

Review

Immune Evasion in Pancreatic Ductal Adenocarcinoma: Mechanistic Insights and Emerging Strategies to Reinvigorate Anti-Cancer Immunity

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most hard to treat malignancies, characterised by significant immune evasion and resistance to current systemic agents. Despite substantial progress in understanding tumour immunology across other cancer types, PDAC continues to exemplify an immunologically “cold” tumour, where a desmoplastic stroma, inadequate T-cell infiltration, and complex immunosuppressive networks combine to impede effective anti-cancer immunity. This review summarises current knowledge on the mechanisms underlying immune escape in PDAC, including aberrant antigen presentation, stromal–immune crosstalk, recruitment of regulatory T cells and myeloid-derived suppressor cells, and the metabolic and hypoxic constraints imposed by the tumour microenvironment. We also discuss recent advances in preclinical and clinical studies aiming to overcome these barriers, ranging from stromal modulation and targeting immune checkpoints to integrating radiotherapy, chemotherapy, and DNA damage response modulation to enhance immunogenicity. Special emphasis is placed on the emerging concept of therapeutic replication stress and its potential to induce immunogenic cell death and reshape the tumour immune landscape. We outline the mechanistic basis for treatment resistance of PDAC and discuss strategies to convert the malignancy from an immune-resistant to an immune-responsive state.

Keywords: pancreatic ductal adenocarcinoma; immunobiology; immunotherapy

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic malignancy, accounting for over 90% of cases [1]. The incidence continues to rise globally, with around 500,000 new diagnoses each year [2]. Despite global advances in surgical techniques and systemic anti-cancer therapy, outcomes remain poor with a 5-year overall survival of less than 10% [2]. High rates of mortality are due to advanced disease at the time of diagnosis and the intrinsic resistance of PDAC to conventional systemic therapy [3].

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A defining feature of PDAC is its highly complex and immunosuppressive tumour microenvironment (TME) which is characterised by a dense desmoplastic stroma comprising immune cells, growth factors, an extracellular matrix (ECM), and fibroblasts, which can make up to 85% of the total tumour mass [4]. This stromal compartment contributes to impaired drug delivery and limited efficacy of cytotoxic chemotherapy, as reflected by modest survival gains with standard systemic regimens [5].

Despite the success of immunotherapy in many solid tumours, there has been limited benefit in PDAC [6]. The notable exception is in the small subset of mismatch-repair-deficient (dMMR) tumours, where immune checkpoint inhibitors have shown efficacy; however, this molecular subtype represents only around 2% of PDAC cases [7,8]. Paradoxically, despite the dense infiltration of immune cells within the TME, PDAC is an “immune-cold” tumour that does not trigger a strong immune response and is generally not responsive to immunotherapy [9].

In this review, we summarise current the understanding of the cellular and molecular mechanisms driving immune evasion in PDAC and discuss emerging preclinical and clinical strategies aimed at overcoming these barriers by converting PDAC into an immune-responsive malignancy (Figure 1).

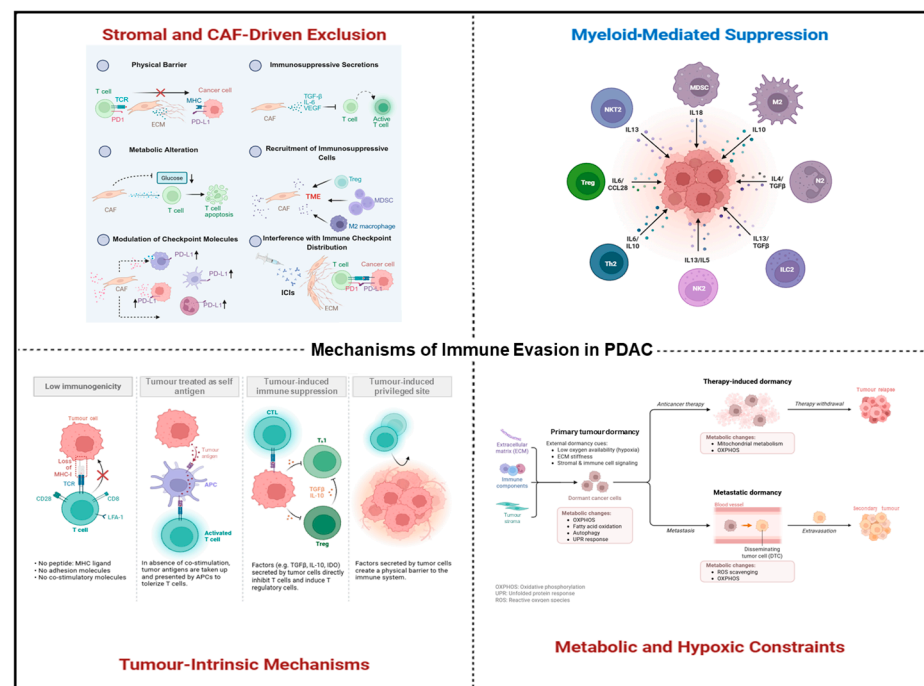


Figure 1. Mechanisms of immune evasion in PDAC. Together, these interconnected processes create a “cold” tumour ecosystem that resists immune recognition and limits the efficacy of immunotherapy (Created in BioRender. Elvis Matini. 2026. <https://BioRender.com>).

2. Immunobiology of Pancreatic Ductal Adenocarcinoma

2.1. The Immunologically “Cold” Phenotype of PDAC

PDAC is characterised by an immunosuppressive TME which underlies its resistance to immunotherapy. Key features of this phenotype include a dense desmoplastic stroma, limited cytotoxic T-cell infiltration, loss of major histocompatibility complex (MHC) class I expression, defects in antigen presentation, and active silencing of innate immune pathways [6,9]. In contrast, “immune-hot” tumours such as melanoma and non-small-cell lung cancer are characterised by a TME rich in tumour-infiltrating lymphocytes, as well as genetic and pre-existing anti-tumour immune responses [10]. Although T cells are abundant

in the PDAC stroma [4], they are predominately immunosuppressive subsets which promote immune tolerance and support pancreatic intraepithelial neoplasia (PanIN) progression and PDAC development [11–14].

Myeloid-derived suppressor cells (MDSCs) represent another dominant immunosuppressive population within the PDAC TME and increase as the disease progresses from pre-malignant lesions to invasive carcinoma [15]. The MDSCs facilitate immune evasion through several mechanisms (Section 3) [16].

Effective anti-cancer immune response also depends on the release and presentation of neoantigens. PDAC has a relatively low tumour mutational burden, resulting in paucity of neoantigens and reduced immunogenicity [17].

