

# Role Of PD-1 Immune Checkpoint Inhibition in Lung Cancer Treatment

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**Abstract.** Non-small cell lung cancer (NSCLC) can be distinguished by histopathology and tumor markers. The treatment methods of NSCLC mainly include radiotherapy, chemotherapy, surgical treatment and TCM therapy. PD-1/PD-L1 immunotherapy has an advantage in combination therapy, producing a low-toxic, long-acting antitumor immune response in cancer therapy. This thesis describes the main methods of NSCLC therapy, details the PD-1/PD-L1 pathway and immunotherapy, and studies applications of three monoclonal antibodies in monotherapy and combination therapy. We conclude that the combination therapy has the outstanding advantage of safety, mild effect and prediction, but the problem of drug resistance to PD-1/PD-L1 needs to be solved urgently.

**Keywords:** NSCLC; PD-1; PD-L1; immunotherapy.

## 1. Introduction

Roughly 80% of total lung cancer is non-small cell lung cancer (NSCLC) and etiology of it include surrounding air pollution, absorption of a large number of harmful chemicals, and second-hand smoke smoking. NSCLC has no obvious symptoms in the early stage, and in the middle and late stages, they are associated with hemoptysis, poor breathing, fever, and weight loss. The diagnostic method is mainly pulmonary CT and tumor marker detection. Once diagnosed in China, the early cure rate is about 80%, and is 30% -40% in the middle and late stages. The first stage occurs mainly in the lungs, and by stage 4, the cancer cells spread to distant organs. Surgery is often the preferred treatment for early-stage NSCLC, while advanced-stage NSCLC may require a combination of treatments. However, NSCLC is often diagnosed at advanced stages, which can make it more challenging to treat and reduce the overall survival rate. Research and advancements in treatment options for NSCLC are ongoing. Combined use of immunotherapies, such as PD-1 immune checkpoint suppression, has reduced distress and improved survival.

## 2. Current research status of NSCLC

### 2.1. Classification of NSCLC

According to the histopathology classification, NSCLC mainly falls into three categories: lung adenocarcinoma, lung squamous cell carcinoma, and large cell lung cancer (LCLC). The top common type is lung adenocarcinoma, and it is more common among women. Adenocarcinoma is mainly derived from bronchial mucus glands and can occur in fine bronchi or central airways. Lung squamous cell carcinoma contributes almost 30% among all the lung cancers, which mainly originates from the segmental or subsegmental bronchial mucosa and has a tendency to grow into the lumen. In the early stages, it often causes bronchial stenosis, leading to atelectasis or obstructive pneumonia. LCLC, which accounts for 5% to 10% of lung cancer, is an undifferentiated NSCLC, which is relatively rare. Due to the updated immunophenotypic technology, the incidence rate is declining.

NSCLC can also be distinguished by the identification of tumor markers. Commonly used immunohistochemical markers include cytokeratins, TTF-1, CK7, CK20, etc. The feasibility of

marker application largely depends on the quality of the patient tumor specimens. At present, the progress of this method is not ideal, lacking a large number of samples to accurately classify the various subtypes of NSCLC.

## **2.2. Treatment progress of NSCLC**

### **2.2.1 Radiotherapy**

Radiotherapy is an effective treatment for NSCLC. With the continuous progress in medical imaging technology in recent years, patients' tumor movement is better measured and tracked to ensure the accurate delivery of agents to the tumor. For patients who are not suitable for surgery, the technique of conventional segmenting radiotherapy is still adopted. Nowadays, because of the highly conformal dose distribution and steep dose gradient, reduces unnecessary killing of healthy cells, radiotherapy has accurate area, overall high efficiency and less side effects, which improves the survival rate of patients.

### **2.2.2 Radiomics**

Imaging omics is an emerging technology that uses AI intelligent algorithms to extract data from medical imaging images and perform advanced analysis to quantify the shape, size, volume and texture of tumor or normal tissue areas, and to build clinically relevant models to predict and even evaluate tumors. Radiomics has not yet been applied in the clinical research of NSCLC, and it needs repeated detection and verification, and authoritative evaluation before it can be put in personalized treatment of patients.

