found that the relapse free survival was 18.54 (8.20-23.22) months, and the overall survival was 18.54 (10.81-28.81) months.

Regarding Pembrolizumab, a clinical trial (NCT02708641) used Pembrolizumab to treat 12 AML patients with a relapse time of 12.14 months. A clinical trial (NCT02996474) regarding the treatment of 10 patients with r/r AML with Pembrolizumab combined with Decitabine, found that the feasibility of this program was 10 people (100%), indicating that the combined drug effect was better.

**Table 6** lists the currently ongoing clinical trials.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| IDX | Disease | Experiment  Title | Status | Intervention  /Treatment | State | Phase |
| 1 | AML | NCT02275533 | Active, not recruiting | Nivolumab | US | II |
| 2 | AML, MDS | NCT02846376 | Active, not recruiting | Nivolumab, Ipilimumab | US | I |
| 3 | AML | NCT02712905 | Active, not recruiting | Nivolumab, INCB059872, ATRA, Azacitidine | US | I/II |
| 4 | AML | NCT03600155 | Recruiting | Nivolumab, Ipilimumab | US | I |
| 5 | AML | NCT04913922 | Recruiting | Nivolumab, Azacitidine injection, Relatlimab | Germany | II |
| 6 | AML | NCT02397720 | Recruiting | Nivolumab, Azacitidine, Ipilimumab | US | II |
| 7 | AML | NCT03825367 | Recruiting | Nivolumab, 5-azacytidine | US | I/II |
| 8 | r/r AML | NCT02845297 | Active, not recruiting | Pembrolizumab, Azacitadine | US | II |
| 9 | AML | NCT02771197 | Active, not recruiting | Pembrolizumab, Fludarabine, Melphalan | US | II |
| 10 | AML, ALL, MDS | NCT03286114 | Recruiting | Pembrolizumab | US | I |
| 11 | AML | NCT04284787 | Recruiting | Pembrolizumab, Azacitidine, Venetoclax | US | II |
| 12 | AML, MDS | NCT03969446 | Recruiting | Pembrolizumab, Decitabine | US | I |
| 13 | AML | NCT04214249 | Recruiting | Pembrolizumab, Cytarabine, Daunorubicin Hydrochloride, Idarubicin Hydrochloride | US | II |
| 14 | AML | NCT03769532 | Recruiting | Pembrolizumab, Azacitidine | Germany | II |
| 15 | AML, MDS, cHL, NHL | NCT02981914 | Recruiting | Pembrolizumab | US | early I |

**2.2.2** **Acute lymphocytic leukemia (ALL)**

Little knows about the role of targeting PD-1/PD-L1 in ALL, and there are few relevant clinical trials. There is currently a trial (NCT02879695) about Nivolumab and Blinatumomab or Nivolumab and Ipilimumab in the treatment of B-cell acute lymphoblastic leukemia patients is currently recruiting, a trial (NCT04546399) on Nivolumab combined with Blinatumomab for the treatment of relapsed B-cell acute lymphoblastic leukemia is under recruitment. And a phase I trial (NCT02819804) for the treatment of Nivolumab combined with Dasatinib in the treatment of ALL patients[[66](#_ENREF_66" \o "Man, 2017 #90)] was terminated because it could not be evaluated and analyzed. Regarding Pembrolizumab, there is a trial (NCT03160079) about Pembrolizumab combined with Blinatumomab in the treatment of adult r/r B-cell acute lymphoblastic leukemia is currently recruiting, looking forward to carrying out more related trials in the future.

**2.2.3** **Chronic myeloid leukemia (CML)**

Studies have shown that, in CML, PD-L1 is upregulated in bone marrow cells and PD-1 is present on T cells[[67](#_ENREF_67" \o "Christiansson, 2013 #149)], but little is known about the appliance of targeting PD-1/PD-L1 in CML. Some scholars have shown that the use of antigen pulses autologous dendritic cells or direct application of in vitro transcribed RNA encoding leukemia-related antigens, combined with targeting PD-1 may help to obtain a stronger immune response and better clinical results[[68](#_ENREF_68" \o "Held, 2013 #91)].

