# Immune Checkpoint Inhibitor (ICI) with PD-1 And PD-L1

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**Abstract.** In the immune system, immune checkpoints play an important role in inhibitory regulatory. Molecules are essential for preventing autoimmune responses, maintaining self-tolerance, and minimizing tissue damage by controlling the timing and intensity of the immune response. In the past few years, immunotherapy has made remarkable achievements in the field of tumor treatment, among which programmed cell death protein 1 (PD-1) inhibitors / programmed cell death protein ligand 1 (PD-L1) inhibitors are currently the most clinically used ICIs, becoming a new means of treating tumors, and have significant efficacy in the progression-free and survival period of tumor treatment.PD-1 and PD-L1 are really important in ICI's develop and drug discovery. In ICI, there are many important checkpoint(e.g. CTLA-4, LAG-3). This review systematically introduces the history and current development of PD-La and PD-1, as well as discusses the applications of ICIs and its potential side effects.

**Keywords:** Immune checkpoint inhibitor, PD-1, PD-L1, Therapy.

## 1. Introduction

Cancer has become a major illness threatening human health, so it is urgent to propose effective cancer treatment programs. Cancer treatment has changed from surgery, radiotherapy, chemotherapy to targeted therapy and tumor immunotherapy, but these treatments exist some side effects. For example, Chemotherapy may lead to alopecia, skin changes such as redness, itching and so on, affect memory and thinking, and changes in bone marrow cause the decline of red blood cells, white blood cells and platelets. Resection is more likely to cause residual cells due to incomplete cutting, and finally cause the spread or aggravation of cancer.

Immune checkpoint inhibitor (ICI) is a type of drugs which can block the checkpoints on immune cells. The function of the checkpoint is to prevent the over react of the immune system. In the blocking situation, T cells are able to act actively and kill target cells. Although it has some side effects like diarrhea, cough, fatigue, nausea, skin rash, constipation, poor appetite, muscle and joint pain, compare with other treatments, ICI's side effect is much lower than chemotherapy and resection.

## 2. The history of PD-L1 and PD-1

In 1992, Professor Tasuku Honjo isolated and identified a gene from mouse lymphocytes and obtained the protein. He published the sequence of this protein and named that "PD-1". In 1994, he obtained the human PD-1 gene and protein, and in 1999 he first proposed that PD-1 was a negative regulator of the immune system.

In October 2000, he and Gordon Freeman of Dana-Farber Cancer Institute discovered that PD-L1 binds PD-1 by binding PD-1 inhibits the proliferation and secretion of cytokines and other functions of T cells.

In 2002, Professor Chen Lieping published an article pointing out that most tumor cells achieve immune escape by expressing PD-L1, it offers a crucial theoretical foundation for the development's research of PD-1/PD-L1 anti-tumor drugs [1].

Nowadays, tumor immunotherapy mostly adopts immunosuppressive checkpoint and adoptive cell therapy (CAR-T, CAR-NK, TAR-T, ILs). PD-1/PD-L1, as the most representative immune checkpoint, has always been a hot spot in the field of tumor immune research. So far, PD-L1 ICIs have demonstrated good remission rates and survival benefits in clinical trials. And for some patients with advanced cancer, inhibitor combined chemotherapy is a more effective choice.

## 3. The inhibit mechanism of PD-1 inhibitor

CD279 also known as PD-1 is a 268 amino acid type I transmembrane protein that is a member of the CD28 family [2]. Three structural components make up the majority of PD-1: the extracellular IgV-like domain (I), the hydrophobic transmembrane region (II), and the cytoplasmic area (III) (Figure 1). Activated T lymphocytes, B lymphocytes, natural killer (NK) cells, immunological cells including monocytes, various tumor cell lines, and tumor cell surfaces have all been discovered to have PD-1, according to studies [3].

In micro environment, cancer cells use PD-L1 to combine with PD-1 on the surface of T cells to decline the host's immune system so that the cancer cells can avoid the attack from immune system [4].

After binding to PD-L1 on the surface of the tumor cells, activated T lymphocytes and B7-1 (CD80) protein produced on antigen-presenting cells prevent the activation of effector T lymphocytes [5]. Regulatory T cells (Treg, CD4+Foxp3+) inhibit the immune system by keeping PD-1 expressed on their surface [6]. In the presence of CD3 and transforming growth factor beta (TGF-), studies have revealed that the PD-1 receptor on the surface of Treg cells supports the retransformation of primitive CD4+ T lymphocytes into Treg cells; in addition, PD-1 can also suppress B lymphocytes. stimulation of T lymphocytes through the cell [7].

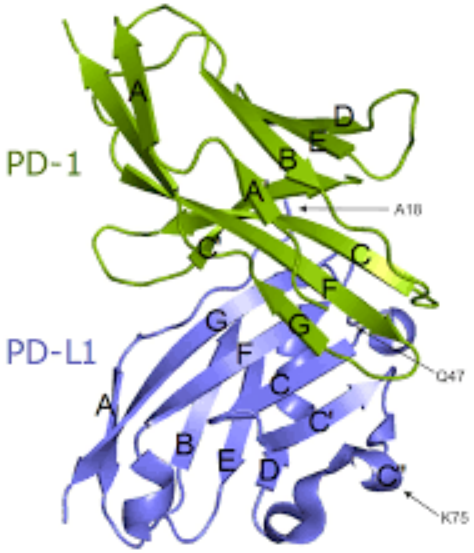


**Figure 1.** The structure of PD-1 [5]

## 4. Side Effects of PD-L1 and PD-1 Inhibitors

Both anti-PD-L1 and anti-PD-1 antibodies have side effects, including fatigue, arthralgia, diarrhea, pruritus, rash, decreased appetite, and nausea [8-11]. Their about 10% of people in research develop 3 or 4 degrees of immune-related adverse events. Unfortunately, recent research about the irAEs is based on clinical data and use the treatment from experience. Clinicians will consider the situation of the patient and use the intravenous corticosteroids. They will use additional immunosuppressive drugs if the corticosteroids failed [10,12].

