



## Review

# Where Do We Stand with Immunotherapy for Advanced Pancreatic Ductal Adenocarcinoma: A Synopsis of Clinical Outcomes

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**Abstract:** Pancreatic cancer is the seventh leading cause of cancer-related mortality in both sexes across the globe. It is associated with extremely poor prognosis and remains a critical burden worldwide due to its low survival rates. Histologically, pancreatic ductal adenocarcinoma (PDAC) accounts for 80% of all pancreatic cancers; the majority of which are diagnosed at advanced stages, which makes them ineligible for curative surgery. Conventional chemotherapy provides a five-year overall survival rate of less than 8% forcing scientists and clinicians to search for better treatment strategies. Recent discoveries in cancer immunology have resulted in the incorporation of immunotherapeutic strategies for cancer treatment. Particularly, immune-checkpoint inhibitors, adoptive cell therapies and cancer vaccines have already shifted guidelines for some malignancies, although their efficacy in PDAC has yet to be elucidated. In this review, we summarize the existing clinical data on immunotherapy clinical outcomes in patients with advanced or metastatic PDAC.

**Keywords:** pancreatic cancer; immunotherapy; immune-checkpoint inhibitors; CAR T-cell therapy; cancer vaccines

## 1. Introduction

Pancreatic cancer is the seventh leading cause of cancer-related mortality in both sexes across the globe [1]. It remains a critical burden worldwide due to its low survival rates and extremely aggressive nature [2]. A total of 95% of pancreatic malignancies arise from exocrine parts (ductal epithelium, acinar cells and connective tissue), and another 5% develop from endocrine parenchyma [3]. Histologically, pancreatic ductal adenocarcinoma (PDAC) accounts for 80% of all pancreatic cancers [4], and the majority of cases are diagnosed at advanced stages (Figure 1) [5]. Localized cases can be treated with surgery; however, the five-year overall survival (OS) rate does not exceed 25% [6]. Unfortunately, there are no curative strategies for advanced stages, and palliative chemoradiotherapy reaches a five-year OS rate of less than 8% [7]. Chemotherapeutic choices of treatment include either modified FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin) [8], gemcitabine monotherapy or gemcitabine in combination with nab-paclitaxel [9].

Recent discoveries in cancer immunology resulted in the incorporation of immunotherapeutic strategies for the treatment of various solid and hematologic malignancies [10]. Multiple clinical trials showed the higher efficacy of immune-checkpoint inhibitors (ICIs) for melanoma, lung cancer, renal cell carcinoma, colorectal cancer and hepatocellular carcinoma [11–15]. Adoptive chimeric antigen receptor (CAR) T-cell therapy is another immunotherapeutic tool being established as effective for hematologic malignancies, particularly relapsed/refractory B cell lymphoma [16] or mantle-cell lymphoma [17]. Unfortunately, early-phase clinical trials have shown limited responses to immunotherapy

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