2.2. Oncogenic Signalling and Tumour Suppressor Mutations Shape the Immune Microenvironment

Around 90% of PDACs have a Kirsten rat sarcoma virus (KRAS) mutation, which presents a major barrier to effective targeted therapies [18]. KRAS-mutant PDAC cells activate stromal cells via stromal reciprocity in a positive feedback loop, which increases tumour mitochondrial activity and cell proliferation [19]. KRAS also drives production of granulocyte-macrophage colony-stimulating factor (GM-CSF), a primary driver of MDSC recruitment and expansion, which facilitate immune evasion and tumour proliferation [20,21]. KRAS signalling also potentiates metabolic reprogramming that suppresses cytotoxic immune cell function [22] and drives epigenetic silencing of the FAS gene, thus reprogramming the microenvironment to reduce FAS-mediated killing by cytotoxic T cells [23].

Up to 75% of PDACs have mutations in tumour protein p53 (TP53) [24]. Mutant TP53 decreases the efficacy of dendritic cells (DCs) and increases interleukin-6 (IL-6) production, thus leading to reduced neoantigen expression and increased metastatic potential, respectively [25]. Mutant TP53 can amplify nutrient competition between cancer cells and effector T cells [26]. Recent evidence suggests that mutant TP53 cells interact with cancer-associated fibroblasts (CAFs) to promote a desmoplastic stroma, limiting T-cell infiltration, and contributing to chemoresistance [27].

The transcription factor MYC plays a critical role in the transition from PanIN lesions to invasive PDAC by reshaping both stromal and immune compartments [28]. Deregulated expression of MYC enables immune evasion through mechanisms that are only beginning to be revealed. Muthalagu et al. demonstrated that evasion of natural killer (NK) cell-mediated immunity is through the combined actions of endogenously expressed mutant KRAS and modestly deregulated MYC expression, via suppression of the type I interferon (IFN) pathway, which leads to reduced recruitment of cytotoxic T cells [29].

2.3. Loss of MHC Class I Expression and Antigen Presentation Cell Defects

Human leukocyte antigen (HLA) class I molecules are essential for presentation of endogenous antigenic peptides to cytotoxic T cells. In PDAC, there is downregulation and loss of HLA class I and transport for antigen presentation (TAP) expression in the majority of tumour samples [30]. DCs, the principal professional antigen-presenting cells, respond to neoantigen recognition by upregulating MHC I and II, as well as costimulatory molecules that interact with and activate T cells. In PDAC, DCs are scarce and, when present, are often immature or functionally impaired, resulting in inadequate early tumour antigen recognition and ineffective priming of T-cell responses [31]. Consequently, loss of MHC class I expression and defects in antigen presentation represent key mechanisms of immune evasion and have been implicated in resistance to immunotherapy in PDAC [32].

2.4. Impaired Interferon Signalling and Immune Pathway Silencing

The PDAC TME is hypoxic due to the dense desmoplastic stroma and scarcity of blood vessels [18]. Hypoxia leads to activation of hypoxia-inducible factor-1- α (HIF-1 α), which induces immunosuppression in part through silencing of the cyclic GMP-AMP synthase–stimulator of IFN genes (cGAS-STING) pathway [33,34]. This pathway is essential for detection of cytosolic deoxyribonucleic acid and subsequent innate immune activation via the type I IFN pathway. Experimental activation of STING in pancreatic CAFs has been shown to exert anti-tumour effects through enhancing immune surveillance [35]. “Immune-hot” tumours that respond to immunotherapy typically express type I IFN and IFN- γ and high levels of IFN stimulation genes [10]. CAFs have been shown to downregulate type I IFN receptor [36], thus impairing the signalling pathway and subsequently stimulating the dense, fibrous stroma that protects the tumour [36]. Given the abundance of CAFs in PDAC and the cooperative effects of KRAS and TP53 mutations in driving fibrosis, hypoxia-induced suppression of IFN signalling represents a central mechanism of immune evasion.

3. Tumour Microenvironment (TME) and Stromal–Immune Crosstalk

3.1. The Desmoplastic Stroma: Barrier and Modulator

The desmoplastic stroma comprises pancreatic stellate cells (PaSCs), CAFs, immune cells, abnormal vasculature and ECM components [37]. This stromal compartment is not merely a passive barrier but a dynamic regulator of tumour behaviour and immune function. Activated PaSCs support tumour growth by promoting cell proliferation and inhibiting apoptosis, partly through platelet-derived growth factor (PDGF) signalling. In parallel, PaSCs drive excessive deposition of ECM proteins, a process reminiscent of hyper-inflammatory conditions such as chronic pancreatitis, thereby reinforcing fibrosis and tissue stiffness [38].

CAFs in PDAC are functionally heterogeneous and can be broadly classified into myofibroblastic CAFs (myCAFs), inflammatory CAFs (iCAFs) and antigen-presenting CAFs [39]. myCAFs are the principal source of ECM proteins, growth factors and cytokines, whereas iCAFs contribute to the recruitment of immunosuppressive myeloid cells and suppression of effector T-cell function (Figure 1) [37].

The ECM is enriched in collagen I, fibronectin, laminin and hyaluronan, which increase tissue stiffness and interstitial pressure. These features contribute to physical exclusion of immune cells and impaired vascular perfusion, limiting the delivery of systemic therapies [40]. ECM stiffness is driven in part by signal transducer and activator of transcription 3 (STAT3) activation downstream of transforming growth factor beta (TGF- β) signalling [40]. The resulting distortion and compression of the vasculature promotes hypoxia, further constraining effective immune surveillance and drug penetration.

3.2. Immunosuppressive Cell Populations

Multiple immunosuppressive cell subsets accumulate within the PDAC microenvironment (Figure 1). Tregs, characterised by CD4, CD25 and forkhead box P3 (FOXP3) expression, are enriched in PDAC and express inhibitory receptors such as programmed death receptor 1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) [41]. Through secretion of TGF- β , Tregs suppress antigen-presenting DCs, thereby dampening anti-tumour T-cell responses and reinforcing immune tolerance within the TME.

MDSCs expand in response to tumour-derived cytokines, growth factors, and chemokines. MDSCs can be broadly subdivided into monocytic (M-MDSCs) and polymorphonuclear (PMN-MDSCs) populations [42]. M-MDSCs mediate broad immunosuppression effects, whereas PMN-MDSCs promote T-cell tolerance.

Macrophages fall into two phenotypes: M1 (classically activated, pro-inflammatory) and M2 (alternatively activated, immunosuppressive). Tumour-associated macrophages (TAMs) are skewed towards an M2-like, immunosuppressive phenotype in PDAC. These cells arise from monocytes recruited into the hypoxic, necrotic tumour bed, where they acquire TAM-like features [42]. M2-polarised TAMs cooperate with MDSCs to inhibit T-cell-mediated anti-tumour immunity and promote tumour growth, invasion and metastasis [43].

3.3. Cytokine and Chemokine Milieu Reinforce Immune Suppression

The cytokine and chemokine milieu within PDAC strongly favours immunosuppression. Key regulatory cytokines such as IL-6, C-X-C motif chemokine ligand 1 (CXCL1) and granulocyte colony-stimulating factor (G-CSF) directly modulate immune cell recruitment and function [44]. Additional mediators including IL-10, IL-12 and chemokine ligand 13 (CCL13) skew T-cell responses towards type 2 helper T-cell polarisation and suppress cytotoxic T lymphocytes.

