# Application of PD-1 and PD-L1 inhibitors in immunotherapy of cancer

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**Abstract.** Cancer is a disease that developed from uncontrolled cells and has become one of the most medical problems that endanger human health. Currently, immunotherapy has replaced traditional treatment acts as the major therapy for cancer patients. The immune checkpoint inhibitor (ICI), which is highly specific and affinity to the immune checkpoint that suppress immune response during tumorigenesis, shows promising result during the clinical study and research. PD-1 and its ligand PD-L1 are the major targets for ICI development, there already have six FDA-approved inhibitors that target PD-1 and PD-L1 are used as a first-line treatment for many cancers. The clinical study of PD-1 and PD-L1 inhibitor application in patients with different cancers not only reveals their efficacy and safety but also indicates the onset of many adverse effects, which are usually called immune-related adverse events (irAE) and could be fatal in particular conditions. However, some research suggests the presence of irAE is a marker for effective of ICI therapy. Therefore, this essay will mainly focus on the application of PD-1 and PD-L1 inhibitors and the efficacy of each inhibitor has been testified via multiple clinical research. The common PD-1 and PD-L1 blockade-associated irAEs also have been discussed and their degree of risk is assessed. This essay also discussed the method that is frequently used in the management of irAEs.

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

## 1. Introduction

Cancer is the main medical issue that shortens people's life and significantly endangers the public health system. It has become a big challenge that modern medicine needs to overcome with the increasing number of patients that suffer from it. For cancer treatment, scientists have developed many available therapies such as surgery, chemo- and radiotherapy. However, the massive clinical data indicate these treatments have significant side effects, for example, patients who accept chemo- or radiotherapy will feel sick or fatigued and sometime with hair loss and diarrhoea. Some patients are unsuitable for these treatments, such as those with cancer with unresectable tumours. These conventional treatments also show limited effects on metastatic cancer and some research reveals their application can result in the generation of resistance, easily. Meanwhile, the statistic of patients with non-specific clinical symptoms reports there have many patients accept those conventional treatments for advanced-stage cancer [1]. This strongly reduces the efficacy of conventional treatment

Therefore, immunotherapy has become an attractive option that changed the pattern of cancer treatment and shows better efficacy in comparison with conventional treatments [1]. Immune checkpoint inhibitors (ICI) that target the immune checkpoints show encouraging results when applied to against various cancer. The immune checkpoint is the negative regulatory pathway of the immune system that is usually utilized by tumour cells to participate in immune suppression and evasion mechanisms [2]. Currently, the FDA-approved ICI drug mainly targets cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed death-1 (PD-1) and its ligand programmed death-ligand 1 (PD-L1). Interestingly, anti-PD-1 and anti-PD-L1 antibodies both aim to terminate the interaction between them, therefore, some research will allocate PD-1 and PD-L1 into one category according to their functions.

PD-1 is the receptor that is mainly expressed on the surface of activated T cells and binds to its ligand, PD-L1 and PD-L2 which are mainly distributed on the surface of non-lymphoid cells. The binding of PD-1 and its ligand will phosphorylate the immunoreceptor tyrosine-based switch motif and immunoreceptor tyrosine-based inhibitory motif of PD-1 and recruit and dephosphorylate src

homology 2 (SH2) domain-containing protein tyrosine phosphatase 1 (SHP-1) and SHP-2. The negative co-stimulatory signal that is generated from this interaction will be transduced via the tyrosine phosphatase of PD-1 and phosphatase SHP-2, and then down-regulate the T cell activity to avoid autoimmunity and host organ injury [3]. Another research reveals that PD-1 is also involved in the suppression of glycolysis via inhibition of protein kinase B (PKB) and promotes fatty acid oxidation and lipid catabolism, which play a central role in the regulation of T cell activity. Therefore, the interaction of PD-1 and PD-L1 can inhibit the proliferative capacity and cytotoxic potential of T cells. This will induce T cell exhaustion.

