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# Recent Clinical Applications of Novel Immune Checkpoint Inhibitors in Tumor Treatment

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**Abstract:**

Surgery, radiotherapy, and chemotherapy remain the primary first-line treatments for malignant tumors, yet these diseases still exhibit high morbidity and mortality. The introduction of immune checkpoint inhibitors (ICIs) has fundamentally reshaped the therapeutic paradigm in oncology. ICIs target CTLA-4, PD-L1, PD-1, blocking the immunosuppressive pathways that tumors initiate against immune cells, which demonstrates efficacy in various types of cancer. In non-small cell lung cancer (NSCLC), ICIs used as monotherapy and in combination of ICIs and chemotherapy can significantly improve clinical survival rates and have become a standard and effective treatment regimen for advanced NSCLC patients. In hepatocellular carcinoma (HCC), the combination use of ICIs and anti-angiogenic drugs have become first-line standards, and dual-blockade strategies also show therapeutic effects. The pan-cancer treatment targeting the MSI-H/dMMR molecular subtype breaks the traditional model and exhibits significant therapeutic potential for various solid tumors, e.g., pancreatic cancer, melanoma, and renal cell carcinoma (RCC). Future efforts need to explore novel checkpoint molecules, identify predictive biomarkers, develop optimized combination regimens, and clarify the differences in ICIs efficacy among HCC patients with different etiologies. This article reviews the mechanism of action of ICIs, their therapeutic applications in NSCLC, HCC, pancreatic cancer, and other cancers, as well as current achievements and future directions.

**Keywords:** ICIs; PD-1; CTLA-4; NSCLC; HCC.

## 1. Introduction

Although treatment strategies centered on surgery, radiotherapy, and chemotherapy have matured, malignant tumors continue to be characterized by high morbidity and mortality rates. Emerging immuno-

therapy mediated by ICIs has modified the paradigm of cancer treatment. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and Programmed death receptor 1 (PD-1) are two types of immune checkpoints, both of which are inhibitory protein receptors expressed on the surface membrane of immune cells. The expression of programmed death ligand-1 (PD-L1) on tumor cells enables binding to PD-1 receptors on surface of T cells, thereby inhibiting T-cell activity. Regulatory T cells (Tregs) also express CTLA-4 in the environment of tumor, competes with CD28 for binding to B7 molecules on the surface of antigen-presenting cells, further enhancing immune suppression and facilitating tumor immune escape. The formation of these immune checkpoint pathways enables tumors to survive, grow, and metastasize under immune system surveillance.

ICIs can target T cells, block the aforementioned inhibitory mechanisms to restore T cell function, and enable T cells to re-recognize and attack tumor cells. Since PD-1, PD-L1, and CTLA-4 are the main checkpoints associated with tumor immune escape, most existing ICIs are developed targeting these three molecules, including anti-PD-1 monoclonal antibodies (e.g., nivolumab, pembrolizumab), anti-PD-L1 monoclonal antibodies (e.g., atezolizumab), and anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). These drugs can block key inhibitory signaling pathways, enhance immune responses and establishing immune-mediated tumor cell killing, present significant efficacy in various cancers. This review aims to present the therapeutic effects of ICIs on different cancers and comprehensively analyze the research progress of ICIs in malignant tumor treatment.

## 2. ICIs for Treatment of Non-Small Cell Lung Cancer

The application of ICIs has profoundly reshaped the treatment landscape for non-small cell lung cancer (NSCLC). For NSCLC treatment, ICIs already was a standard second-line treatment regimen with previous treatment failure patients. Furthermore, it can also be employed as first-line treatment strategy for advanced-stage driver mutation-neg patients.

The OAK trial represents a pivotal phase 3 clinical trials, played as a key randomized controlled trials to confirming the efficacy of ICIs. The trial compared the anti-PD-L1 drug atezolizumab with docetaxel in patients with NSCLC who had previously received platinum-based chemotherapy. After randomizing nearly 1,000 patients, the trial demonstrated a significantly superior overall survival (OS) with atezolizumab compared to docetaxel. In the intention-to-treat (ITT) population and the PD-L1-expressing subgroup, the median OS reach to 13.8 in ITT subgroup, 9.6 months in PD-L1 subgroup, and a hazard ratio present at 0.73. Grade 3/4 adverse events are defined as severe or life-threatening reactions that typically require medical intervention, making this difference clinically meaningful—atezolizumab's significantly lower rate suggests it imposes less severe toxicity on patients, which can improve treatment adherence and quality of life, especially for those with advanced or refractory cancers who may tolerate chemotherapy poorly. The OAK trial also found that in the treatment of patients with previous treatment failure, atezolizumab demonstrated consistent efficacy and produced durable responses across all patient subgroups, independent of PD-L1 expression levels, which demonstrated the superiority of ICIs in the second-line treatment. [1]