TAMs are a major source of IL-10, which can induce T-cell apoptosis via cluster of differentiation 120a/b (CD120a/b) signalling and upregulate the immune checkpoint molecule B7-H3 via epidermal growth factor receptor (EGFR)/mitogen-activated protein kinase (MAPK) signalling, further suppressing CD8⁺ T-cell activity [45]. MDSCs contribute to immune dysfunction by generating reactive oxygen species (ROS), creating an oxidative microenvironment that impairs both T-cell and NK cell activity. This process is sustained by cytokines such as TGF- β , IL-10, and IL-6 (Figure 1) [45].

3.4. Metabolic and Hypoxic Constraints

HIF2 acts on innate lymphoid cells in hypoxic environments, leading to secretion of IL-10 as they assume an immunosuppressive profile [46] in hypoxic conditions via the phosphoinositide 3-kinase gamma (PI3K γ)/phosphatase and tensin homologue (PTEN) pathway [46]. Hypoxia also reshapes macrophage function, with TAMs producing elevated levels of pro-angiogenic and pro-metastatic mediators such as vascular endothelial growth factor (VEGF), tumour necrosis factor-alpha (TNF- α), and IL-1 β [45]. In parallel, NK-cell cytotoxicity is significantly impaired in hypoxic environments, further weakening innate immune surveillance [47].

At the metabolic level, PDAC cells exhibit enhanced glycolytic metabolism (the Warburg effect), with increased glucose uptake via glucose transporter type 1 (GLUT1) and upregulation of rate-limiting glycolytic enzyme [48]. The resultant lactic acid accumulation inhibits cytotoxic T-lymphocyte proliferation and effector function [49]. Together, hypoxia and metabolic reprogramming create unfavourable conditions for anti-tumour immunity.

Collectively, these features underscore that the PDAC TME is a highly coordinated ecosystem composed of multiple overlapping barriers which effectively inhibit anti-tumour immunity. The desmoplastic stroma is likely the dominating factor, which, via excessive ECM deposition, tissue stiffening and vascular compression, leads to restricted immune infiltration and drug delivery. Additionally, stromal-derived signalling, particularly via TGF- β -STAT3 pathways, reprograms immune cells towards immunosuppressive states, establishing a therapy-resistant immunosuppressive microenvironment.

4. Mechanisms of Immune Escape

4.1. Antigen Presentation and Immunoediting

Effective anti-tumour immunity depends on the generation and presentation of tumour-derived neoantigens. PDAC is characterised by a relatively low tumour mutational burden and a limited neoantigen repertoire. Whereas highly immunogenic malignancies such as melanoma harbour an average of approximately 370 neoantigens per tumour, PDAC typically contains fewer than 40 [50]. This intrinsic paucity of neoantigens substantially limits T-cell priming and contributes to low baseline immunogenicity.

Beyond neoantigen scarcity, preclinical and translational studies have shown that in PDAC there is a consistent reduction in the HLA class I molecules. These defects in antigen processing and presentation are discussed in detail in Section 2.3.

4.2. Checkpoint Ligand Upregulation and Immune Exhaustion

Immune checkpoint pathways play a central role in maintaining T-cell dysfunction within the PDAC microenvironment. Programmed death-ligand 1 (PD-L1) expression on pancreatic tumour cells has been shown to be upregulated through the EGFR/MAPK signalling pathway [51]. In addition, lymphocyte activation gene-3 (LAG-3) overexpression suppresses CD4 T-cell function via interaction with MHC class II, while stimulating Treg activity [52]. Furthermore, T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) has been shown to be co-expressed with PD-1 on exhausted T-cell populations and is associated with inferior clinical outcomes in PDAC [52].

Beyond classical checkpoints, alternative inhibitory pathways are particularly prominent in PDAC. Blando et al. demonstrated that V-domain Ig suppressor of T-cell activation (VISTA)-expressing macrophages are present at a higher density in PDAC compared with melanoma. Functional studies using patient-derived tumour-infiltrating lymphocytes showed that both PD-L1-Ig and VISTA-Ig significantly reduced CD8⁺ T-cell degranulation and cytokine production, with VISTA exerting a more potent inhibitory effect than PD-L1 [53]. These findings help explain the limited activity of PD-1/PD-L1 blockade alone and highlight the need for combinatorial checkpoint strategies in PDAC.

4.3. Stromal Sequestration and Immune Exclusion

Physical and chemokine-mediated immune exclusion represents another key mechanism of immune escape in PDAC. The chemokine CXCL12 and its receptor CXCR4 are highly expressed in pancreatic cancer. Furthermore, stromal cells within the TME secrete CXCL12, which, via CXCR4 on PDAC cells, induces cell survival via crosstalk with multiple intracellular pathways [54]. They play a role in promoting tumour cell growth and neo-angiogenesis leading to increased rates of metastasis, and CXCL12 has also been shown to inhibit dendritic cell maturation [51].

Moreover, studies examining the evolution of the microenvironment during progression from intraductal papillary mucinous neoplasia (IPMN) to invasive PDAC demonstrate a consistent redistribution of T-cell subsets: Tregs infiltrate neoplastic epithelial regions, whereas cytotoxic CD8⁺ T lymphocytes remain sequestered in peritumoral stromal compartments [55]. This spatial immune exclusion prevents effective tumour cell killing even in the presence of immune infiltration.

Together, these mechanisms highlight that overcoming immune escape in PDAC will require strategies that extend beyond checkpoint inhibition alone. Defective antigen presentation and pervasive checkpoint signalling limit T-cell activation, but their impact is compounded by chemokine-driven sequestration of cytotoxic lymphocytes within the

stroma. Thus, combination strategies that integrate stromal modulation with multi-checkpoint blockade may be essential to convert PDAC from an immunologically “cold” to a treatment-responsive tumour.

5. Emerging Strategies to Overcome Immune Resistance (Figure 2)

Given the multifactorial nature of immune resistance in PDAC, effective immunotherapy is likely to require combination strategies that target both tumour-intrinsic pathways and the immunosuppressive tumour microenvironment. Several emerging approaches aim to reprogramme the stroma and restore antigen presentation, thereby enhancing anti-tumour immune responses (Figure 2).

