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# Immune checkpoint inhibitor therapy in pancreatic cancer: terra incognita

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Pancreatic cancer is among the most aggressive of all malignancies and urgently requires effective therapeutic strategies. One promising treatment for solid tumors, like those found in pancreatic tissues, is the use of immune checkpoint inhibitors. These inhibitors have not yet undergone clinical trials in patients with pancreatic cancer, but some studies have revealed promising preliminary findings, such as delay in disease progression and enhancement of overall survival when immune checkpoint inhibitors are administered alone or in combination with other therapies. The present article is a review of current immunotherapeutic strategies and clinical trials for pancreatic cancer.

**Keywords:** pancreatic cancer; immune checkpoint inhibitor; programmed death 1; programmed death-ligand 1

**Coretip:** Most patients with pancreatic cancer are diagnosed at an advanced stage, making curative therapy difficult and increasing the likelihood of a poor clinical outcome. The use of immune checkpoint inhibitors as an immunotherapeutic strategy is a novel option for these patients and clinical trials are ongoing. The data resulting from upcoming clinical trials should provide valuable information for identifying the best combinations of immunotherapy, targeted therapy, chemotherapy, and/or radiotherapy.

## INTRODUCTION

Pancreatic cancer is one of the most lethal malignant neoplasms in the world. The GLOBOCAN 2012 project ranks pancreatic cancer as the seventh leading cause of cancer death in both genders (accounting for 4.0% of all cancer deaths) [1]. The incidence and mortality of pancreatic cancer vary across regions and populations and are highest in developed countries and in regions with higher scores on the human development index [2, 3]. Several studies have indicated an increasing incidence of pancreatic cancer in recent years [2, 4, 5].

The causes of pancreatic cancer are still unclear, although some risk factors have been identified, such as smoking, obesity, diabetes, calorie-rich diet, and reduced physical activity. These risk factors have become common in modern populations. This, in conjunction with improvements in detection and diagnostic certification, might explain the increases in pancreatic cancer incidence [2, 5]. Pancreatic cancer remains one of the most devastating malignancies and has one of the highest mortality-to-incidence ratios (MIR) worldwide (incidence: 2.4%, mortality: 4.0%, MIR: 1.60) [1, 2]. For all stages combined, the 5-year relative survival is about 8%, which partly reflects the varying quality of global

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data [1]. Current treatment protocols include surgery (for surgical candidates), with a combination of adjuvant therapy, such as chemotherapy and/or radiation therapy. Nevertheless, most patients are diagnosed at an advanced stage and treatment options are limited.

Decades of research have led to a better understanding of pancreatic cancer. However, only a few therapies have been developed to target this cancer with limited efficacy. Over half of pancreatic cancer patients are diagnosed at an advanced stage, which lowers the 5-year survival to 3%. Furthermore, even the small percentage of people who are diagnosed with local disease (10%) have a 5-year survival rate of only 32%. Outcomes have improved modestly for patients with this cancer, but a pressing need exists for more effective treatments that can achieve durable clinical responses. Studies on the pancreatic tumor microenvironment have established its immunosuppressive nature, which could explain the observed high resistance of pancreatic cancer to chemotherapy. Novel therapies that target this microenvironment have shown improvements in immune tolerance and enhancement of treatment efficacy, as indicated by promising preliminary results from clinical trials. Therapies utilizing immune checkpoint molecules have shown particularly encouraging results in clinical trials in patients with solid tumors. Here, we review the current advances in the use of these inhibitors and their effectiveness as a potential strategy for the treatment of pancreatic cancer.