Unlike the OAK trial, the KEYNOTE-024 trial also represent a phase 3 clinical trial, previously untreated patients with advanced NSCLC and a PD-L1 tumor proportion score (TPS) of ≥50% were enrolled in the study. By comparing pembrolizumab with platinum-based chemotherapy, results similar to those of the OAK trial were obtained. Chemotherapy demonstrated a higher incidence of adverse events, and immunotherapy resulted in a significantly longer overall survival (OS). However, the KEYNOTE-042 trial showed that when PD-L1 expression is limited (i.e., TPS < 50%), the efficacy of ICIs monotherapy represented by pembrolizumab is limited. Compared with the TPS ≥ 50% group, the progression-free survival of the TPS 1-49% group decreased from 7.1 months to 5.4 months, and the objective response rate decreased from 39% to 33%. [2]

Higher PD-L1 expression indicates a stronger dependence of tumors on this pathway for evading immune surveillance. Low PD-L1 expression leads to insufficient immune cell infiltration, and T cells cannot recognize tumor antigens even after the removal of inhibition, which results in failure to initiate immune responses. Therefore, ICIs combined with chemotherapy can actively unlock tumor immune responses through chemotherapy, allowing ICIs to block immune checkpoints and enabling T cells to successfully kill tumor cells. Compared with chemotherapy alone, ICIs combined with chemotherapy show better median overall survival and 4-year survival rates. Although chemotherapy toxicity cannot be avoided, the overall safety is controllable. Patients under 75 years of age benefit significantly from both ICIs monotherapy and ICIs combined with chemotherapy. For patients over 75 years of age with high PD-L1 expression, ICIs monotherapy with better safety is more suitable, while patients with low expression can receive dose-reduced chemotherapy.

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[3]

ICIs have completely transformed the treatment of NSCLC. Whether used as monotherapy or in combination with chemotherapy, they significantly improve survival rates compared with chemotherapy alone, and also have more reliable safety due to reduced toxicity compared with chemotherapy alone. A large amount of clinical data confirms that ICIs serve as a standard and reliable treatment regimen for advanced NSCLC and accumulate important research experience for the treatment of other cancers.

## 3. ICIs for Treatment of Hepatocellular Carcinoma

In the treatment of this cancer, although its clinical application strategies are different, ICIs treatment still shows similar potential as NSCLC. To avoid excessive immune responses caused by intestinal bacteria and antigens, the liver develops immune tolerance through multiple mechanisms, including upregulation of the PD-1 pathway. Hepatocellular Carcinoma (HCC) utilizes this physiological characteristic to continuously upregulate the PD-1 pathway, which enables tumors to evade immune surveillance. This laid a theoretical basis for the clinical use of ICIs in HCC treatment and promotes the initiation of clinical trials.

The tumor microenvironment of HCC is extremely complex, with abnormal and dysfunctional vascular systems. Although nivolumab and pembrolizumab show certain anti-tumor activity in early clinical trials, these two ICIs used as monotherapy failed to reach the expectations of overall survival (OS) in the two phase 3 trials (CheckMate-459 and KEYNOTE-240). ICIs have been proven to be suitable only for the treatment of specific populations and are difficult to become the standard first-line treatment option. However, the clinical benefits they demonstrate still have important value, which promotes the development of various ICIs combination treatment strategies for HCC [4].

The ICIs dual-blockade strategy uses two ICIs in combination to simultaneously block the PD-1 and CTLA-4 pathways, achieving a stronger therapeutic effect than either of the two alone. The PD-1 pathway acts inside the tumor microenvironment: after T cells reach the tumor tissue, tumor cells use this pathway to inhibit the killing function of T cells; the CTLA-4 pathway acts in lymph nodes: it inhibits the initial activation of T cells when it first activated by antigen-presenting cells. Simultaneously blocking these two pathways can produce synergy in terms of temporal sequence and different locations in the human body, which results in a stronger anti-tumor effect compared with the use of a single ICI. Although the incidence of adverse events caused by toxicity is significantly higher than that of ICIs monotherapy, most cases can be controlled through drug withdrawal and glucocorticoid treatment.