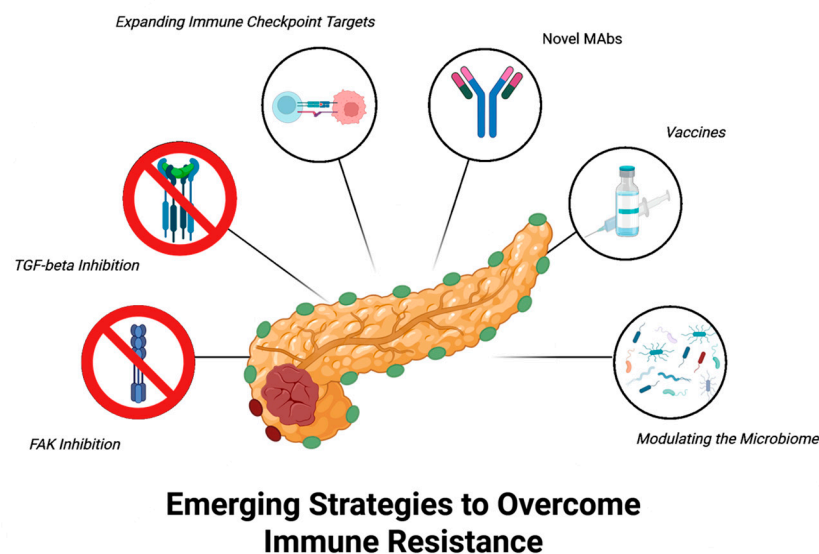


Figure 2. Emerging strategies to overcome immune resistance . FAK: focal adhesion kinsase, TGF-beta: transforming growth factor-beta, MAbs: monoclonal antibodies. (Created in Biorender. Elvis Matini. (2026). <https://BioRender.com>).

5.1. Focal Adhesion Kinase (FAK) Inhibition

FAK is frequently activated in many malignancies, including PDAC. It has a role in multiple oncogenic signalling pathways, including PI3K, extracellular signal-regulated kinases (ERK) and Src, thereby promoting growth, invasion and metastasis [56]. FAK has also been shown to regulate antigen presentation in both mouse models and in human pancreatic cancer cell lines. Canel et al. showed that loss of FAK improves antigen binding to MHC-1, improving immune recognition and surveillance [57].

Defactinib, a small-molecule FAK inhibitor, is currently being evaluated in both neoadjuvant and metastatic PDAC settings in combination with immune checkpoint inhibitors and chemotherapy [58]. Several ongoing clinical trials are exploring these combinations, including NCT03727880 and NCT02758587, with the aim of overcoming stromal-mediated immune exclusion and improving immunotherapy efficacy [Table 1] (Supplementary Materials).

Table 1. A summary list of ongoing immunotherapy trials across multiple disease settings in PDAC.

Strategy Category	Representative Agents	Disease Setting	Key Aim/Rationale	Example Trials
Cancer vaccines (KRAS/neoantigen/GVAX)	KRAS-targeted peptide or mRNA vaccines, GVAX ± cyclophosphamide, yeast-based neoepitope vaccines	Adjuvant, neoadjuvant, metastatic	Enhance tumour-specific T-cell priming; most effective in low-disease-burden settings	NCT05726864, NCT03552718, NCT02451982, NCT06782932, NCT04117087, NCT05968326
Checkpoint inhibition (PD-1/PD-L1 ± CTLA-4)	Pembrolizumab, nivolumab, durvalumab, camrelizumab, toripalimab, dostarlimab	All stages	Overcome T-cell exhaustion; limited efficacy as monotherapy in PDAC	NCT06094140, NCT03323944, NCT06333314
Dual or novel checkpoint combinations	PD-1 + CTLA-4, TIGIT, LAG-3, VISTA combinations	Mostly metastatic	Address adaptive immune resistance	NCT05419479, NCT07049055, NCT05927142
Chemotherapy + immunotherapy	FOLFIRINOX or gem-nabP + ICIs	Neoadjuvant, metastatic	Induce immunogenic cell death and TME remodelling	NCT06051851, NCT06621095, NCT04543071
Radiotherapy-based immune priming	SBRT or hypofractionated RT + ICIs	Neoadjuvant, locally advanced, metastatic	Promote antigen release and STING activation	NCT06573398, NCT06378047, NCT06009029, NCT06843551
Innate immune activation (TLR, CD40, STING)	TLR agonists, CD40 agonists, Dectin-1	Locally advanced, metastatic	Enhance dendritic cell priming and macrophage reprogramming	NCT05651022, NCT06205849, NCT07199764
Stromal and TME targeting	FAK inhibitors, CXCR1/2 inhibitors, hypoxia-targeted agents	Neoadjuvant, metastatic	Reduce immune exclusion and suppressive stroma	NCT03727880, NCT05604560, NCT06782555
DDR-based strategies	PARP inhibitors, ATR/WEE1 combinations + ICIs	Biomarker-selected metastatic	Increase genomic instability and tumour immunogenicity	NCT05093231, NCT04548752, NCT04753879
Cellular therapies (CAR-T, TILs)	Mesothelin CAR-T, CD318 CAR-T, engineered TILs	Advanced/metastatic	Direct tumour targeting	NCT03323944, NCT07153289, NCT04426669
Oncolytic and viral-based therapies	Oncolytic viruses + ICIs + chemotherapy	Neoadjuvant, locally advanced	Promote immunogenic tumour cell lysis	NCT06346808

GVAX—GM-CSF-secreting allogeneic pancreatic cancer vaccine; STING—stimulator of interferon genes; PARP—poly ADP-ribose polymerase; CAR-T—chimeric antigen receptor T cell.

5.2. Targeting TAMs with Anti-CSF1R Antibodies

TAMs are key mediators of immune suppression in PDAC, making colony-stimulating factor 1 receptor (CSF1R) an attractive therapeutic target. Preclinical models show that anti-CSF1R antibodies reduce TAM infiltration and attenuate their immunosuppressive functions. However, macrophage depletion alone leads to compensatory upregulation of immune checkpoints such as PD-L1 and CTLA-4 [51].

Combination strategies pairing CSF1R inhibitors with PD-1 blockade have shown encouraging results in preclinical models and early-phase clinical trials across several malignancies, including glioblastoma, colorectal cancer, and urothelial carcinoma [43,59,60]. This data supports further exploration of TAM-targeted therapies in PDAC.

5.3. TGF- β Inhibition

TGF- β is a key driver of epithelial–mesenchymal transition (EMT), immune suppression, and metastatic progression in PDAC. Preclinical studies demonstrate that dual blockade of TGF- β and PD-L1 enhances CD8⁺ T-cell infiltration and reduces immunosuppressive signalling within the tumour microenvironment. Early-phase clinical trials combining TGF- β inhibitors with PD-L1 blockade, such as bintrafusp alfa (M7824) or galunisertib plus durvalumab, have reported modest clinical activity in advanced PDAC, including occasional partial responses and stable disease [61]. Interpretation of these results is limited by small patient numbers and heavily pretreated populations, highlighting the need for earlier-line and biomarker-driven studies.

5.4. Expanding Immune Checkpoint Targets Beyond PD-1/CTLA-4

Preclinical animal studies have demonstrated an enhanced immunogenicity of the TME when PD-1 blockade is combined with inhibition of TIGIT [62]. More complex combination strategies incorporating 4-1BB agonists, LAG-3 antagonists, and CXCR1/2 inhibitors have also shown synergistic anti-tumour effects in mouse models [63].