## PANCREATIC CANCER TREATMENT WITH IMMUNE CHECKPOINT INHIBITORS

Many checkpoint molecules have been designed, but initial clinical success has mainly been observed for therapies targeting cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1). Blocking either CTLA-4 or PD-1 with monoclonal antibodies has demonstrated a durable clinical response in patients with solid tumors (such as melanoma) and renal cell carcinoma [6]. However, previous trials that have used these antibodies as a single therapy have demonstrated a lack of efficacy in the treatment of pancreatic cancer [6, 7]. This type of cancer presents some obstacles to immunotherapy, such as low mutational load and low activity of tumor infiltrating lymphocytes [8, 9]. The unique microenvironment of pancreatic tumors is unfavorable to immunotherapy, necessitating the use of combination strategies [7]. The current literature indicates a wide variability of 12–90% in the expression of PD-L1 in pancreatic cancer, making its involvement controversial [8]. The response to single immune checkpoint inhibitors tends to be insufficient. However, a subset of patients that harbor mismatch repair deficiency appear to respond well to PD-1 inhibitors and these inhibitors are recommended as a second-line treatment in advanced pancreatic cancer [8, 10].

Several clinical trials using PD-1 or PD-L1 inhibitors are ongoing. For example, a clinical trial conducted at the MD Anderson Cancer Center is investigating the effects of a combination of pembrolizumab and paricalcitol, with or without standard chemotherapy, in patients with surgically resectable pancreatic cancer (ClinicalTrials.gov Identifier: NCT02930902). However, patients with advanced stage pancreatic cancer are an emergent problem for clinicians. One clinical trial investigating advanced disease is a phase 1b/2, open-label study of niraparib - a small molecule poly ADP-ribose polymerase (PARP) inhibitor - in combination with either ipilimumab or nivolumab in patients whose disease has not progressed following platinum-based therapy (ClinicalTrials.gov Identifier: NCT03404960). This trial is still under recruitment and its clinical outcome is unclear, but it emphasizes that novel combination strategies are necessary to combat this malignant disease.

Several ongoing or completed clinical trials investigating PD-1/PD-L1 blockade with combination chemotherapy have shown positive results. A phase Ib study of a combination pembrolizumab- and gemcitabine-based regimen indicated that these drugs can be safely combined in patients with advanced solid cancers [11]. A phase Ib/II study in chemotherapy-naïve patients with metastatic

pancreatic cancer has shown that application of pembrolizumab in combination with gemcitabine and nanoparticle-albumin-bound (nab)-paclitaxel is safe, but the efficacy is low [12].

The lack of a signal for the immune response with the use of single checkpoint inhibitors, combined with additional strategies such as chemotherapies and cancer vaccines, may activate the tumor microenvironment. Conversely, unlike CTLA-4 ligands, PD-L1 is more selectively expressed in many tumors and in cells within the tumor microenvironment in response to inflammatory stimuli [13]. The ongoing COMBAT/KEYNOTE-202 study, a phase II, open-label, single-arm trial is focused on a combination of BL-8040 and pembrolizumab for the treatment of metastatic pancreatic adenocarcinoma (ClinicalTrials.gov Identifier: NCT02826486). BL-8040 is a short peptide that functions as a high-affinity antagonist of CXCR4, making this approach a novel concept for combination therapy in this field. The irreversible Bruton's tyrosine kinase inhibitor, acalabrutinib (ACP-196), which has shown a promising safety and efficacy profile in the treatment of chronic lymphocytic leukemia, is now being used in combination with pembrolizumab in a phase 2 randomized clinical trial in patients with pancreatic tumors (ClinicalTrials.gov Identifier: NCT02362048). At the time of this writing, more than 20 clinical trials targeting immune checkpoint inhibitors are recruiting participants, and we believe that the results will bring about important information for treating patients with pancreatic cancer.

## PERSPECTIVES

In recent years, several clinical trials have focused on the efficacy of immune checkpoint inhibitors, especially anti-PD1 and anti-PD-L1, in the treatment of pancreatic cancer. These trials have recruited patients with pancreatic cancers ranging from resectable tumors to advanced stage disease, depending on the designed therapeutic strategies. Monotherapy with immune checkpoint inhibitors has been enhanced by combining with immunotherapy, targeted therapy, chemotherapy, or radiotherapy, opening up new and uncharted territories in the pursuit of novel therapies for this aggressive malignancy.

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