# Immune Checkpoint inhibitor Therapy in Various Cancers

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**Abstract.** Immune checkpoint inhibitors (ICIs) are a new way of immunotherapy, not simply refers to the improvement of immunity to the body, but by improving the immune microenvironment around the tumor, thereby activating immune cell activity in vivo to achieve anti-tumor purposes. Now, CTLA‐4 and PD‐1 or PD‐L1 monoclonal antibody are mainly developed relatively successfully for immune checkpoints, in addition to other new immune checkpoints that have been discovered and clinically tested. However, while immune checkpoint inhibitors have been developed successively, some vague problems still need to be solved, such as the large gap between the immunotherapy effects of different patients. These issues are critical to the selection of immune checkpoint inhibitors. In this review, based on the study of the immunosuppressive mechanism of CTLA-4 and PD-1/PD-L1, the application of related immune checkpoint inhibitors in cancer treatment is discussed starting from three representative types of cancer. At the same time, according to the existing problems, some common immune-related adverse events and newly discovered immune checkpoints are summarized, and the future research direction of ICIs is further explored.

**Keywords:** Checkpoint inhibitors, Therapy, Cancer.

## 1. Introduction

Cancer has the characteristic of genomic instability, in which a great number of point mutations build up and structural alterations take place as the tumor progresses (Zhang & Zhang, 2020). Until today, cancer is still one of the diseases that cause major death globally [1]. Chemotherapy, radiation and surgery were considered the conventional therapy methods of cancer treatment. However, these kinds of therapies have some adverse effects and may not be suitable for all patients. Scientists found a revolutionary new therapy to treat cancer, which is called immunotherapy. It has rejuvenated the field of tumor immunology [2]. Immunotherapy uses patients' immune systems to combat cancer cells. Immunotherapy combats cancer cells by utilizing the patient's immune system. Scientists discovered that tumor cell gene mutations can produce tumor antigens, which can induce an immune response. Cancer development and progression are linked to immune suppression. Scientists found that cancer cells can activate different immunological checkpoint pathways that have immunosuppressive properties.

Because ICIs targeting CTLA-4 and PD-1/PD-L1 have recently been successfully applied in a variety of advanced cancers [3]. Since the first discovery of CTLA-4 in 1987 [4], PD-1 and PD-L1 were discovered in decades [5], thus has been widely investigated. Their application in anti-tumor immunity makes them the most promising targets for drug development [6]. ICIs enhance T cell-mediated immune by binding of immune checkpoint proteins to partner proteins to prevent tumor cells from evading immune system recognition and attack using negative feedback mechanisms of immune checkpoint pathways.

Although PD-1 blockade has brought a glimmer of hope for cancer immunotherapy, there are still some problems [7]. In addition to cancer cells using PD-1 for camouflage, some other normal cells also use PD1 to avoid being attacked by T cells. Once this PD-1 blocker works, these normal cells will also be listed as attack targets, which will bring great side effects [8]. Addressing this problem is

still the direction that scientists still need to work on. In addition to PD-1, there is another target of immune checkpoint blockade CTLA-4, which is a receptor expressed on the cell membrane in the early stage of T cell. CTLA-4 can inhibit the binding of CD28 to B7-1/B7-2 through competitive, thereby inhibiting the costimulatory signal that plays a positive regulatory role, making T cells inactive [9]. The reason is that this method targets the PD-1 or CTLA-4 pathway. The premise of its effect is that the expression levels of these two genes in patients are relatively high. It is difficult to have obvious effects. Therefore, it is necessary to carry out genetic screening for patients and apply them to eligible patients.

This review introduced the development and application of CTLA-4 blocking therapy and PD-1/PD-L1 blocking therapy. The discovery of some new immune checkpoints and related clinical trials of inhibitors were also introduced. These may contribute to understand immune checkpoint inhibitor therapy.