Clinically, a phase I/IIa single-arm trial evaluating an EGFR-targeted drug, PNU-159682-packaged nanocells, combined with an immunomodulatory agent, α -galactosyl ceramide-packaged nanocells, demonstrated safety and improved overall survival in patients receiving at least one treatment cycle [64]. An ongoing phase I/IIa trial is aiming to evaluate the efficacy of this drug in combination with gemcitabine and nab-paclitaxel NCT07049055 [Table 1]. Schoffski et al., in a phase I/II study, demonstrated response to anti-LAG-3/anti-PD-1 combination therapy in patients with various cancers, including PDAC [65]. This is hypothesis-generating, and further studies in this space are required to evaluate to potential benefit for patients with PDAC.

Although no phase III trials of VISTA blockade are currently underway in PDAC, early-phase studies of CA-170, an orally bioavailable small-molecule inhibitor targeting both PD-L1 and VISTA, have shown acceptable safety and preliminary activity, with phase IIb/III evaluation anticipated [66].

5.5. Cancer Vaccines and Adoptive Cell Therapies

Therapeutic cancer vaccines have been investigated at multiple points along the PDAC treatment pathway, with limited efficacy observed in the metastatic setting. In contrast, the adjuvant setting appears more promising, likely reflecting lower tumour burden and reduced immune suppression (Table 1) [62].

An ongoing clinical trial is evaluating an individualised mRNA-based cancer vaccine in combination with FOLFIRINOX chemotherapy and the PD-L1 inhibitor atezolizumab in resected PDAC (NCT05968326). Early phase I studies demonstrated durable vaccine-induced T-cell responses in the adjuvant setting, providing proof-of-concept for personalised immunisation strategies in PDAC [67].

5.6. Modulating the Microbiome and Tumour Metabolism

The gut microbiota-immune system interactions influence cancer progression and treatment responses. Specific microbiota compositions have been associated with improved responses to anti-PD-1 therapy, while dysbiosis correlates with poor prognosis and resistance to immune checkpoint inhibitors [68].

Metabolic reprogramming within the TME (Section 3.4) further contributes to the immunosuppressive landscape. Indoleamine 2,3-dioxygenase (IDO), a metabolic enzyme expressed in PDAC, catalyses the conversion of tryptophan into kynurenine, leading to T-cell dysfunction and immune tolerance [48]. Beatty et al. explored the addition of IDO inhibitor to gemcitabine plus nab-paclitaxel (gem-nabP). While the study did not meet its primary endpoint, responding patients exhibited increased infiltration of CD3⁺ and CD8⁺ T cells and enhanced anti-proliferative capacity [69] (Table 1).

6. Integrative Approaches to Transform “Cold” into “Hot” PDAC

6.1. Combining Cytotoxic Therapy with Immune Therapy

FOLFIRINOX is currently considered a standard-of-care regimen for PDAC and confers a survival advantage over gemcitabine monotherapy in both the adjuvant and metastatic settings [70,71]. Beyond its cytotoxic effects, FOLFIRINOX exerts immunomodulatory activity within the TME. Transcriptomic analyses demonstrate downregulation of immunosuppressive chemokines such as CXCL5 following treatment [72], alongside reductions in suppressive immune populations [73]. These changes are also accompanied by a shift toward type 1 helper T-cell-polarised immunity and an increase in CD8⁺ cytotoxic T-cell infiltration [73]. Gemcitabine acts mainly by inhibiting DNA synthesis through masked chain termination and activation of apoptotic pathways via caspase signalling and activation of p38-MAPK signalling [74].

Pancreatic cancer cells exhibit innate gemcitabine resistance through nuclear factor-kappa B (NF-κB)-driven overexpression of NME5 and through dynamic intercellular communication mediated by tumour-derived exosomes [75]. CAF-derived exosomal miR-3173–5p downregulates ACSL4, suppressing ferroptosis and contributing to chemoresistance [76]. Resistance to FOLFIRINOX has also been linked to GALNT overexpression, which interacts with MYH9 to activate NOTCH signalling, impair DNA damage responses and promote treatment resistance [77]. Key aspects of therapy-induced immune resistance are outlined in Figure 3.

To overcome the poor survival in pancreatic cancer, several trials have evaluated the role of immunotherapy either alone or in combination with other modalities: chemotherapy, radiotherapy, targeted therapy and vaccines [78] [Table 1].

Single-agent CTLA-4 blockade with ipilimumab or tremelimumab resulted in no objective responses in advanced disease [79]. In contrast, pembrolizumab demonstrated an objective response rate of 18.2% in MSI-H/dMMR PDAC in the KEYNOTE-158 study [80].

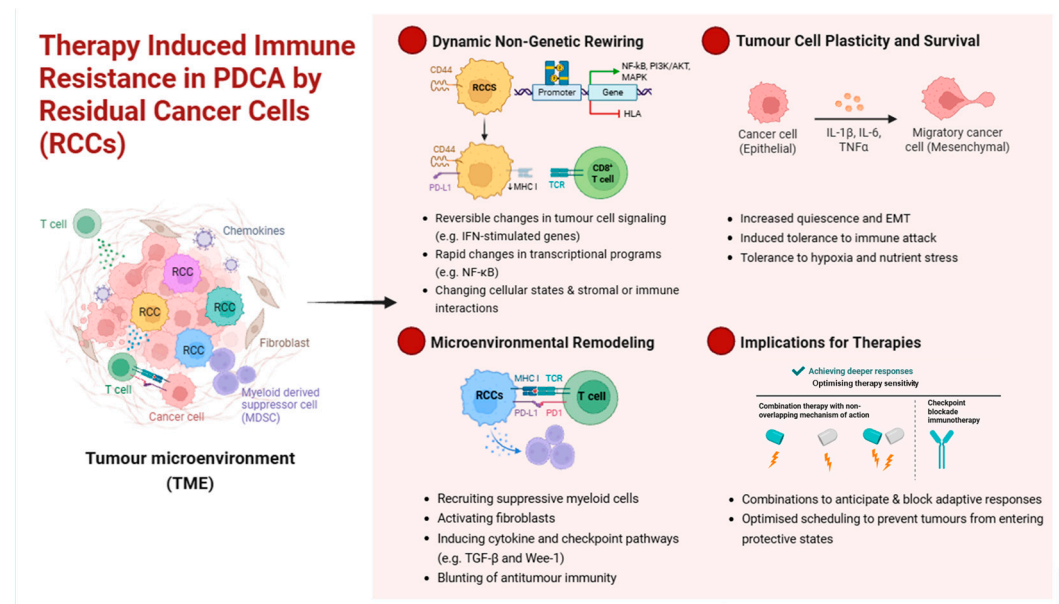


Figure 3. Therapy-induced immune resistance in PDCA by residual cancer cells (created in BioRender. Elvis Matini. (2026). <https://BioRender.com>).

