# The current achievements of immune checkpoint inhibitor therapy in the treatment of cancer and the newly discovered immune checkpoints in recent years

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**Abstract:**

Immune checkpoint inhibitor therapy (ICIs) is a new type of cancer treatment method developed in the past 20 years and is a very eye-catching innovation in the development of clinical immunotherapy. With the emphasis on cancer treatment and our deepening understanding of the human immune system and malignant tumors, the mechanisms of various immune cell responses involved in cancer recognition and elimination have been gradually discovered and clarified one by one [2]. This therapy aims to enhance and activate the anti-tumor immune activity of cytotoxic T cells by blocking negative regulatory molecules on anti-tumor T cells or ligands on antigen-presenting cells and tumor cells through immune inhibitors. This therapy is of considerable importance in the current treatment and research of immuno-oncology. From the beginning, it was only used to treat a specific tumor to gradually treat a variety of different and common tumors. At the same time, it has also been used since the beginning. What started as a single specific inhibitor or two gradually developed into various dosage forms that can be combined. It has become one of the most clinically important methods for treating cancer.

**Keywords:** Immune, inhibitor therapy, immunotherapy, anti-tumor

## 1 Introduction

Immune checkpoint inhibitor therapy (ICIs) is a new cancer treatment method developed in the past 20 years. It is a very eye-catching innovation in the development of clinical immunotherapy. With the emphasis on cancer treatment and our deepening understanding of the human immune system and malignant tumors, the mechanisms of various immune cell responses involved in cancer recognition and elimination have been gradually discovered and clarified one by one [2]. This therapy aims to enhance and activate the anti-tumor immune activity of cytotoxic T cells by blocking negative regulatory molecules on anti-tumor T cells or ligands on antigen-presenting cells and tumor cells through immune inhibitors. This therapy is of considerable importance in the current treatment and research of immuno-oncology. From the beginning, it was only used to treat a specific tumor to gradually treat a variety of different and common tumors. At the same time, it has also been used since the beginning. What started as a single specific inhibitor or two gradually developed into various dosage forms that can be combined. It has become one of the most clinically important methods for treating cancer.

## 2 Basic mechanisms of immune checkpoint inhibitor therapy

The key to immune checkpoint inhibitor therapy is co-stimulation between antigen-presenting or cancer cells and T cells. In the lymph node, the antigen is presented to the TCR on the T cell through the MHC molecule on the APC cell, which can be regarded as the first signal. However, there is also costimulation, a second signal to activate immunity. The two signals jointly activate immunity by combining CD 80 or CD8 6 on the surface of APC with CD 28 on T cells. However, the body does not want a completely overwhelming activation, so checkpoints or interruption points appear to control immune activation. CTLA 4 comes to the surface of T cells, defeats costimulatory signals, and serves as a checkpoint to obtain a negative regulatory response. Similar to T cells located in lymph nodes, T cells located in peripheral tissues express signals like tissue cells. But T cells expressing PD 1 soon bind to the tissue cell ligand PD - L 1. Both checkpoints are negative regulators that reduce immune binding. So, it's this mechanism that cancer uses to evade immunity and take advantage of the immune system. To activate the adaptive immune system to recognize cancer, blocking and inhibiting immune checkpoints avoids the inhibitory signals of T cell activation, allowing tumor-reactive T cells to overcome their negative regulatory mechanisms and generate an effective anti-tumor immune response. Drugs have been developed that target the PD - L1 ligand, target PD 1 on the surface of T cells, and target CTLA 4.

3 Immune checkpoint inhibitors currently in clinical use

in 2011, the FDA approved ipilimumab (anti-CTLA4) for

treating metastatic melanoma. Ushering in a new era of clinical cancer treatment through immune checkpoint inhibitor therapy. "As of June 30, 2022, the FDA and NMPA have approved 9 and 15 ICIs, respectively. Among them, the ICIs approved by the FDA include 1 CTLA-4 inhibitor, 4 PD-1 inhibitors, 3 PD-L1 inhibitors and 1 fixed-dose combination of PD-1 and LAG-3 inhibitors; NMPA-approved ICIs include 1 (foreign) CTLA-4 inhibitor, 9 (2 foreign, 7 domestic) PD -1 inhibitor, 4 (2 domestic, 2 foreign) PD-L1 inhibitors, and 1 bispecific antibody against PD-1 and CTLA-4[3]." "Even including but not limited to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), lymphocyte activation gene 3 (LAG-3), T cell immunoglobulin and mucin-containing Immune checkpoint targets such as protein domain 3 (TIM-3), T cell immunoglobulin and ITIM domain (TIGIT) have been extensively studied. However, the currently certified checkpoint monoclonal antibodies only target three checkpoint targets, namely PD - L1, PD -1, and CTLA - 4[3]."