### **2.2.3 Monoclonal antibodies**

Monoclonal antibodies are mainly used for the targeted therapy of NSCLC after the progression of chemotherapy. The anticancer effect of monoclonal antibodies combined with chemotherapy or targeted therapy is more significant than the single use. Amivantumab is a bispecific antibody that suppresses *EGFR* and *MET*, thereby inhibiting tumor proliferation, with remarkable efficacy in patients with *EGFR* [1]. By blocking PD-L1, the cancer cells will be recognized and eventually killed. In new study, Durvalumab combined with other cancer drugs has been an available treatment to NSCLC [2].

### **2.2.4 Herbal medicine and acupuncture**

At present, the conventional cancer treatment methods around the world are surgery, radiotherapy and chemotherapy. However, during these treatments, the cells in the patient's body are damaged and poisoned, and patients feel very painful. Herbal medicine and acupuncture are used as traditional means of cancer treatment in many countries in the Far East. It also reduces patients' pain and reduces the side effects of chemotherapy and radiation therapy. At the same time, it has the advantages of mild effects and small side effects.

## **3. PD-1/PD-L1 inhibitor therapy**

### **3.1. PD-1/PD-L1 pathway**

#### **3.1.1 Molecular structure and background**

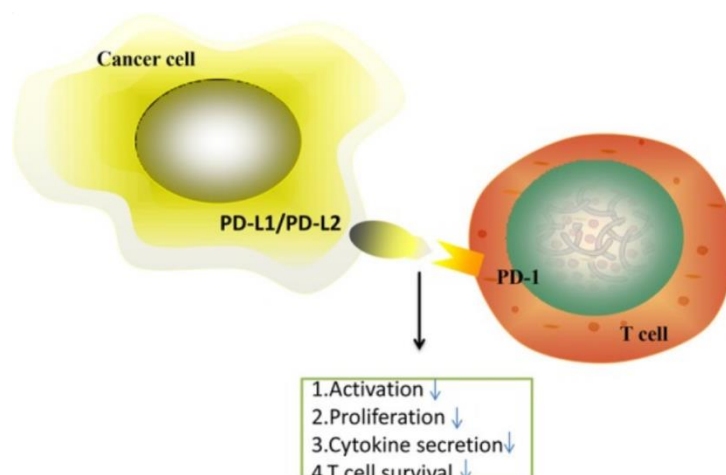
PD-1 is involved in the immunoglobulin gene superfamily, also called CD279. PD-1 belongs to the type-I transmembrane glycoprotein and contains 288 amino acids, a single N-terminal Ig-V like domain in the extracellular area and a hydrophobic membrane domain. Additionally, PD-1 also has a cytoplasmic tail with two tyrosine bases. PD-1 is homologous to many immune-related proteins, CTLA4 and it are 20% alike, induced T-cell co-stimulator has 13% similarity to it and the amino acid sequence of PD-1 has a similarity of 28% to CD15.

PD-L1 (also called B7H1) is the member of B7 protein family. PD-L1 contains 290 amino acids whose molecular weight is 33-kDa. PD-L1 as a form of type I glycoprotein, has both IgV and IgC

domains in its extracellular area, with a hydrophobic transmembrane domain, and a cytoplasmic tail structure domain.

### 3.1.2 PD-1/PD-L1 expression

PD-1/PD-L1 axis has crucial influence on tumorigenesis by modulating signals in cancer cells. Maintaining and inducing immune tolerance within the tumor microenvironment (TME) can be achieved through the immune-L1 pathway. PD-1 has the ability to combine with ligands, and the activity of this kind of combination has a significant role in activating and proliferating T cells and secreting cytotoxic in tumor tissues, so anti-tumor immune responses are inhibited (Fig. 1)[3].