Dual checkpoint blockade has not substantially improved outcomes. In a randomised trial comparing durvalumab alone versus durvalumab plus tremelimumab in metastatic PDAC, no improvement in progression-free or overall survival was observed [81]. Similarly modest activity was reported when ICIs were combined with chemotherapy: gemcitabine plus tremelimumab achieved a 7% objective response rate (ORR) with a median overall survival (mOS) of 7 months [82], while a trial of ipilimumab with gemcitabine resulted in an ORR of 14% and a mOS of 6.9 months [83]. The reason for IO failure in PDAC is multifactorial. The disease is characterised by a highly desmoplastic stroma, dominated by immunosuppressive cytokine signalling, sparse CD8⁺ T-cell infiltration, and enrichment of TAMs and MDSCs, together with a relatively low somatic mutational burden. The absence of reliable predictive biomarkers has further limited the identification of patient subgroups most likely to benefit from immunotherapy [84]. Current research efforts therefore focus on enhancing the immunogenicity of PDAC and remodeling the TME to enable more effective engagement of existing therapeutic modalities, including immunotherapy, chemotherapy and radiotherapy.

6.2. Radiotherapy as an Immune Primer

Two meta-analyses reviewed different studies of radiochemotherapy in the adjuvant setting using different drugs and different doses and fractionations. While adjuvant chemotherapy resulted in significant improvement in disease-free survival and OS, adjuvant radiotherapy failed to add any survival benefit in this setting [85,86].

In the neoadjuvant setting, the ALLIANCE trial demonstrated that chemotherapy alone was superior to combined chemoradiotherapy in all aspects, including R0 and OS [87]. In contrast, the PREOPANC-2 trial showed comparable OS with neoadjuvant FOLFIRINOX when compared to radiochemotherapy with gemcitabine alone and radiotherapy 36 Gy in 15 fractions, and concluded that chemoradiotherapy is a possible option if the patient cannot tolerate the three-drug regimen [88]. A meta-analysis of seven trials (938 patients) showed that neoadjuvant gemcitabine-based chemo(radio)therapy improved OS survival mainly in the borderline resectable pancreatic cancer but not in the upfront resectable disease [89].

Nevertheless, radiotherapy (RT) has long been recognised for its local cytotoxic effects, but growing evidence highlights its capacity to modulate anti-tumour immunity. RT can promote immune activation through several mechanisms that collectively contribute to “cold-to-hot” conversion [90]. These include induction of immunogenic cell death with release of damage-associated molecular patterns (DAMPs), ATP, and high-mobility group box 1 (HMGB1), which activate dendritic cells and enhance antigen presentation [91]. RT also upregulates MHC class I expression through increased intracellular peptide availability, independent of type I IFN or STING signalling [92]. RT-induced cytokine release further shapes the immune milieu. Pro-inflammatory cytokines such as IFN- γ and tumour necrosis factor- α promote effector T-cell recruitment and activation, while concomitant induction of immunosuppressive mediators such as TGF- β facilitates recruitment of Treg MDSCs [93]. RT-induced DNA damage can activate the cGAS-STING pathway, although its activity is often suppressed in PDAC due to hypoxia and CAF-mediated signalling (Section 2.4). However, chronic STING activation may paradoxically enhance immune suppression through non-canonical NF- κ B signalling and upregulation of PD-L1 [94]. Additionally, RT can generate novel tumour neoantigens through radiation-induced mutagenesis, further enhancing immunogenicity [93].

Several mechanisms have been suggested as driving radiotherapy resistance in PDAC, including SMAD4 depletion, which results in RT resistance through induction of autophagy and ROS [95], increased expression of DNA-binding protein, such as DNA-binding protein inhibitor (ID1), and upregulation of immunosuppressive cytokines [93,96].

The growing evidence of the immune effects of radiotherapy has encouraged trials combining RT with immune checkpoint inhibitors. Early-phase studies combining stereotactic body radiotherapy with durvalumab $\pm$ tremelimumab have demonstrated acceptable safety but limited objective responses.

6.3. DNA Damage Response and Replication Stress Modulation

Defects in DNA damage response (DDR) pathways represent an attractive therapeutic opportunity to enhance tumour immunogenicity in PDAC. Germline and somatic alterations in key DDR genes, including ataxia-telangiectasia mutated (ATM), BRCA1/2, and ataxia telangiectasia and Rad3-related protein (ATR), occur in a subset of pancreatic cancers and are associated with genomic instability and replication stress.

The ATM–ATR signalling axis coordinates cellular responses to DNA damage, activating cell cycle checkpoints and p53-mediated repair pathways. Loss of homologous recombination (HR) repair enforces reliance on error-prone non-homologous end joining (NHEJ), resulting in genomic instability and a “BRCAness” phenotype. Pharmacological inhibition of ATR sensitises PDAC cells to DNA-damaging agents such as cisplatin and gemcitabine, as demonstrated with agents including VX-970 [97]. PARP inhibitors exploit synthetic lethality in HR-deficient tumours through catalytic disruption of PARP ϵ enzymatic activity, resulting in genomic instability, DNA–protein crosslinks, and thus “trapping” PARP on the DNA, failing to repair of strand breaks and ending in apoptosis.

Errors at cell cycle checkpoints are another cause of replication stress and DNA damage. DNA-dependent protein kinase (DNA-PK) catalytic subunit activity is essential for effective repair by classic non-homologous end joining, which occurs through all phases of the cell cycle. DNA-PK inhibition sensitises cells to replication-independent double-strand-break-inducing agents such as topoisomerase inhibitors. New DNA-PK inhibitors have been developed, including MSC2490484A [97], which is being tested in pancreatic cancer.

Checkpoint kinase 2 (CHK2) activation, a substrate of ATM, is important for the G1/S checkpoint. An ATM inhibitor, AZD0156, is currently under clinical trials [98]. CHK1 is a substrate of ATR. When activated, it inhibits CDK. CHK1 regulates G2/M and intra S checkpoints [98].

WEE1 is a protein kinase important for cell cycle progression. It inhibits CDK1 activity, leading to G2/M checkpoint activation [99]. In preclinical models, MK-1775, a selective WEE1 inhibitor, increases cytotoxicity of many DNA-damaging agents with different mechanisms of action (gemcitabine, topoisomerase inhibitors, cisplatin), especially in p53-mutated cancers [100].

Epigenetic changes in pancreatic cancer: During transformation from IPMN to cancer, there is progressive methylation of multiple tumour suppressor genes leading to loss of gene function and progression to cancer [101]. Also, methylation of tumour suppressors, including SOX17, HIN-1, DACT2, and NKD2 leads to silencing of these genes and further replication stress [102].

Oncogene activation through RAS and MYC in pancreatic cancer leads to replication stress, defects in DNA repair and genomic instability [103].

cGAS-STING pathway

The STING pathway is an important response to tissue damage and is implicated in different types of cell deaths including necroptosis [104], apoptosis [105], pyroptosis, and ferroptosis [106].

The presence of cytosolic DNA caused by tissue damage is detected by the cGMP, leading to the synthesis of 2,3-cGMP, which binds to the STING protein and initiates an immune cascade. CD8⁺ T cells produce IFN- γ to reduce myeloid-derived suppressor cells and delay their immune-suppressive activities. STING also produces type I IFN and primes T cells. It also increases the infiltration of T cells and NK cells [107].