### 3.1 _ Monoclonal antibody checkpoint inhibitors targeting CTLA-4 and their mechanisms of action

#### 3.1.1 CTLA -4 monoclonal antibody inhibitors

As of June 30, 2022, the CTLA -4 checkpoint inhibitors approved for clinical use include Ipilimumab and Candonilimab, a bispecific antibody targeting PD -1 and CTLA -4. Ipilimumab monoclonal antibody is mainly targeted at treating melanoma and malignant pleural mesothelioma, while Candonilimab is mainly targeted at treating cervical cancer. Ipilimumab is the earliest monoclonal antibody approved and put into clinical use with sufficient clinical data. Research and data show that ipilimumab combined with anti-cancer treatments can improve advanced melanoma and lymph node-positive cervical cancer in the clinic with a controllable safety profile. Candonilimab bispecific antibody is a newer dual immune checkpoint inhibitor. "A phase III clinical study of candonilimab combined with platinum-based chemotherapy with or without bevacizumab in the treatment of persistent, recurrent or metastatic cervical cancer has been completed[4]."

#### 3.1.2 Mechanism of action of CTLA -4 monoclonal antibody inhibitors

L ipilimumab is a monoclonal antibody immune checkpoint inhibitor that acts on the CTLA -4 molecular target on the surface of T cells. Prevents the presentation between APC expression B 7 and CTLA -4, preventing the negative regulation of immune activation between immune cells and antigen-presenting cells. It enhances T cells' immune expression and improves tumor-specific T

cells' ability to eliminate tumor cells to a greater extent. Candonilimab, as a bispecific antibody, can simultaneously block the interaction of PD -1 and CTLA -4 with their ligands PD - L 1/PD - L 2, B 7.1/ B 7.2, thereby inhibiting the immunity of the signaling pathway. Inhibit the reaction, promote tumor-specific T cell immune activation, and inhibit tumor growth.

### 3.2 Monoclonal antibody checkpoint inhibitors targeting PD -1 and PD - L1 and their mechanisms of action

#### 3.2.1 PD -1, PD - L1 monoclonal antibody inhibitors

As of June 30, 2022, 22 PD -1 and PD - L1 checkpoint inhibitors have been approved for clinical use, including 13 PD - 1 checkpoint inhibitors and 13 PD - L1 checkpoint inhibitors. - There are 7 types of L1 checkpoint inhibitors, one type of PD -1/ LAG 3 dual-target inhibitor, and 1 type of PD - 1/ CTLA- 4 dual-target inhibitor.

The 13 PD -1 inhibitors and PD -1/ LAG -3 inhibitors mainly target melanoma (Pembrolizumab, Nivolumab, Nivolumab and relatlimab - rmbw, Toripalimab ), cutaneous squamous cell carcinoma ( Cemiplimab - Rwl ), endometrial cancer ( Dostarlimab - Gxly ), non-small cell lung cancer (Nivolumab), classical Hodgkin lymphoma ( Sintilimab, Camrelizumab, Tislelizumab, Penpulimab, Zimberelimab ), solid tumors ( Serplulimab ). Candonilimab has been mentioned in the CTLA -4 section, so it is omitted here. Seven total PD - L1 inhibitors, respectively, mainly target urothelial cancer (Atezolizumab, Durvalumab )

Merkel cell carcinoma (Avelumab), non-small cell lung cancer (Durvalumab, Sugemalimab ), small cell lung cancer (Atezolizumab), and solid tumors ( Envafolimab ).

#### 3.2.2 Mechanism of action of PD -1 and PD - L1 monoclonal antibody inhibitors

PD -1 and PD - L1, as monoclonal antibody immune checkpoint inhibitors, respectively act on the PD -1 molecular target expressed by T cells and its ligand PD-L1 molecular target, preventing APCs from expressing PD -1 and Pre-presentation of PD - L1 prevents negative regulation of immune activation between immune cells and antigen-presenting cells. It enhances T cells' immune expression and improves tumor-specific T cells' ability to eliminate tumor cells to a greater extent.