**Fig. 1** The PD-1/PD-L1 axis regulates cancer cell signaling and influences tumorigenesis [3].

PD-1 expresses on a large amount of immune-related cells, like activated T, natural killer (NK), dendritic cells (DCs) and monocytes. It is worth paying attention to that high expression of PD-1 on tumor specific T cells have been observed. PD-1 expression marks that T cells have been depleted, and its expression also maintains high level in chronic virus infection. Under normal conditions, PD-L1 also expressed by immune-related cells like macrophages, DCs and some epithelial cells, but when inflammation arises, this course will improve.

Since PD-1 and PD-L1 express at higher level can cause the immunosuppression, it is valuable to control this course. The presence of a complicated principle to control PD-L1 expression has been revealed by numerous researches. This network may be split into two parts: non-immune mechanisms and immune mechanisms.

The primary mechanism contains (1) amplifications and translocations in genome, (2) microRNA negatively regulate PD-L1 expression, (3) activation of various signaling pathways and transcription factors, and (4) posttranslational regulation and controlled transportation. The secondary mechanism induced by soluble factors produced in TME by immune cells with the inflammatory signaling activation.

### 3.2. PD-1/PD-L1 inhibitor immunotherapy

Sometimes, cancer cells are observed to have the ability to avoid the host immunity into the TME. The reason why cancer cells have such ability is that cancer cells can express a high level of signaling protein to inhibit immune. Media tumor-inducing immune suppression (immune checkpoint) is a crucial role for PD-1 and PD-L1 when they combine. So how to suppress it has become an urgent problem. More and more researches demonstrated that improved T-cell response and anti-tumor response can be achieved by blocking the above-mentioned course.

## **4. PD-1/PD-L1 combination therapy**

### **4.1. Overview**

Comparing to traditional therapy like surgery, chemotherapy and radiotherapy, the cutting-edge therapy combining with PD-1/PD-L1 have demonstrated better treatment outcomes. For example, combination therapy with chemotherapy can increase the activity of cytotoxic T-lymphocyte (CTL). And in this way, the treatment effect is enhanced. Additionally, the newly proposed therapy that applying anti-PD-1 antibodies in the radiotherapy is reported available in improving the activation of tumor specific T cells. Those who have accepted combination therapy showed higher CD8 T cells expression and lower MDSCs and regulatory T cells accumulations.

#### **4.1.1 Resistance to cancer immunotherapy**

The resistance to the immunotherapy is observed in some clinical cases. Although long-period existed in some of the patients treated with immune checkpoint inhibitor (ICI), most of them were not able to maintain such durable responses [4]. There are two kinds of resistance: primary and acquired.

Generally, to evaluate the patients' response to ICIs, proper biomarkers should be selected. One of the most widely chosen biomarkers is the PD-L1 expression on tumor cells. Two reasons can help explain why the tumor tissue is crucial in regulating PD-L1 expression. Firstly, tumors are capable of binding to PD-1 receptors and ligands at the most basic level. Secondly, the quantity that PD-L1 express in TME is linked to parameters that indicate immune activation in the tumor. As the result, in the case of the tumor tissues that express PD-L1 at lower level or even lack, blockade therapy is more likely to fail.

Another biomarker that exists the similar effect is the mutational burden of the tumor. Anti-PD-1 regulation in many cancers is closely linked to the tumor's higher mutational burden, as found in the new study.

There is another situation that if the critical pathways which are responsible for delivering signals are blocked in the tumor, primary resistance to ICIs can also happen. For instance, IFN- $\gamma$  plays a key role in starting and maintaining antitumor response through two main methods.

IFN- $\gamma$  is able to upward CD8 cytotoxic T cell activity and Th1 response. Moreover, it has the ability to exert antiproliferative, proapoptotic effects and trigger the upregulation of MHC I in tumor cells [5]. From the new study, it has been observed by the researchers that in subjects who have not responded to anti-CTLA-4 or anti-PD-1, genes such as JAK1/2 and IFNGR1/2 mutated in the tumors of these patients. This result revealed that resistance to ICIs is caused by tumor-intrinsic mutations that disrupted IFN- $\gamma$  signaling pathway [6].