**Table 1.** Degree of toxicity performance.

| Degree | Toxicity performance |
|---|---|
| Maculopapule | |
| 1 degree | Spot/papule area<10% BSA of the whole body |
| 2 degree | The rash/papule area accounts for 10% - 30% of the total body BSA |
| 3 degree | The rash/papule area is more than 30% of the BSA of the whole body, with or without symptoms (such as erythema, purpura or epidermal shedding); Limited self-care in daily life |
| Itch | |
| 1 degree | Minor or limited |
| 2 degree | intense or extensive, intermittent, skin damage caused by scratching (such as edema, papule, scaling, lichen, exudation/scab); Limited tools for daily use |
| 3 degree | Strong or extensive, persistent; Self-care in daily life is obviously limited or affects sleep |

Dermal toxicity is the adverse effect that is most likely to occur. PD-1/PD-L1 blockers are said to cause cutaneous toxicity in 30% to 40% of patients, but CTLA-4 checkpoint inhibitors cause more frequent and severe skin toxicity. Overall incidence and grade 3-5 toxicity incidence range from 47% to 68% and 2%, respectively. Additionally, the incidence of cutaneous toxicity caused by the combination inhibition of CTLA-4 and PD-1/PD-L1 ranges from 58% to 71%.

The second most frequent side effect of ICI treatment is gastrointestinal damage. A significant fraction of deaths from ICI-related poisoning are attributable to its consequences. Grade 3–4 gastrointestinal toxicity is the most frequent cause of ICI medication discontinuation. 2-4 months after the initiation of treatment, the anti-PD-1 / PD-L1 monoclonal antibody had a median incidence of gastrointestinal toxicity. Additionally, the frequency of gastrointestinal damage from the same medicine used in various tumor treatments varies. For instance, melanoma patients are more likely to experience gastrointestinal side effects from PD-1 inhibitors than those with non-small cell lung cancer and renal cell cancer [13].

## 5. Clinical trial drugs about PD-L1 And PD-1

Currently, U.S. Food and Drug Administration (FDA) had improved 6 types of death CTLA-4/PD-L1/PD-1 inhibitors in clinical practice which are nivolumab, pembrolizumab, atezolizumab, avelumab, ipilimumab, and durvalumab. This paper will discuss one treatment.

For example, durvalumab. In a phase I/II clinical trial, after the dose of 10my/kg was determined, patients were treated every two weeks regardless of the expression of tumor PD-L1. The highest benefit was observed in tumor patients with high expression of PD-L1.

A total of 444 patients with advanced NSCLC took part in the II phase of the study between February 2014 and October 2015. Patients treated with 10 mg/kg durvalumab for 2 weeks, lasting for 12 months, under the condition that the disease had progressed following at least two prior systemic therapy plans.

**Table 2.** Cohorts included in the ATLANTIC clinical trial.

| Cohort | EGFR/ALK status | PD-L1 expression | Number of patients |
|---|---|---|---|
| 1 | Mutated/positive | <25% or ⩾25% | 111 |
| 2 | Wild type/wild type | <25% or ⩾25% | 265 |
| 3 | Mutated/positive | ⩾90% | 68 |

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PD-L1, programmed death ligand 1.

**Figure 2.** The table of treatment [13]

In some patients who have received a lot of prior treatment, duvalumab is active and causes a sustained response. Patients with NSCLC who tested positive for EGFRmut/ALK had a worse

response than those who tested positive for EGFRwt/ALKwt. Higher expression of PD-L1 may improve the response in EGFRmut/ALK positive NSCLC and EGFRwt/ALKwt non-small cell lung cancer patients (ORR 16.4 percent, 95 percent confidence interval: 10.8-23.5, cohort 2).

In II phase, 256(58%) patient in 444 patients meet the irAEs, some common irAEs are diarrhoea (27; 6%), nausea (28; 6%), asthaenia (31; 7%), hypothyroidism (36; 8%) and fatigue (50; 11%) [13].

## 6. Conclusions

In the realm of cancer immunotherapy, ICIs have permanently changed the landscape. With the US Food and Drug Administration's swift approval of ICIs for the treatment of a variety of cancer types beginning with the approval of anti-cytotoxic T lymphocyte-associated protein 4 (anti-CTLA-4) for the treatment of advanced-stage melanoma in 2011, which now also includes antibodies against programmed cell death 1 (PD-1) and its ligand (PD-L1), patient survival has been extended to previously unheard-of levels. Nevertheless, despite ICIs' success, resistance to these drugs limits the number of patients who can develop long-lasting responses, and immune-related side effects make treatment more challenging. Therefore, a deeper comprehension of the prerequisites for a reliable and secure antitumor immune response after ICI therapy is required. As an indispensable member of ICI, PD-L1 and PD-1 plays a key role in the fight against cancer. As a drug to stimulate the body's autoimmunity and kill cancer cells, it can better control the probability of cancer recurrence. It is believed that the side effects of immune checkpoint inhibitors can be effectively controlled in the future, the therapeutic effect in clinical aspects can be improved, and even new and more effective anti-cancer drugs can be developed [14].

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