A trial (NCT02011945) studied the treatment of 16 CML patients with Nivolumab combined with Dasatinib, found that the incidence of dose-limiting toxicity was 0%. A trial (NCT03516279) studying Pembrolizumab, Dasatinib, and Imatinib Mesylate or Nilotinib for the treatment of CML is under recruitment, looking forward to carrying out more related trials in the future.

**2.2.4 Chronic lymphocytic leukemia (CLL)**

Ramsay [[69](#_ENREF_69" \o "Ramsay, 2012 #33)] confirmed that the expression of PD-1 on CD3+ cells in CLL patients was significantly higher than that in healthy individuals, and PD-1 was found to be a feature of CD4+ and CD8+ T cells exhaustion in CLL, which can make CD4+ and CD8+ T cells unable to produce certain cytokines (interferon γ [IFN γ], tumor necrosis factor [TNF])[[70](#_ENREF_70" \o "Riches, 2013 #34)].

However, the effectiveness of targeting PD-1/PD-L1 for CLL is low, a phase II study (NCT02332980) found that Pembrolizumab is not effective against CLL, but effective against RS, because patients with RS have higher PD-L1 expression and low TCR clonality[[71](#_ENREF_71" \o "Wang, 2018 #160)]. There are currently two trials (NCT03153202, NCT03514017) for Pembrolizumab combined with Ibrutinib in the treatment of CLL patients are being recruited. Regarding Nivolumab, there is a trial (NCT04781855) on the combination of Ipilimumab, Ibrutinib, and Nivolumab in the treatment of CLL that has not yet been recruited. A trial (NCT03884998) on Copanlisib combined with Nivolumab in the treatment of patients with NHL involves CLL is currently recruiting. Research on immunotherapy for CLL patients is still ongoing, and more data to guide treatment needs to be confirmed in the research[[72](#_ENREF_72" \o "Yinjuan, 2020 #150)].

**2.3** **Multiple myeloma (MM)**

Studies have found that the expression level of PD-L1 in plasma cells is different, its expression in MM patients is higher than that in healthy volunteers and patients with unexplained monoclonal gamma disease (MGUS). And in r/r MM, the level is significantly increased[[73](#_ENREF_73" \o "Tamura, 2020 #151)]. Similar to CHL, the expression of PD-L1 protein in myeloma cells is related to the increase of PD-L1 copy number. And studies have shown that targeting PD-1 can improve survival in mouse models of myeloma[[74](#_ENREF_74" \o "Hallett, 2011 #41)]. Unlike PD-L1, PD-L2 is not expressed in myeloma cells[[75](#_ENREF_75" \o "Görgün, 2015 #40)].

A phase I study found that 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[[33](#_ENREF_33" \o "Lesokhin, 2016 #100)]. A phase II study (NCT02612779) used Nivolumab combined with Elotuzumab to treat 6 MM patients, found that the progression-free survival period was 16.7 months, and the objective remission rate was 51.5%, which did not show better results than Monotherapy. There are also some clinical trials underway, such as Nivolumab combined with Melphalan for the treatment of MM (NCT03292263). Nivolumab, Carfilzomib, Dexamethasone, Pelareorep combined for r/r MM (NCT03605719), etc.

Regarding Pembrolizumab, a phase I study found that Pembrolizumab combined with Lenalidomide and low-dose Dexamethasone in the treatment of r/r MM, 20 patients (50%) experienced remission[[76](#_ENREF_76" \o "Mateos, 2016 #152)]. At present, this treatment method is not mentioned in the treatment guidelines of MM and there are few related clinical trials, more research and exploration are needed in the future.

**CONCLUSION**

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 of various tumors, and has satisfactory therapeutic effects. In addition, with the gradual deepening of research and the increase of technical level, the therapeutic range of targeting PD-1/PD-L1 in tumors has gradually expanded, 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 lack of standardized PD-1 detection procedures, etc. It is believed that with the deepening of research and the improvement of 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 anti-tumor therapy in the future.

**DECLARATIONS**

**Competing interests**

All authors declare no conflicts of interest.

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