## 2. Mechanism of CTLA-4

CLTA-4 plays a role in inhibiting T cell activation. T cell is activated when a T cell receptor (TCR) binding to major histocompatibility complex (MHC) presented by an antigen–presenting cell [10]. The binding of CD28 with CD80/CD86 causes CTLA-4 to be expressed. CLTA-4 and CD28 are homologous costimulatory receptors that bind to the CD80 and CD86 [11]. Anti-CTLA-4 antibodies block CTLA-4, increasing the chance and probability of CD80 and CD86 interaction with the costimulatory CD28, promoting CD28 signaling over CTLA-4 signaling (Figure 1). This enhances the T cells and makes them stronger to fight against cancers. The tumor site may also be affected by anti-CTLA-4 antibodies as exhausted T cells and Tregs that express CTLA-4 may assemble within the tumor microenvironment [12].

## 3. Mechanisms of PD-1/PD-L1

The monoclonal antibody inhibitors are intended to block either PD-1 or PD-L1; thus PD-L1 can no longer bind with PD-1 and send off signals to $CD8^{+}$T cells (Figure 2). This will turn on T-cell mediated immunity and enhance the pre-existent antitumor immune effect [13].

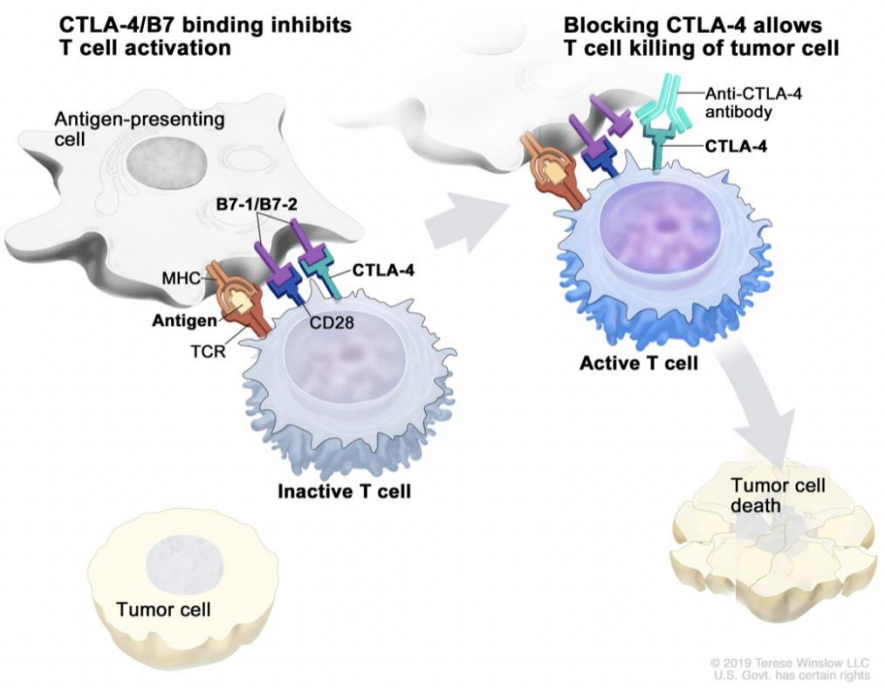



**Figure 1.** Mechanisms mediating the clinical activities of anti-CTLA-4.

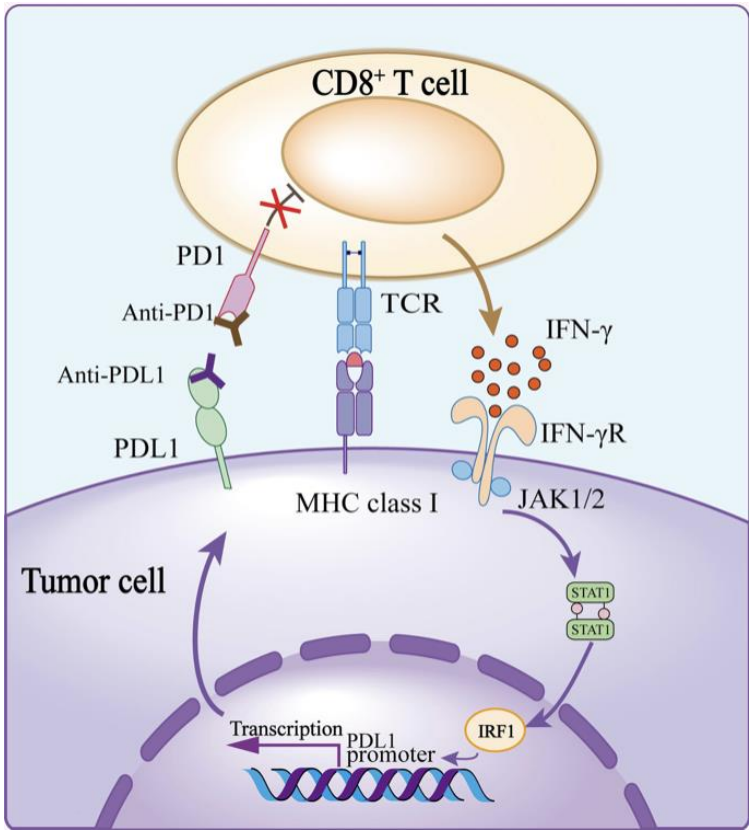



**Figure 2.** Mechanisms mediating the clinical activities of anti-PD1 and anti-PD-L1.

## 4. Therapy in Advanced NSCLC

When Jedd Wolchok started studying melanoma 20 years ago, the average life expectancy for people with advanced melanoma was six to seven months. Now, the survival rates have improved a lot because of blockade therapy. The ipilimumab was approved in March 2011 to treat melanoma that has spread or cannot be treated with surgery. The drug significantly improved survival compared with the melanoma vaccine being tested. Checkpoint inhibitors are a type of cancer immunotherapy drug. Checkpoint inhibitors that stimulate an immune response against cancer cells are not the first cancer immunotherapy drugs, but they are by far the most successful, especially in melanin in tumor [14]. They also have a strong effect on lung and urinary tract cancers. Melanoma is the type of cancer most sensitive to checkpoint inhibitors. In recent years, immune checkpoint blockers have achieved positive results in the clinical application of many solid tumors and hematological malignancies, but the immune-targeted drugs related to liver cancer are limited to Sorafenib. With the continuous approval of two PD-1/PD-L1 pathway blockers by the US FDA in 2014, researchers have become interested