### 3.3 Current Achievements

From 2011 to June 30, 2022, dozens of different immune checkpoint inhibitors have been used clinically, from the initial CTLA -4 monoclonal antibody inhibitors that only targeted melanoma to the later Checkpoint inhibitors for many types of cancers and tumors that have achieved

corresponding results in clinical practice and cancer treatment. The combination of ICIs and different types of cancer therapies has achieved relatively satisfactory results in clinical practice.

# 4 Newly discovered immune checkpoints in recent years

and used in clinical applications mainly target three targets: CTLA -4, PD -1, and PD - L1. Because we have obtained extensive and detailed research and understanding of the mechanisms of action of these three targets and their operating rules, the current research and application of immune checkpoint inhibitors targeting these three targets has been relatively mature. So now, for immune checkpoint inhibitor therapy, attention has been directed to other checkpoints that may become new ICI targets. Only some immune checkpoints with a certain research basis will be mentioned in this review.

## 4.1 Lymphocyte activating gene 3 (LAG-3)

"Lymphocyte activating gene 3 (LAG-3 or CD223) is a single transmembrane protein with three Ig extracellular domains. It is found in activated T cells, regulatory T cells, natural killer (NK) cells, and trees, and it is expressed in dendritic cells (DCs) and B cells. LAG -3 interacts with its binding ligand MHC -II; evidence suggests that LAG -3 can act as a co-inhibitory molecule, and blocking LAG -3 with mAb can lead to greater T cell proliferation in vitro. LAG -3 is co-expressed with other immune points in exhausted T cells. LAG 03 blockade of exhausted CD 8 + T cells can lead to the recovery of immune function and has a synergistic effect with simultaneous blockade of PD -1. LAG-3 was also found to be up-regulated on Treg cells and conferred regulatory functions. Blocking LAG-3 on Treg cells in vitro and in vivo reduced suppressive activity. These findings suggest that LAG-3 suppresses immune responses by directly inhibiting effector T cell killing and Treg cell-mediated immune inhibitors [5]."

## 4.2 B and T lymphocyte attenuation factor (BTLA)

"B and T lymphocyte attenuator (BTLA) is an immunoglobulin domain-containing glycoprotein expressed on T cells, resting B cells, macrophages, DCs, and, to a lesser extent, NK cells. BTLA acts as an inhibitory receptor for T cells because anti-BTLA treatment leads to T cell proliferation, and BTLA knockout mice exhibit hyperresponsive immune activation. Subsequently, herpesvirus entry mediator (HVEM), a tumor necrosis factor receptor, was identified as a natural ligand of BTLA in mice and humans. HVEM expressed on antigen-presenting cells (APCs) is able to induce BTLA-dependent T cell suppression. BTLA, like CTLA-4 and PD-1, belongs to the immunoglobulin superfamily and is characterized by binding to B7 family members. HVEM is a member of the tumor necrosis factor receptor family, and the BTLA/HVEM interaction provides the first demonstration of crosstalk between these two receptor families. Before the BTLA/HVEM interaction was discovered, HVEM was known to bind lymphotoxin-alpha and LIGHT, two tumor necrosis factor ligands. The BTLA/HVEM interaction generates a costimulatory signal, while the HVEM/LIGHT interaction generates a costimulatory signal through HVEM [5]."

## 4.3 T cell immunoreceptor with Ig and ITIM domains (TIGHT)

"TIGHT is a T-cell receptor that limits T-cell function and adaptive immune responses. TIGIT is primarily expressed by T cells and natural killer (NK) cells. Different T cell subsets, such as CD4+ T cells, CD8+ T cells, regulatory T cells (Treg), follicular T helper cells, and NK cells, show different levels of TIGIT expression. TIGIT acts as a negative regulator of cancer cell-targeted T cell responses and has been identified as a potential target for immune checkpoint inhibition in different malignancies [1]."

"The TIGIT effect is mediated by binding to CD155, the primary receptor for TIGIT, and directly inhibiting T cell responses. TIGIT interacts with CD155 on DCs, resulting in increased interleukin (IL)-10 secretion and decreased pro-inflammatory cytokines (e.g., IL-12p40, IL-12p70, and IL-18). These impaired DCs lead to an indirect decrease in T-cell responses. In TIGIT-regulated DCs, T cell proliferation is reduced by at least 50%, and T cell activation is inhibited [1]."