Although there have two ligands for PD-1, PD-L1 is the only ligand that acts as the target for immunotherapy of ICI due to it being widely expressed in normal and tumour cells. Many studies find that the level of PD-L1 will be up-regulated in tumour cells and deletion of PD-L1 results in autoimmune disorders, such as lupus-like syndrome, in healthy mice [4]. There have many ICI that target PD-L1 and aim to disrupt the interaction of PD-1 and PD-L1 to treat cancer.

To this day, there have some FDA-approved ICI drugs that target PD-1 and PD-L1 that already show well clinical response and anti-tumour activity in clinical studies [5]. However, there have many clinical applications of ICI also reported some side effects called immune-related adverse events (irAEs), including fatigue, musculoskeletal pain, nausea, decreased appetite, cough, some autoimmune disorder and inflammation in different organs [6]. These adverse events usually are mild to patients and could be treated in one to two months, but there also have some severe effects that are associated with fatal outcomes, for example, stroke, colitis and cardiorespiratory arrest [7]. A recent study defines irAEs as the off-target effect of the excessively activated immune system by reason of the combination of ICI and other therapy shows increased toxicity and frequency of adverse events in contrast to monotherapy of ICI [8].

This essay has focused on applying those PD-1 and PD-L1 inhibitors in cancer treatment. The efficacy of each FDA-approved inhibitor will be revealed via the statement of clinical data, such as overall survival (OS) and overall response rate (ORR), and the data comparison of patients who accept ICI with those who receive traditional treatment. This essay will also briefly discuss the common irAEs associated with cancer therapy of PD-1 and PD-L1 inhibitors to highlight the importance of improving clinical presentation, diagnosis and management of irAEs, and mentioned some approaches that improving the management of irAE.

## 2. Application of ICI

Immune checkpoint inhibitors (ICI) are the specific antibodies that target the immune checkpoints to block their interaction with corresponding ligands to terminate the downstream inhibitory signalling pathway, therefore, boosting the anti-tumour activity of T cells and initiating an immune response against tumour cells. The application of ICI has become the common treatment for various cancer [5]-[9].

## 3. Hepatocellular carcinoma

Currently, liver cancer still acts as a big challenge for the global health system. Hepatocellular carcinoma (HCC) is the most common version of this cancer which occurs mainly because of the hepatitis B virus (HBV) infection. Conventional treatments for HCC are surgery radio- and chemotherapy whereas local ablation with radiofrequency is another option for those patients with unresectable tumours. However, the emergence of ICI has changed therapy for HCC [10].

Atezolizumab, which is a fully humanized, highly affinity IgG1 monoclonal antibody that targets PD-L1, has replaced the traditional sorafenib group as the novel standard first-line treatment for HCC. The clinical data of the American Society of Clinical Oncology (ASCO) shows the combination of atezolizumab and bevacizumab, a non-specific VEGF inhibitor, perform longer overall survival (OS), higher overall response rate (ORR) and shorter duration of response in comparison with traditional

treatment, sorafenib, in patients with HCC. Another clinical study from China shows the efficacy of atezolizumab is greater and significantly elongated the OS in patients with HCC in contrast to those who accept sorafenib. In addition, the longest OS of atezolizumab is reached in a first-line phase III clinical study of patients with advanced HCC [11].

PD-1 inhibitor also shows well anti-tumour activity in HCC treatment. Sintilimumab can significantly elongate progression-free survival (PFS) when combined with IBI305, a bevacizumab biosimilar, according to an associated clinical study. The PFS of patients who accepts sintilimumab plus IBI305 is around 5 months whereas those who accept sorafenib are nearly 3 months [12]. The results not only show the ability of ICI to act as the first-line treatment for HCC but also indicates the combination of ICI and VEGF inhibitor is an effective strategy for HCC treatment.

Pembrolizumab is a full-length humanized IgG4 anti-PD-1 inhibitor which is also used in HCC treatment when combined with tyrosine kinase inhibitors. The application of pembrolizumab combined with lenvatinib shows a well clinical response with a median OS of around 2 years, ORR of 46% and PFS of nearly 9 months. The first-line clinical data of pembrolizumab that combined with regorafenib shows one-third of patients get partial response whereas more than half of patients show stable disease (SD). The overall disease control rate (DCR) is nearly 90%. These results show the combination of ICI and tyrosine kinase inhibitor is an available strategy for HCC treatment.