Therapeutic targeting of cGAS-STING in cancer treatment

As the cGAS-STING pathway is involved in both innate and humoral immunity, it has been an attractive target to improve tumour immunogenicity. Several strategies have been tried to develop STING agonists to improve tumour immune response and enhance response to different types of cancer treatment (chemotherapy, radiotherapy and immune checkpoint inhibitors. Treatments targeting both the cGAS and the STING pathway have been studied. Direct cGAS agonists include metal ions, B arrestin, and chitosan. Direct STING agonists include CDN, a non-nucleotide small molecule agonist. Indirect agonists have also been investigated, including iron oxide nanoparticles, ectonucleotide pyrophosphatase phosphodiesterase 1 inhibitors, and transcriptional regulation agonists [108].

7. Biomarkers

In view of the poor outcomes in pancreatic cancer, the heterogeneity of the tumour and the novel targets, it is increasingly important to identify predictive and prognostic biomarkers to allow for individualised therapy, early diagnosis and better response to treatment. For a summary of trials regarding biomarkers, see Tables 2 and 3.

7.1. CA19.9

Carbohydrate antigen 19.9 (CA19.9) remains the most widely used biomarker in routine clinical practice for PDAC. It is commonly employed to monitor treatment response and to facilitate early detection of disease recurrence following curative-intent therapy. However, CA19.9 lacks tumour specificity and may be elevated in several benign conditions, including biliary obstruction, gallstones, and pancreatitis, limiting its utility as a diagnostic or predictive biomarker when used in isolation [109].

7.2. Exosomal mRNA

Studies examining exosomal RNA profiles across pancreatic pathologies—including chronic pancreatitis, intraductal IPMN, and PDAC—have demonstrated that these lesions are characterised by distinct exosomal microRNA (miRNA) signatures [110]. Such profiles have potential applications in early diagnosis, disease classification, and treatment monitoring, although clinical validation remains ongoing.

7.3. Molecular Diagnosis of Cyst Fluid

Endoscopic ultrasound (EUS)-guided cyst fluid aspiration enables molecular characterisation of pancreatic cystic lesions. In the PANDA study, molecular analysis of cyst fluid demonstrated that KRAS mutations in exon 1 were highly specific for mucinous cysts, albeit with limited sensitivity. In contrast, allelic loss amplitude greater than 80% emerged as the most accurate marker for identifying malignant cysts [111]. These findings highlight the value of integrating molecular diagnostics with radiological and cytological assessment to improve risk stratification and clinical decision-making.

7.4. Transcriptomic Subtypes

Transcriptomic profiling has refined the molecular classification of PDAC. Tumours are broadly categorised into a classical pancreatic subtype (encompassing pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine–exocrine subtypes) and a squamous subtype, which is consistently associated with poorer prognosis and aggressive clinical behaviour [112].

Extending these approaches to precursor lesions, Lye et al. performed whole-transcriptome digital spatial profiling (DSP)-RNA on IPMN specimens and identified three molecular subtypes: “normal-like”, “low-risk”, and “high-risk”, each correlating strongly with pathological grade [113]. This molecular stratification has the potential to improve surveillance strategies and guide timing of surgical intervention in patients with IPMN.

7.5. Markers of DDR Deficiency and Replication Stress

Defects in DNA damage response (DDR) pathways represent an important source of therapeutic vulnerability in PDAC. Germline or somatic BRCA mutations define an unstable genomic subtype and predict sensitivity to platinum-based chemotherapy and PARP inhibitors. More broadly, alterations in homologous recombination repair genes have been associated with improved responses to DDR-targeted therapies [114].

Beyond static DDR mutations, dynamic measures of replication stress are emerging as powerful predictive biomarkers. Dreyer et al. demonstrated that a replication stress signature was more predictive of response to ATR and WEE1 inhibition than DDR mutation status or transcriptomic subtype alone [103]. In vivo patient-derived cell line models with high replication stress exhibited increased sensitivity to ATR and WEE1 inhibitors, independent of classical DDR alterations. In the same study, high replication stress was associated with the squamous subtype [103].

7.6. Circulating Tumour Cells (CTCs) and Liquid Biopsy

Liquid biopsy approaches offer a minimally invasive means of capturing tumour heterogeneity and monitoring disease evolution. CTCs have been extensively investigated in PDAC; however, technical challenges related to enrichment and recovery have limited sensitivity. Nevertheless, multiple studies have shown that CTC positivity is associated with shorter disease-free and overall survival, increased risk of postoperative recurrence, and inferior prognosis. The presence of cytokeratin-positive CTCs has been identified as an independent predictor of survival [115].

Circulating tumour DNA (ctDNA) has emerged as a complementary and often more sensitive alternative to CTC analysis. ctDNA enables detection of tumour-specific genetic alterations and longitudinal monitoring of disease burden, with growing evidence supporting its prognostic and predictive utility in PDAC [116].

Table 2. Biomarkers from different sites of the body used as diagnostic, prognostic, predictive or potential therapeutic targets in pancreatic cancer.

	Serum	Pancreatic Juice	Urinary	Faecal	Salivary
Proteins/ glycoproteins	CA19.9 [117], C242 [118], DUPAN [119], TGF-B [120], (MIC-1/GDF15) [121], ICAM-1 [122], MMP-7 and MMP-12 [123], MUC1, MUC4, MUC5AC and MUC16 [124], DKK-1 [125]	CA19.9 [126], REG1A and REG1B [126], MMP [127]	REG1A [128] MMP [129]	Adnab-9 [130]	Polyamines [131]
Exosomes	Exosomes [132]	Exosomes [133]			
Liquid biopsy	CTC [134]		KRAS mutation [135]	KRAS mutation [136]	
	ctDNA [137]	Telomerase activity [138]			
miRNA	miRNAs [139]	miRNA [140]	miRNA [141]	miRNA [140]	miRNA [142]

Table 3. Ongoing studies to evaluate diagnostic, predictive, and prognostic biomarkers in pancreatic cancer patients.

Trial	Site	Aim
NCT06574373 [143]	Serum	Identify and validate biomarkers capable of distinguishing between low-risk and high-risk IPMN progression to PDAC.
NCT05853198 [144]	Serum	Evaluation of ctDNA across various treatment courses in patients with PDAC to assess its efficacy as a prognostic and predictive marker of treatment response.
NCT06694792 [145]	Cyst	To analyse exosomes, somatic/germline genetic variability, metabolomics and transcriptome profile to identify new biomarkers; to use nonparametric epidemiologic approaches and machine learning algorithms to compute a progression score to offer clinicians an innovative tool towards the goal of a personalised medicine approach using the invasive cyst biomarker detection (INCITE) consortium between the participant centres to collectively enrol an adequate number of patients to fulfil the previous aims.
NCT07030348 [146]	Pancreatic juice	Identify biomarkers for the early diagnosis of pancreatic cancer through duodenal pancreatic juice, which can be easily obtained through an endoscopy.
NCT05475366 [67]	Tissue & Serum (PACsign)	Assess the clinical value of 5 transcriptomic signatures prognostic of chemotherapeutic sensitivity to improve the objective response rate (ORR) of first line (L1). Chemotherapy regimen (FOLFIRINOX vs. Gem-nabP) will be selected based on transcriptomic signatures applied to the pre-therapeutic liver biopsy of newly diagnosed PDAC patients.