in whether immune checkpoint blockade can achieve good anticancer effects in the treatment of liver cancer. At present, molecular blockers are in the Related studies have been carried out in liver cancer. Among them, the preliminary results of the clinical trials of the checkpoint blockers Nivolumab and Tremelimumab in liver cancer are optimistic, and the prospects are worth looking forward to.

Most of the patients in our country are in the advanced stage when they go to the clinic and are not suitable for surgical resection. They are mainly treated with targeted therapy, radiotherapy, chemotherapy and other comprehensive treatments, and the 5-year survival rate is low. In recent years, research in the field of immune checkpoints has progressed rapidly, and many new drugs have emerged. EGFR-TKI has now developed to the third generation osimertinib. Although osimertinib has improved efficacy for some rare EGFR mutations and can effectively reduce the risk of brain metastases from lung cancer, drug resistance is inevitable in the later stages of disease development.In addition, traditional chemotherapy drugs such as platinum or paclitaxel can cause 3-4 toxic side

effects to the body. Immune checkpoint inhibitors (ICIs) can not only ensure the safety of the treatment process, but also improve the efficacy [15]. Therefore, it has great potential therapeutic value in the treatment of EGFR mutation-positive advanced NSCLC.

## 5. Therapy in Renal Cell Carcinoma (RCC)

RCC has an incidence rate of 2% - 3% in adult malignant tumors, accounting for 85% of renal malignant tumors. RCC originates from renal tubular epithelial cells, which include a group of heterogeneous cancers with different histological, molecular and genetic changes. And ccRCC represents 70-75% of the cases, and the nonclear cell subtypes account for approximately 25% of the cases. In this review, ccRCC is discussed in more detail below.

Advanced renal cell carcinoma has considerable morbidity and mortality. Particularly, in recent years, immunotherapy has made a breakthrough in the field of renal cancer treatment, substantially improving the treatment opportunities. ccRCC as an immunogenic tumor type, including nonspecific immunotherapy and dendritic cell vaccines. Therefore, this immunotherapy has been replaced by therapies such as targeted antiangiogenic drugs. Now, the ICIs are the new backbone in the therapeutic landscape of renal cancer. In 2017, nivolumab combined with ipilimumab was listed in the recommended drugs for the treatment of middle renal cancer patients.