The monotherapy of pembrolizumab is also effective for patients who are intolerant to sorafenib. The ORR is near 20% with 1 case of complete response (CR) and 17 cases of partial response.

## 4. Biliary tract cancer

Biliary tract cancer (BTC) is a rare and highly fatal malignancy that can be divided into three different solid tumours: gall bladder carcinoma (GBC), intrahepatic cholangiocarcinoma (iGC) and extrahepatic cholangiocarcinoma (eGC). Surgery is the most common therapy for BTC whereas the application of radio- and chemotherapy do not perform the survival benefit. However, surgery will lead to significant side effects and is not effective for BTC patients with metastatic tumours [13].

Some clinical data shows ICI significantly controls tumour progression but only for the BTC patient with specific molecular markers. This result suggests the BTC is an immune “cold” tumour that lacks T cell infiltration. The mismatch repair deficient (dMMR) and microsatellite instability-high (MSI-H) are the markers that are frequently detected in BTC tumour cells. The clinical research that uses pembrolizumab in BTC patients who carry the marker dMMR/MSI-H shows a disease control rate of 100%. Another clinical study that applied pembrolizumab in patients with MSI-H and/or dMMR shows an ORR of nearly 40% and median OS of over 2 years. Pembrolizumab also shows a good clinical response when applied in pediatric patients according to a phase I/II clinical study with a duration of response of around 6 months and ORR of nearly 40%.

Nivolumab is another PD-1 inhibitor used in BTC treatment. It is a fully humanized IgG4 antibody that is usually used in the treatment of unresectable and metastatic tumours. A phase II clinical study shows the application of nivolumab in patients with advanced BTC significantly increased their ORR and DCR, the median OS of these patients is not reached.

PD-L1 inhibitor also is a potent treatment for BTC. A phase III clinical study that endpoint is ORR uses durvalumab combined with tremelimumab to treat BTC patients. This study divided patients into 3 cohorts. The result shows ORR of 50%, 73% and 73%. A further study shows patients who accept durvalumab have longer OS and PFS in contrast to patients who accept chemotherapy. These results show ICI is an effective treatment for BTC patients in presence of specific molecular markers.

Recent study proposes an available pattern of ICI combination therapy that can treat BTC without the molecular markers. The altered FGFR2 signalling plays an important role in the immune evasion mechanism of BTC tumour cells whereas the IDH1 mutation results in the suppression of immune response specific to BTC. Therefore, the combination of ICI with inhibitors that target FGFR2 and IDH1 can regulate the tumour microenvironment (TME) to transform the cold tumour into a hot tumour, therefore, the ICI become effective for all BTC patients.

The following clinical study that focuses on the safety and efficacy dose of ICI when combined with FGFR2 and IDH1 inhibitor is now in progress.

## 5. Colorectal cancer

The increased ageing population, unfavorable diet, obesity and lack of physical exercise result in the increase of colorectal cancer (CRC) in the global range. The conventional treatments for CRC patients usually have side effects whereas the immune suppression of TME of CRC results in the limited effect of majority immunotherapy. However, the ICI that can block the inhibitory checkpoint to enhance immune response shows promising results [14].

Nivolumab is the most common monotherapy for CRC. Phase I and II clinical studies that use this ICI in the treatment of patients with dMMR/MSI-H metastatic CRC (mCRC) show one-third of patients get an objective response and the rest patients show disease get control in 12 months or longer. Another clinical study that uses a combination therapy of nivolumab and ipilimumab on patients with dMMR and/or MSI-H mCRC shows an ORR of nearly 50%, and the median OS and PFS are not reached in this study.

Pembrolizumab also be considered a standard treatment for CRC. Its efficacy is revealed by a phase I and II clinical study when combined with napabucasin. Another clinical study shows monotherapy of pembrolizumab is effective for patients with PD-L1 positive CRC.