The other type of resistance is acquired resistance, also called secondary resistance. Although the specific mechanism of this kind of resistance is not explained clearly, it is believed that through some specific and crucial pathways related to checkpoint blockade response the tumors acquire mutations. In the case of the patients with melanoma who have reported acquired resistance to pembrolizumab, the tumor relapsed because of the function of JAK1 and JAK2 had lost. This case showed loss of response to IFN- $\gamma$  can be a key reason to resistance to cytostatic effects.

## **4.2. Application of Nivolumab**

### **4.2.1 Nivolumab monotherapy in cancer**

Nivolumab, also called Opdivo, a PD-1 ICI for IgG4, is applied to prevent regulation of PD-1/PD-L1. The FDA approved nivolumab in 2014 as a treatment for melanoma, and in the following year, it was also approved for metastatic NSCLC and squamous lung cancer (SLC). The phase 3 CheckMate 17 study has got an excellent therapeutic outcome with nivolumab therapy. Among subjects with squamous NSCLC, whose 2-year overall survival rate (OS) was around 23% with nivolumab, much higher than 8% with docetaxel. And the 2-year OS for patients with nonsquamous NSCLC was about 29% with nivolumab and 16% with docetaxel. And it also showed that nivolumab has durable

responses, after two-year minimum follow-up, in 27 cases proved effective squamous NSCLC patients and 56 cases of nonsquamous NSCLC patients, there were 10 cases and 19 cases continue to ease [7]. The results of trail shows that nivolumab therapy has been an effective treatment. Nonetheless, the nivolumab monotherapy is useless in significant proportion of patients, and many of them will get acquired resistance after primary responses.

#### **4.2.2 Nivolumab combination therapy with ipilimumab**

Although ICIs monotherapy has an acceptable safety profile and also show some effects on part of patients, the lower response rates would be a limitation in its use. Therefore, the combination therapies are considered for improving the response rates.

Evaluation of ICIs combined treatment phase 3 studies through targeted and CTLA-4 channel show the clinical value. As a monoclonal antibody, ipilimumab is able to block CTLA-4 effectively. So far, nivolumab has been combined with ipilimumab to treat NSCLC, and get a higher clinical activity than nivolumab monotherapy in vivo. NSCLS study showed that nivolumab combined with ipilimumab was effective in improving PFS, delaying symptom worsening, and providing improvements in symptoms and life quality in comparison to chemotherapy in those have higher tumor mutational burden. Nivolumab and ipilimumab group showed 22.3% of symptom deterioration by week 12, which was lower than that of 35% with chemotherapy, irrespective of discontinuation [8]. Although there are promising outcomes, the combination therapy with nivolumab and ipilimumab hasn't been approved for NSCLC.

### **4.3. Application of Pembrolizumab**

#### **4.3.1 Pembrolizumab monotherapy in cancer**

PD-1 can be recognized and bound with pembrolizumab on the membrane of T cells. Furthermore, in a phase III trial for the NSCLC patients whose tumor proportion score (TPS) was more than half, the medium PFS of pembrolizumab group was about 10.3 months, while it in the chemotherapy group was about 6 months. Estimated OS of 80.2% at 6 month was shown in pembrolizumab group, while that of chemotherapy group 72.4% [9]. This trial found that, compared with platinum-doublet chemotherapy, pembrolizumab has benefits regarding PFS and OS. But similar to the nivolumab, only small part of all patients with NSCLC responds well to this monotherapy, which means there also need some other treatment considered to treat patients in combination to improve the efficacy of ICIs.