The trial demonstrated in clinical single-agent ipilimumab treatment. Although treatment is efficacy, the emergence of ICI has replaced ipilimumab. Another trial identified that a clearly predictive biomarker was not identified in tumour and serum samples. The above clinical trials of single-agent ICIs in RCC showed that only a small number of patients had objective response to ICIs, accompanied by immune-mediated adverse events. And ICIs can improve OS. Therefore, the strategy of combined treatment was adopted to improve the response rate of ICI.

However, sunitinib patients were also found to be more advantageous in terms of PFS, with a lower incidence of associated deaths than the ICIs combined therapy. In conclusion, many patients have no response to ICIs therapy of single-agent, and combined therapy might make patients receive unnecessary treatment with increasing adverse reactions. Before pending longer-term trial data, patients should be treated carefully for the choice of the treatment method of ICIs, and the development of biomarkers can also improve selection.

## 6. Therapy in Breast Cancer

In addition to these two cancers, checkpoint inhibitors also work in breast cancer patients. PD-L1 expression has also been shown in breast malignancies, with a high proportion of breast cancers expressing these co-inhibitory molecules. In 2006, the first study investigated and found that nearly half of the primary breast cancer samples expressed PD-L1 [16].

According to another study, the same chromosomal amplification in breast cancer, which is linked to higher expression of PD1 ligands, was seen in some cases. TNBC is a highly heterogeneous subtype that is sensitive to chemotherapy but has poorer overall outcomes than other breast cancers. Poorer outcomes are related to TNBC patients due to tumor-derived IL-18, which also caused tumors to express PD-1. The relationship between PD-L1 and TNBC cells allows treatment strategies targeting PD-1/PD-L1 to be used to effectively kill TNBC cells. A study demonstrated that inhibiting PD1 signaling in this subtype of breast cancer produced some encouraging results.

## 7. Immune-related adverse events (irAEs)

In a number of cancer patients, ICIs helped to prolong survival. However, the absence of immunoregulatory control may result in uncontrolled immune response activation.

This adverse event might happen at any moment, generally they were more common in the early stage of the treatment, such as the first 3 months. A number of studies have shown that combining ICIs, such as ipilimumab and nivolumab, can result in remarkable efficacy while causing more irAEs

than using single ICIs alone. The occurrence of myocarditis caused by the combined use of inhibitors is higher than that caused by the single use of inhibitors. As a result, the sensible use of inhibitors and treatment of associated adverse effects will be studied more in the future.

CIC is another irAE which is most widely reported, but poorly understood. This is due to the fact that the gut microbiota mechanism, the misdiagnosis of CIC as inflammatory bowel disease (IBD), the reintroduction of ICIs, and the contentious prognostic aspects all have an impact on the thorough understanding [17]. The common symptoms of CIC are diarrhea, vomiting, abdominal pain, fever and so on. Similar to ICI-associated myocarditis, the increased T-cell activity would cause fatal colitis; besides, the CIC is usually more severe and presents a higher occurrence with combined ICIs.

## 8. Conclusions

Blockade therapy is by far the most successful, especially in melanin in tumor. It also works well in cuing liver and lung cancer in most cases. CTLA-4, PD-1 and PD-L1application in anti-tumor immunity makes them the most promising targets for drug development. The emergence of immune checkpoints such as CTLA4, PD-1 and PD-L1 has revolutionized the field of cancer immunotherapy. With the deepening of the clinical application of ICI, its indications are gradually expanding, and more and more advanced cancer patients have the opportunity to use ICI to prolong their life. The addition of novel immune checkpoints such as PTP1B and LAG-3 has enriched the selection window of cancer immunotherapy. However, problems such as irAEs and drug resistance are still very serious. Combination therapy may become a more promising treatment method. Some clinical applications have shown good therapeutic effects. In the future, a large number of clinical studies are still needed to prove its feasibility.

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