The standard combination therapy for CRC is atezolizumab and bevacizumab. The associated clinical data shows this combination performs a well clinical response with ORR of 30%, DCR of 90% and without anticipated toxicity.

Monotherapy of PD-L1 inhibitor also is an available treatment for CRC. The clinical study of durvalumab in patients with CRC or MSI-H mCRC shows an ORR of over 20%. The application of avelumab, another fully humanized IgG1 monoclonal antibody, in patients with mCRC is now in clinical study. Its effectiveness does need to be testified in further study.

## 6. Limitation of ICI

The development of ICI, including PD-1 and PD-L1 inhibitors, was the most important advancement in cancer therapy over the past decade. It provides efficient and effective treatment for patients. However, ICI is not completely safe as its wide application results in the presence of a spectrum of immune-related adverse events (irAEs), which also is the major side effect of ICI. The number of rare irAEs detected in clinical treatment is increasing with the increased application of ICI in cancer therapy. Therefore, improving understanding of clinical presentation, diagnosis and management of irAEs has become the top priority [15].

The safety and tolerability of PD-1 and PD-L1 inhibitors are evaluated through a meta-analysis of nearly 3,500 patients with various advanced cancers. The result indicates that the application of ICI significantly reduces the risk of all- and high-grade side effects whereas the frequency of adverse events (AEs) caused by PD-1 and PD-L1 inhibitors is much lower than AEs caused by the anti-CTLA-4 antibody. The intensity of PD-1 and PD-L1 blockade-associated AEs is much lower than CTLA-4 blockade-associated side effects and has usually been defined as well tolerated and manageable.

The most common PD-1 and PD-L1 associated irAE is cutaneous irAE. This irAE has been identified in nearly half of patients who accept ICI treatment. The common patterns of cutaneous irAEs are rash, pruritus and vitiligo. The presence of these irAEs is usually associated with favourable outcomes for cancer patients. Associated research shows the presence of lichenoid and spongiotic histopathological patterns of dermatitis is strongly associated with the favourable prognosis of malignancy patients who accept PD-1 and PD-L1 inhibitors. Cutaneous irAEs will be treated for 1 to 2 months after accepting ICI treatment but could result in recurrent outcomes in further treatment, such as pembrolizumab-associated rash.

In addition, the cancer therapy of PD-1 and PD-L1 inhibitors is not recommended for patients who got active and past psoriasis or have a family history of psoriasis. Recent research reveals the application of PD-1 and PD-L1 inhibitors will result in a worsening condition. Another research proposes the occurrence of PD-1 and PD-L1 inhibitor-associated cutaneous irAEs is more frequently compared with CTLA-4 inhibitors. However, the application of anti-PD-1 and anti-PD-L1 antibodies is much more than anti-CTLA-4 antibodies in clinical treatment, therefore, this result may not be accurate enough.

Pulmonary irAE is more likely to be found in patients who accept PD-1 and PD-L1 inhibitors, such as cryptogenic organizing pneumonitis (COP). It is hard to detect in clinical diagnosis and extremely hard to be detected in patients whit lung cancer. Meanwhile, this irAE is the major fatal irAE for patients who accept anti-PD-1 and anti-PD-L1 therapy. Associated clinical study shows there have nearly 30% of patients got grade 3 or higher grade pulmonary irAE after being treated with anti-PD-1 and anti-PD-L1 antibodies and 12% of patients got fatal outcomes. Further research shows there have many factors, such as the previous radio- and chemotherapy, smoking, will affect the occurrence of pulmonary irAE. The PD-1 and PD-L1 inhibitor-induced pneumonitis are more popular in a patient with non-small cell lung cancer and the severity and incidence are much higher.

Hepatic irAE is another fatal irAE for patients who accept PD-1 and PD-L1 inhibitors. Its incidence is equal between patients who accept anti-CLTA-4 therapy and those who accept anti-PD-1 therapy. The most common feature of ICI-induced hepatitis is the isolated elevation of liver transaminases, the progression of this symptom is limited after ICI is discontinued. Recent research shows that the increased evidence of acute liver failure is associated with fatal outcomes and increasing liver dysfunction associated with severe conditions. Therefore, the patient whose transaminases level climbed to 2 to 5 times of basal level need to stop taking ICI inhibitors and accept steroid therapy.