Another combination strategy involves ICIs and anti-angiogenic drugs: vascular endothelial growth factor (VEGF) inhibitors or tyrosine kinase inhibitors (TKI) can inhibit abnormal angiogenesis, improve blood circulation inside tumors, promote T cell infiltration, and optimize the delivery of ICIs, thereby creating suitable conditions for ICIs to exert their effects. VEGF itself is an immunosuppressive factor that can inhibit the maturation of dendritic cells, the function of T cells, and recruit inhibitory cells such as Tregs and myeloid-derived suppressor cells (MDSCs). Blocking VEGF can directly relieve this immunosuppression. In clinical trials, ICIs combined with TKI significantly prolong overall survival and progression-free survival compared with sorafenib, and greatly improve the objective response rate (ORR) [5]. Compared with the dual-blockade strategy, ICIs combined with anti-angiogenic drugs have lower toxicity and a wider applicable population, and are currently the standard first-line treatment regimen for HCC. When using ICIs-related strategies to treat hepatitis B virus (HBV)-related HCC patients, ICIs may disrupt the immune system's control over HBV, which leads to HBV reactivation (HBVR), which can cause hepatic failure due to hepatitis and result in the interruption of anti-cancer treatment or even death. For HBV-related HCC patients receiving ICIs treatment, HBVR is a non-negligible risk, but it can be effectively resolved through preventive antiviral treatment.

Although ICIs and their combination strategies have brought changes to HCC treatment, not all patients derive equal benefit in this treatment. Therefore, the discovery of predictive biomarkers is imperative for enabling precision medicine and maximizing clinical outcomes. The latest research and trials focuses on using single-cell RNA sequencing or spatial transcriptomics to deeply analyze the tumor microenvironment, identify and screen biomarkers that may affect the response to ICIs before treatment (e.g., specific inflammatory gene expression, unique CD8+ T cell subsets such as "4-1BB lo" cells, mucosal-associated invariant T (MAIT) cells, and dual metabolic peaks of glycolysis and oxidative phosphorylation in early activated T cells), which thereby improves the precision of ICIs treatment. The future development of ICIs in HCC treatment will focus on analyzing the mechanism of action of different combination regimens and clarifying the differences in ICIs efficacy among HCC patients with different etiologies such as NASH and NAFLD [6].

## 4. ICIs in the Treatment of Pancreatic Cancer

Unresectable advanced pancreatic cancer has an extremely poor prognosis. For patients who cannot receive local regional treatment or surgery, systemic chemotherapy is the clinical focus, but the median OS is still no more than 12 months. The efficacy of ICIs monotherapy in pancreatic cancer treatment is very limited. The tumor microenvironment of pancreatic cancer lacks T cell infiltration and is defined as a "cold tumor". Its microenvironment contains immune cells e.g., dendritic cells (DCs), Treg, and myeloid-derived suppressor cells (MDSCs), non-immune cells such as pancreatic cancer stem cells (PCSC) and cancer-associated fibroblasts (CAF) are also include. These cells result in a strong immunosuppressive tumor microenvironment. Even if ICIs relieve T cell immunosuppression, it is still difficult to eliminate tumor immune escape without sufficient active T cells or under the operation of multiple inhibitory mechanisms.

The microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) subtype of pancreatic cancer shows a significant and durable response to inhibitors especially inhibits PD-1/PD-L1. This subtype is very rare in pancreatic cancer, with an incidence of approximately 1%, but ICIs show effective therapeutic performance for it. The KEYNOTE-158 study used pembrolizumab for non-colorectal MSI-H/dMMR cancers, including 22 pancreatic cancer patients, with an ORR of 18.2%. [7] This study demonstrates the necessity of MSI-H/dMMR detection for all advanced pancreatic cancer patients. Although the incidence is low, once MSI-H/dMMR patients are identified, treatment regimens using ICIs such as pembrolizumab can bring long-term survival opportunities.