NCT06706700 [147]	Serum & cyst (EMI-IPMN)	To identify pre-operative biological and/or radiological/endosonographic biomarker(s) able to distinguish low- versus high-risk IPMN for cancer progression.
NCT06305728 [148]	Serum & pancreatic cyst plus MRI	Look at whether a combination of the following types of imaging with blood tests can detect PDAC in pancreatic cysts: the ImmunoPET scan (immune positron emission tomography scan) with the imaging agent 89Zr-DFO-HuMab-5B1; the HP MRI scan (hyperpolarised pyruvate magnetic resonance imaging scan).
NCT04449406 [149]	Urinary & serum	Establish the accuracy of a urinary biomarker panel (LYVE1, REG1B, TFF1), and affiliated PancRISK score alone or in combination with plasma CA19-9 for early detection of pancreatic ductal adenocarcinoma (PDAC).
NCT06605404 [150]	Serum & tissue	Collect clinical information, blood, and tumour tissue samples from participants diagnosed with stage I, stage II, or operable stage III cancer in select solid tumours, including exocrine pancreatic cancer.
NCT03334708 [151]	Serum	Develop a minimally invasive test to diagnose pancreatic cancer at early stages of disease and monitor response to treatment.
NCT05743049 [152]	Serum	Collection of blood samples from patients with a diagnosis of pancreatic adenocarcinoma for evaluation of circulating biomarkers.
NCT02000089 [153]	Serum & pancreatic juice (CAPS5)	Evaluate pancreatic fluid mutations and circulating pancreatic epithelial cells as accurate markers of neoplasia by comparing their prevalence in cases with sporadic pancreatic neoplasia to healthy and disease controls.
NCT04406831 [154]	Serum	To assess miRNAs as a diagnostic and predictive test.
NCT05802407 [155]	Serum	Assess the prognostic value of baseline MRD and the role of MRD dynamic changes after treatment in guiding treatment. Peripheral blood derived from participants will be obtained for MRD test before adjuvant chemotherapy initiation and at the first imaging assessment after chemotherapy.

8. Future Perspectives

Despite substantial advances in our understanding of PDAC biology, clinical outcomes remain similar with most patients presenting with advanced, incurable diseases. Increasing insights into tumour immunobiology, stromal interactions, and genomic instability are now driving the development of rational combination strategies aimed at remodelling the immunosuppressive tumour microenvironment and enhancing therapeutic efficacy (Figure 3).

8.1. Vaccination Against Tumour Antigen

An optimal tumour vaccine should target antigens that are tumour-specific or exhibit minimal expression in normal tissues, thereby maximising on-target efficacy while limiting off-tumour toxicity. Several vaccine platforms have been developed, including:

1. Whole-cell vaccines:

These generate immune responses against a broad repertoire of tumour-associated antigens and are not restricted by the patient's HLA genotypes, potentially overcoming inter-patient variability in antigen presentation [156,157].

2. Peptide vaccines:

Peptide-based vaccines are designed to enhance the CD8⁺ T-cell response. KRAS-targeted peptide vaccines have shown encouraging signals in early-phase clinical studies in PDAC, with reported disease-free survival of 35 months and overall survival of 44 months in a pilot study [158].

3. DNA vaccines:

DNA vaccines enable endogenous expression of tumour antigens, allowing presentation of multiple epitopes and induction of both CD4⁺ and CD8⁺ T-cell responses, independent of the recipient's major MHC profile. Ongoing clinical trials are evaluating their therapeutic potential in pancreatic cancer [159,160].

4. Microorganism-based vaccines (viral or bacterial vectors):

These platforms deliver transgenes encoding tumour antigens, enabling infected cells to produce and present the antigen of interest, thereby amplifying immune priming. Many early-phase trials have shown promising activity in pancreatic cancer patients [161–163].

Challenges in vaccine therapy:

- Although cancer vaccine therapy is conceptually attractive and clinically promising, it faces several significant challenges that limit widespread implementation and consistent efficacy. One major barrier is technological complexity. Personalised vaccine approaches require sophisticated tumour sequencing, advanced bioinformatic pipelines for neoantigen identification, scalable and timely vaccine manufacturing, and robust platforms to monitor vaccine-induced immune responses. These processes are resource-intensive, costly, and difficult to standardise across centres.
- Patient selection and response assessment represent additional challenges. Conventional radiological response criteria, such as RECIST, may not adequately capture vaccine-induced immune responses, including delayed responses or pseudo-progression, potentially underestimating clinical benefit [164]. Furthermore, it remains unclear whether vaccine-induced T cells can sustain durable effector function within the immunosuppressive tumour microenvironment of PDAC, or whether repeated booster vaccinations are required to maintain effective anti-tumour immunity [165].

8.2. Monoclonal and Bispecific Antibodies

A wide range of monoclonal antibodies targeting PDAC-associated surface antigens—such as mesothelin, MUC-1, carcinoembryonic antigen (CEA), and HER-2/neu—have been developed. These agents exert anti-tumour effects primarily through antibody-dependent cellular cytotoxicity (ADCC). In addition, antibody–drug conjugates, immunotoxins, and radioisotope-linked antibodies enable direct tumour cell killing following antigen internalisation [166–168].

The use of bispecific antibodies is an emerging therapy. However, it is still in the early phases and requires advanced technology and careful, rationalised selection of the antibodies used.

8.3. CAR-Based Therapies

CAR are synthetic transmembrane proteins composed of an antibody-derived single-chain variable fragment (scFv) specific for a tumour antigen attached to a hinge region, a spacer, a membrane spanning element and a signalling domain. CAR engagement triggers T-cell activation, proliferation, and cytotoxicity independent of MHC presentation [169,170]. Although CAR-T-cell therapy has transformed the management of haematological malignancies, its application in solid tumours and PDAC remains challenging due to

antigen heterogeneity, stromal barriers, and immunosuppressive signalling. Ongoing trials address these limitations through improved CAR design and combinatorial approaches.

9. Conclusions

The advancements in the understanding of PDAC immunobiology have identified multiple mechanisms underpinning immune evasion, including dense fibrotic stroma, infiltration of immunosuppressive cells and oncogenic pathways that silence innate and adaptive immune responses. Therefore, conventional therapeutic strategies have failed to translate to clinically meaningful results. Reducing immune escape in PDAC will involve promoting CD8 T-cell infiltration, restoring antigen presentation, inducing interferon signatures and promoting immune architecture reorganisation.

Future therapeutic strategies will require a multifaceted combination approach with aim to convert “cold” PDAC phenotype into an immune-responsive “hot” tumour with integration of immune-modulating interventions with conventional and targeted therapies. Indeed, strategies such as combining immunotherapy with agents to deconstruct fibrotic stroma, disrupt immunosuppressive metabolic adaptations and use high-throughput immunophenotyping to develop personalised immunotherapy are promising to improve the prognosis and treatment of PDAC.

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