## 7. Improvement of irAEs

Currently, the incidence of irAEs is increased with the widely use of immune therapy, especially ICI. Many scientists have noticed that the improvement of early recognition of treatment initiation is key to the management of irAE [15].

However, the majority of communication between patients and caregivers are lack associated education and understanding that result in the failed recognition of symptom and toxicity of irAE, so that, the symptom of patients cannot be monitored effectively. Meanwhile, the limited understanding of irAE leads the patients and caregivers difficult to construct available management of irAE and realize some of the irAE will occur even the ICI therapy was discontinued. These conditions will result in the fear of patients and caregivers and reduce the efficacy of treatment, the entire cancer therapy will probably be discontinued [15].

The current strategy to improve the education and understanding of irAE for patients is spread the irAE-associated knowledge in various pattern, such as online, printed brochures and standalone programme, to enhance the understanding of irAE of patients. Therefore, patients are able to make an informed decision when they can foresee the effect of their irAE. Professional and standard guidance is also important for clinical diagnosis. The panel of experts which come from each cancer research institute, such as ASCO, is assembled to guide the management of irAE within clinical diagnosis. Therefore, these strategies can significantly improve the prognosis and reduce the toxicity of irAE.

The application of steroids in the management of irAE is another common strategy except for the enhancement of patient education and clinical diagnosis. Many associated clinical studies reveal the efficacy of steroids in response to irAE. A first-line clinical study shows around 60% of patients with pneumonitis had improved since the application of steroids and discontinued the ICI therapy. Another clinical study shows that patient who accepts steroids have a longer duration of treatment and greater cumulative doses in contrast to those who accept corticosteroids.

However, some research suggests that long-term steroid use are associated with various complications, such as hypertension, new-onset hyperglycemia and opportunistic infections. Therefore, the steroid-sparing immune-modulating agent are developed to against the severe and steroid-refractory irAE. To this day, there have many biological immunosuppressive agents already into the clinical study to testify their efficacy and safety. For example, anti-tumour necrosis factor-alpha antibody infliximab, gut-specific immunosuppressant vedolizumab and intravenous immunoglobulin. In addition, the application of these agents is limited due to their mechanism, such as infliximab being banned for patients with hepatic irAE and gastrointestinal perforation [15].

## 8. Conclusions

Cancer is a major risk factor that limits human life span and endangers public health, currently, it has become a severe medical problem that results in a lot of death. Traditional therapy, such as surgery, radio- and chemotherapy, shows the limited effect on patients with advanced and metastatic tumour, and usually cause significant side effects. Immunotherapy, especially ICI, shows better efficacy and limited adverse effects within cancer treatments in contrast to conventional therapy. PD-1 and PD-L1 inhibitor is a major category of ICI that can significantly elongate the overall survival and increase the response rate of patients, currently, they are involved in the standard treatment of many cancers, such as melanoma, colorectal cancer, hepatocellular carcinoma etc. However, the application of ICI is not always safe as many clinical studies report patients to get some adverse effects after they accept ICI. These adverse effects usually are belonged to irAEs and common in patients who accept immunotherapy, especially ICI. Although most irAE is mild to patients, such as cutaneous irAE, there are also some irAEs associated with fatal outcomes, such as pulmonary and hepatic irAEs. Fortunately, the application of steroids can decrease the toxicity of these irAE and there are already some available strategies which can be against irAE by enhancing the clinical diagnosis and education of patients. However, there still have many topics that require further study to improve the cancer therapy of ICI. There have many immune checkpoints, such as LAG-3 and TIM-3, that could be targeted for cancer therapy. The inhibitors that are specific to these checkpoints are not yet been developed and require more clinical study. The safe dose of steroid and steroid-sparing immune-modulating agents needs to be determined in future. The discovery of steroid and agents dose which generate minimal side effects in the management of irAE is key to the improvement of irAE treatment.

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