Review Article

Recent advances in immunotherapy for pancreatic cancer: a narrative review

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Background and Objective: Pancreatic cancer is the twelfth most common cancer worldwide. While cytotoxic chemotherapy remains the standard treatment, outcomes remain poor with a 5-year overall survival (OS) rate of only about 10%. The study of immunotherapy in pancreatic cancer is an area of active investigation. The objective of this work is to review innovations in immunotherapy for management of pancreatic ductal adenocarcinoma (PDAC), including checkpoint inhibitors (CIs), CD40 agonists, vaccines, bi-specific antibodies and chimeric antigen receptor (CAR) T-cell therapy.

Methods: Searches of the PubMed database and Google Scholar were completed with search terms "pancreatic cancer" and "immunotherapy" for articles published between January 1, 2000–December 20, 2023. A clinicaltrials.gov search was performed using the same search terms.

Key Content and Findings: Unlike the progress seen in survival of other solid tumors, pancreatic cancer remains a highly deadly disease. Poor disease survival is largely due to the tumor's immunosuppressive microenvironment and low tumor mutational burden, resulting in an "immunologically cold tumor" with low response rates to currently available therapies. New therapies are urgently needed. This article provides a comprehensive update of various novel immunotherapy approaches to treat pancreatic cancer. Checkpoint inhibitors, CD40 agonists, vaccines, bi-specific antibodies, and CAR T-cell therapies aim to "warm up" the tumor through different biologic mechanisms reviewed herein. This article also provides an introduction of ongoing clinical trials that pertain to these categories. The limited number of tumor samples in these early clinical trials underscores the need to identify and evaluate expression of tumor markers, and their correlation to the effectiveness of the new therapeutic agents. Furthermore, identification of surrogate markers for treatment efficacy are needed to guide future research.

Conclusions: The field of immunotherapy is rapidly evolving and emerging as a promising modality for treatment of pancreatic cancer, requiring further research.

Keywords: Pancreatic cancer; tumor microenvironment; immunotherapy; checkpoint inhibitors (CIs); vaccines

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Introduction

Despite improvements in survival of most solid malignancies, pancreatic cancer continues to have poor outcomes. While the greatest chance for cure is with surgical resection, fewer than 20% of patients have resectable disease at the time of diagnosis, thus there is an urgent need for new and effective therapies.

The low survival rate is multifactorial and related to the characteristics of the tumor and its microenvironment which maintain a highly immunosuppressive state. Pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer, has a microenvironment characterized by high expression of matrix metalloproteinases and tissue serine proteases, features that contribute to tumor invasion and metastatic spread (1). Further, stellate cells, stimulated by inflammatory cytokines and abnormal hedgehog signaling, produce collagen, fibronectin, laminin and hyaluronan deposits, causing stromal desmoplasia; this results in a physical barrier that impedes local blood supply, limiting drug delivery and the accessibility of cytotoxic immune cells (2,3). PDAC typically has a low tumor mutational burden, resulting in a depletion of tumor-specific antigens, hindering immune-surveillance and rendering it an "immunologically cold tumor", with low response rates to immunotherapy (4,5). Additionally, in PDAC, NRB1-mediated ubiquitination of lysosomes and autophagosomes storing major histocompatibility complex (MHC)-1 leads to reduced MHC-1 expression thereby hindering neo-antigen presentation (6). Lastly, tumor cells produce tumor-promoting cytokines, which modulate the immune response to favor production of immunosuppressor cells including myeloid derived suppressor cells (MDSCs), regulatory T-cells (Tregs), cancer associated fibroblasts (CAFs), and immunosuppressive tumor associated macrophages, as opposed to tumor-inhibiting dendritic cells or cytotoxic T-cells (7,8).

This work provides an update of various immunotherapy approaches to treat pancreatic cancer, specifically using immune checkpoint inhibitors (CIs), CD40 agonists, vaccines, bi-specific antibodies, and chimeric antigen receptor (CAR) T-cell therapy. *Figure 1* illustrates these treatment modalities. We present this article in accordance with the Narrative Review reporting checklist (available at https://dmr.amegroups.com/article/view/10.21037/dmr-24-2/rc).

Methods

As noted in *Table 1*, a PubMed database search, Clinicaltrials.gov search and Google Scholar search were performed for articles with search terms "immunotherapy" and "pancreatic cancer" published between January 1, 2000 and December 20, 2023. Results in the English language were reviewed and included based on the authors' discretion.

CIs

Immune checkpoints are inherent regulators of the immune system and crucial for self-tolerance but are exploited by cancer cells as a defense mechanism. Checkpoint proteins currently under investigation include cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1). T-cell activation requires binding of T-cell receptor to MHC-bound antigen and co-stimulatory binding of CD28 on T-cells to B7 ligands (CD80 or 86) on antigen presenting cells (APCs), resulting in T-cell growth and differentiation (9). CTLA-4, which is expressed primarily on naïve Tregs, binds B7 ligand to regulate and limit T-cell activity. Anti-CTLA-4 antibodies block CTLA-4, thereby removing its inhibitory effect. Activated T-cells, B-cells and natural killer (NK) cells express PD-1 (10). Upon recognizing MHC-bound antigen on tumor cells, T-cells release cytokines that stimulate target cells to express PD-L1. Binding of PD-L1 to PD-1 suppresses cytotoxic T-cell activity. Blockade of either PD-1 or PD-L1 thus removes this inhibition on T-cell activity. CIs have been tested as monotherapy, in dual-therapy, and in combination with chemotherapy, as well as in a variety of other approaches, as outlined below.