#### **4.3.2 Pembrolizumab combination therapy with chemotherapy**

A phase 3, double-blind trial has been conducted to confirm the difference between pembrolizumab combine with platinum-pemetrexed and placebo with platinum-pemetrexed as primary treatment for metastatic nonsquamous NSCLC patients [10]. The pembrolizumab group had an estimated OS at 12 months of 69.2%, which was higher than 49.4% for the placebo group after nearly 10.5 months of follow-up; meanwhile, the medium PFS of the pembrolizumab group is 8.8 months, while that of placebo group is 4.9 months. In addition, 67.2% of patients had grade 3 and above adverse events with placebo and platinum-pemetrexed, compared to 65.8% with pembrolizumab combine with platinum-pemetrexed. According to the positive results of the trial, pembrolizumab gets approval to combine with other chemotherapy such as platinum-pemetrexed to treat advanced squamous or nonsquamous NSCLC by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan.

### **4.4. Application of Camrelizumab**

#### **4.4.1 Camrelizumab monotherapy in cancer**

Camrelizumab, a human IgG4 anti-PD1 monoclonal antibody, has received conditional approval in treating a number of refractory solid tumors in China, such as NSCLC, hepatic cell carcinoma, esophageal cancer and Hodgkin's disease. In a phase II trial conducted among advanced NSCLC

patients treated previously, camrelizumab monotherapy brings in an improvement in PD-L1 expression, which was proportional to response rates in subgroup analyses. And the median PFS and OS were respectively 3.2 months and 19.4 months [11]. Thus, it can be seen that the ORR, PFS and OS of camrelizumab in the treatment of Chinese patients are improved compared with previous data with second-line chemotherapy, and camrelizumab is well tolerated. These mean camrelizumab is expected to become a routine drug in the field of cancer treatment.

#### **4.4.2 Camrelizumab combination therapy with chemotherapy**

There has been a double-blind and randomized trial investigating the safety and effect of camrelizumab or placebo in addition to chemotherapy as a primary therapy for NSCLC patients [12]. Out of 389 patients, there were 193 patients given camrelizumab and chemotherapy, and the remaining patients were given placebo instead of camrelizumab for efficacy and safety analyses. The results show that in camrelizumab group, the median PFS was 8.5 months while that of placebo was 4.9 months; and medium OS in the camrelizumab group hadn't reach in this trail while it in the placebo group was 14.5 months. Both of the two group were not observed immune-related adverse events. Based on the promising results, camrelizumab plus chemotherapy is expected to be advanced squamous NSCLC first-line treatment option.

## **5. Conclusion**

To sum up, the treatment of cancer is increasingly dependent on the use of combined therapy with PD-1/PD-L1. From many cases, such original therapy opens up possibilities for the treatment of NSCLC. As an important signaling pathway, higher expression of PD-1/PD-L1 was showed in solid cancers. PD-1 can be combined with its ligands and thus lowers the immune response which kills cancer cells, causes the proliferation of tumor cells. As the result, inhibitory treatment on PD-1/PD-L1 may bring further survival benefits for patients. Recently, PD-1/PD-L1 blockade combination therapy gets proved effective in causing the long-acting antitumor immune response with lower toxicity, this novel therapy has improved on existing cancer treatments. For example, it can improve the effect of chemotherapy by raising CTL and can promote the proliferation tumor-specific T cells when it combines with radiotherapy.

Nivolumab, Pembrolizumab and Camrelizumab are three commonly used monoclonal antibodies, and they are proved remarkable to improve tumor response and survival in NSCLC patients. In the new studies, Nivolumab showed durable efficacy in treating NSCLC, lung cancer patient response better to Pembrolizumab than those of liver cancer patients. In addition to the advantage of high efficacy, the combination therapy also shows safety, the side effect of the treatment is mild, predictable and reversible.

Although this new therapy is gradually becoming a mainstream treatment, in many clinical cases, the patients are observed resistance to cancer immunotherapy, and the resistance can be drove by two different mechanisms: primary and acquired. How to reduce the resistance has also become an urgent problem.

## **Author Contribution**

All the authors contributed equally, and their names were listed in alphabetical order.

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