CD226 is a costimulatory receptor widely expressed by immune cells, including T cells, NK cells, and monocytes. TIGIT impedes CD155-mediated activation of CD226, which ultimately impairs T-cell function in different T-cell subsets.

"TIGIT-CD155 signaling through the intracellular ITIM structural domain of TIGIT restricts T-cell and NK-cell responses. TIGIT plays an important role in NK-cell depletion and limits the cytotoxic effects of tumor-cell-directed NK cells. TIGIT-positive NK-cells exhibit diminished killing, reduced cytokine production and proliferation, and other features of exhaustion and dysfunction. TIGIT inhibits NK cell degranulation, cytokine production, and NK cell-mediated cytotoxicity against CD155-expressing tumor cells [1]."

"The basic principle of targeting TIGIT is to reverse the immune invasion of cancer cells and re-establish cytotoxicity against cancerous T cells and NK cells. In the last few years, monoclonal antibodies (mAb) have been established that bind to the TIGIT receptor in T cells and NK cells. Administration of anti-TIGIT mAb therapy in the

establishment of CT26 subcutaneous tumors and methyl-cholanthrene-induced fibrous carcinomas inhibits tumor growth. It protects mice from experimental metastases of 4T1 or B16 in a melanoma patient-derived xenograft model reconstituted with human hematopoietic stem cells, etigilimab, a TIGIT-targeting monoclonal antibody, impaired tumor growth. In another group, anti-TIGIT mAb protected mice from Vk12653 myeloma recurrence after hematopoietic stem cell transplantation. In another myeloma mouse model, a TIGIT-blocking monoclonal antibody reduced tumor load and prolonged overall survival in a CD8+ T-cell-dependent manner.

TIGIT-targeting monoclonal antibodies alone may not be sufficient to have an adequate impact on tumor progression, so combined immune checkpoint inhibition strategies were evaluated in different cancer entities. TIGIT is commonly co-expressed with programmed cell death protein 1 (PD-1) on CD8+ TIL in mouse models and patient samples across cancer entities. PD-1 checkpoint blockade is a highly effective therapeutic approach for a variety of cancer entities, including melanoma and non-small cell lung cancer. TIGIT+PD-1 combination blockade therapy has shown therapeutic and metastasis-blocking efficacy in mice with a wide range of tumors.

TIGIT is a major immune checkpoint that promotes tumor cell immune evasion of T cell and NK cell cytotoxicity through binding to its primary ligand, CD155. TIGIT overexpression is present in a wide range of malignant tumors and correlates with cancer progression, distant metastasis, and impaired patient prognosis. The combination of TIGIT+PD-1 checkpoint blockade showed impressive in vivo tumor regression, and the first clinical trials have yielded encouraging results for this combination therapy. Challenges remain unresolved [1]."

## 4.4 Feasibility

There are already ongoing clinical experimental data and completed experimental data and theories proving that many potential new immune checkpoints, such as BTLA and LAG -3, that are gradually emerging have the feasibility of research and clinical application, including the current LA G - 3/CTLA_4 bispecific antibody already on the market also shows the feasibility of LAG -3 in clinical applications.

## 5 Summarize

Immune checkpoint inhibitor therapy has been a popular and innovative new treatment method for cancer and tumors in the past five or even ten years. After nearly a decade of research, understanding checkpoint inhibitors targeting PD - 1, PD - L1, and CTLA -4 has been profound and mature. Therefore, some current studies on ICIs have focused on new, newly discovered immune checkpoints or some that have been studied but are not well understood and the combination of different immunotherapies. In the clinical trials that have been conducted, there are already signs that these new immune checkpoint inhibitors have certain improvements and advantages over previous inhibitors in terms of side effects, efficacy, and other aspects. Therefore, the future of immune checkpoint inhibitor therapy is very promising and may even play a leading role in improving clinical response rates. "Although only a small proportion of cancers currently show good response rates to immune checkpoint therapy, partly due to the different immunogenicity of the immunosuppressive tumor microenvironment in different tumors, as research and discovery can be achieved through a combination of therapies and optimization of therapies to Tumor T cell immunity provides new avenues. In conclusion, many immune checkpoints have been identified so far and are in different stages of clinical development. Combining immune checkpoint inhibitor therapy with different anti-tumor therapies can improve response rates and the prospects of immunotherapy application in different tumors [5]."

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