Single or dual CI

Single and dual CIs, when used in isolation, have limited effectiveness for PDAC. Both phase I and phase II trials evaluating single agent CI for locally advanced or metastatic PDAC (mPDAC) found no objective response to therapy (11,12). Similarly, a randomized, phase 2 trial of 65 patients with metastatic or recurrent PDAC investigating dual *vs.* single agent immunotherapy failed to achieve an overall response rate (ORR) of 10% in either arm, thus was

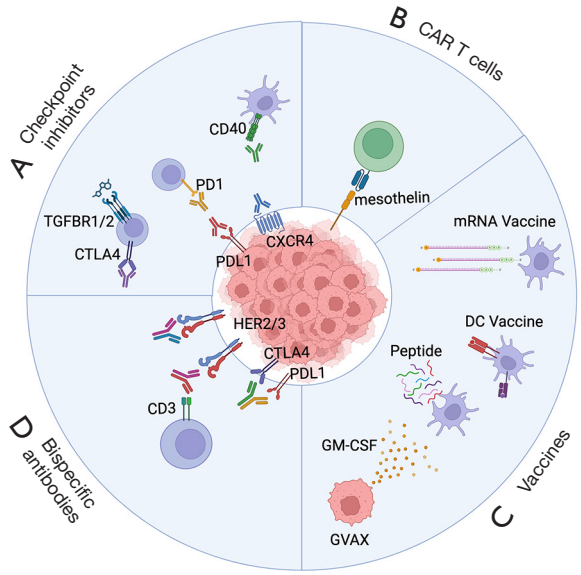

Figure 1 Current methods in immunotherapy for pancreatic cancer. (A) Checkpoint inhibitors such as PD-1/PD-L1 blockade to reprogram CD8 T cells, TGFBR1/2 inhibition and CTLA-4 blockade to impair regulatory T cells, and CD40 agonist to activate dendritic cells. (B) CAR T cells targeting tumor-specific antigens using a chimeric antigen receptor. (C) Vaccines against tumor antigens, including mRNA and peptide vaccines, dendritic cell vaccines that are generated through pulsing of autologous dendritic cells with tumor lysate or specific antigens, and GVAX, where irradiated autologous or allogenic tumor cells are engineered to express GM-CSF to promote dendritic cell maturation. (D) Bispecific antibodies targeting two different cell surface receptors on cancer cells, such as HER2 and HER3, PD-L1 and CTLA-4, as well as bispecific antibody armed activated T cells where the antibody targets a tumor cell surface receptor such as HER2, as well as CD3 on the surface of T cells to induce their activation. CAR, chimeric antigen receptor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte associated protein 4; GM-CSF, granulocyte-macrophage colony-stimulating factor; DC, dendritic cell.

Table 1 Summary of literature search strategy used for this review

Items	Specification
Date of search	December 20, 2023
Databases and other sources searched	PubMed, Clinicaltrials.gov, Google Scholar
Search terms used	“immunotherapy”, “pancreatic cancer”
Timeframe	January 1, 2000–December 20, 2023
Inclusion and exclusion criteria	Inclusion: immunotherapy treatments for pancreatic cancer; exclusion: non-English articles
Selection process	Articles were reviewed by S.F.

terminated (13).

The effectiveness of immunotherapy is more promising, however, for microsatellite instability-high (MSI-H) PDAC, which is hypothesized to arise from its higher mutational load and thereby higher tumor neoantigen burden (5). In a study of 32 patients with PDAC with MSI-H, patients treated with CIs achieved a 75% ORR and 20% complete remission (CR) rate, compared to cytotoxic chemotherapy, which yielded a 30% ORR (14). Single-agent CIs can thus be effective therapy for the 1–2% of mPDAC patients who have MSI-H disease (15,16). The effectiveness of CIs in this population has sparked interest in the development

of combination therapies that would improve antigen presentation and T-cell activity and infiltration while reducing immunosuppressive cells (4,17).

CI with chemotherapy

Chemotherapy has cytotoxic and immunomodulatory tumor effects. Gemcitabine, an apoptotic pyrimidine antimetabolite, reduces MDSCs and Tregs, and increases antigen presentation by dendritic cells to promote cell-mediated immunity (18-20). Nab-paclitaxel, a colloidal suspension of paclitaxel and albumin nanoparticles, increases inflammatory polarization of macrophages, promotes antigen presentation and maturation of dendritic cells, and reduces immunosuppressive MDSC, Tregs and CAF activity while increasing anti-tumor NK cell and $CD8^+$ activity (21).