Current primary research in immunotherapy is aimed at overcoming the immunosuppressive tumor microenvironment (TME) of pancreatic cancer through combination strategies that integrate ICIs with other therapeutic approaches. When a PD-1 inhibitor is combined with nab-paclitaxel and gemcitabine, the resulting median overall survival (OS) reaches 12.8 months. The combination with radiotherapy lacks clear evidence of synergy; although it shows a high disease control rate (DCR) in individual cases, it cannot become a universal strategy. The combination of ICIs with experimental drugs such as TGFβ inhibitors and MEK inhibitors (Cobimetinib) enhances the response to ICIs; although the average ORR is 10%, it provides a reliable research direction for future development. [8] Currently, ICIs monotherapy is only effective for a small number of pancreatic cancer patients, so the clinical application of combination strategies is the key to future immunotherapy for pancreatic cancer. To promote the development of this therapy, more controlled trials are needed to obtain data to provide evidence for the reliability of strategies.

## 5. Other Cancers

Research and application of ICIs treatment are not limited to NSCLC, HCC, and pancreatic cancer; ICI-led immunotherapy strategies have also achieved breakthroughs in other types of tumors. Advanced melanoma was among the first cancers in which immunotherapy demonstrated marked efficacy. Clinical evidence demonstrates that the combination of ipilimumab and nivolumab can achieve a median overall survival of about 6 years. Considerable clinical benefit is also provided by either agent alone for a subset of patients [9]. For renal cell carcinoma (RCC), the use of dual immune checkpoint inhibitor (ICI) blockade or ICIs combined with tyrosine kinase inhibitors (TKI) yields high objective response rates (ORR), making them key first-line treatment regimen. For patients who have not previously received immunotherapy, monotherapy with an ICI is regarded as the standard second-line regimen.[10] For triple-negative breast cancer (TNBC) treatment, monotherapy with pembrolizumab and atezolizumab shows considerable clinical benefits, and synergy after combination with radiotherapy, chemotherapy, or targeted therapy can further enhance efficacy [11].

MSI-H/dMMR solid tumors are a molecular subtype present in various solid tumors including pancreatic cancer. Their defining characteristic is mismatch repair deficiency (dMMR), which leads to high microsatellite instability (MSI-H). This subtype exhibits high tumor mutation burden (TMB-H), a large number of neoantigens, and abundant tumor-infiltrating lymphocytes (TILs). These characteristics impart significant sensitivity to ICIs, which makes them vital biomarkers for ICI therapy. In addition to the aforementioned MSI-H/dMMR subtype of pancreatic cancer, ICIs show predictable and clear efficacy in the treatment of MSI-H/dMMR molecular subtypes of other solid tumors such as colorectal cancer, which indicates that precision medicine can better exert the role of ICIs in cancer treatment. Future research on MSI-H/dMMR solid tumor treatment will focus on addressing drug resistance caused by B2M mutations or tumor microenvironment heterogeneity. [12]

## 6. Conclusion

Immune checkpoint inhibitors (ICIs) have become a cornerstone in treating various malignancies, especially transforming the treatment patterns of NSCLC and HCC. For the "cold tumors" such as pancreatic cancer, it

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also shows good clinical potential through combination treatment strategies. It has a great impact on the formulation of first-line and second-line treatment regimens for various cancers, bringing significantly improved clinical benefits with fewer adverse reactions than radiotherapy and chemotherapy. Breakthrough progress has also been made in pan-cancer treatment targeting MSI-H/dMMR, which breaked the traditional treatment model based on anatomical location and shifting to precision treatment based on biomarkers. Researchers have started to concentrate on other new checkpoint molecules that play a role in immune regulation in recent years, including B7-H3, VISTA, T cell immunoglobulin and ITIM domain (TIGIT), T cell immunoglobulin and mucin domain-containing molecule 3 (TIM-3), and lymphocyte activation gene 3 (LAG-3). These molecules have complementary or synergistic effects with the PD-1/CTLA-4 signaling pathway in the tumor microenvironment. The therapies via targeting those molecules is expected to further enhance immune responses and solve the limitations caused by ICIs resistance and limited response rates. An important direction for the research community is to elucidate further biomarkers that can reliably predict treatment outcome, for maximize the clinical benefits of ICIs and bring hope for long-term survival to more tumor patients.

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