Combination therapy of CI with chemotherapy has thus far been unsuccessful at improving outcomes. In CCTG PA.7, a randomized, multi-center phase II study, 180 patients with mPDAC were randomized to receive either chemotherapy (gemcitabine with nab-paclitaxel) alone or in combination with CIs (durvalumab and tremelimumab), and failed to yield a significant difference in median overall survival (OS) (8.8 *vs.* 9.8 months, respectively, P=0.72) or progression-free survival (PFS) (5.4 *vs.* 5.5 months, P=0.91) (22).

There are ongoing investigations to optimize the combination of chemotherapy with CIs, such as camrelizumab, botensilimab and spartalizumab (23,24). These studies aim to broaden the applicability and durability of CI response.

Dual CI with radiation therapy

Pre-clinical evidence demonstrates that CIs used with radiation therapy affect expression of cell surface targets of immunotherapy. An *in vitro* study found that murine PDAC cell lines treated with chemotherapy and radiation therapy had increased percentage and intensity of $PD\text{-}L1^+$ cells (24). *In vivo* murine models similarly found that the combination of radiation therapy with anti-PD-L1 caused greater tumor infiltration of $CD8^+$ and $CD4^+$ T cells, increased $CD8^+$ T cell activity [as noted by interferon-gamma (IFN-γ) expression], and reduced infiltration of MDSCs and Tregs compared to controls.

These favorable results led to the development of a phase I, open-label study which enrolled 59 patients with previously treated mPDAC (25). While combination therapy of radiation with dual CIs (durvalumab and tremelimumab) was associated with a higher PFS of 2–3 months compared to radiation alone (PFS of 1–2 months), it was associated with an increased incidence of adverse events, including grade 3–4 lymphopenia and autoimmune colitis, suggesting the combination elicited greater, albeit undesirable, pro-inflammatory response.

Alternative combinations of immunotherapy and radiation have been explored. In CheckPAC, a randomized, phase II, open-label study, 84 patients with mPDAC received stereotactic body radiation therapy (SBRT) with either dual CIs (nivolumab and ipilimumab) or nivolumab alone (26). The clinical benefit rate (complete response, partial response, or stable disease) of patients who received SBRT with nivolumab alone was 17.1% *vs.* 37.2% in the dual CI arm. Clinical outcomes were not correlated to PD-L1 expression or biomarkers of cytotoxic or Treg infiltration. Nevertheless, five of six patients who received SBRT with dual CIs had an abscopal effect, with reduction in tumor mass at non-radiated sites, suggesting that there are yet unmeasured immunomodulatory effects which warrant further investigation.

Building on the results of CheckPAC, the ongoing LAPTOP trial is investigating dual CI (nivolumab and ipilimumab) with chemotherapy (gemcitabine and nab-paclitaxel) and SBRT in patients with borderline resectable, locally advanced or mPDAC (27). This combination aims to increase antigen exposure and lymphocyte antitumor activity.

CI with CXCR4 inhibitor and chemotherapy

CXCR4, a G-protein coupled transmembrane chemokine receptor expressed on B-cells, naïve T-cells, monocytes, and bone marrow progenitor cells, interacts with ligand CXCL12 chemokine to modulate the tumor immune microenvironment and appears associated, if not directly implicated, in tumorigenesis (28). In pancreatic cancer, CXCR4 promotes progression of precursor pancreatic intraepithelial neoplasia to PDAC and metastatic growth (29). CXCR4-CXCL12 interaction has activating downstream effects on the MAPK, PI3K, Sonic Hedgehog, Wnt, paracrine and autocrine signaling cascades. A meta-analysis identified that CXCR4 overexpression was more common in PDAC than in normal pancreatic tissue [odds ratio (OR) =132.07, P=0.03]. CXCR4 is thus an attractive therapeutic target.

AMD3100 (plerixafor) is a small molecule CXCR4

inhibitor. In murine models, AMD3100 infusion resulted in reduction of CAFs expressing fibroblast activation protein (FAP), increased T-cell infiltration of the tumor, and improved anti-PD-L1 therapy responsiveness with an associated 15% decline in PDAC volume (30). In a study of 26 patients at two centers with colorectal cancer and PDAC, seven-day continuous infusion of AMD3100 resulted in significantly increased intratumoral CD8+ T cell density (P<0.05) (31). Patients also saw a significant decrease in circulating tumor DNA level (n=15, P=0.03), and a significant rise in FAP^+ cells expressing CCL19 (from 5.8% to 25.7%), which indicates an immune responsive rather than immune suppressive fibroblast cell development. While CR or PR were not achieved, 13 patients (57%) had stable disease by day 24, indicating clinical potential for CXCR4 inhibitors.

Motixafortide (BL-8040) is a high-affinity small peptide inhibitor of CXCR4. In a phase II, open-label, two-cohort study, patients with mPDAC after progression on at least one line of chemotherapy were treated with motixafortide, pembrolizumab and chemotherapy had a disease control rate (DCR) of 34.5% and median OS of 3.3 months (32). Paired screening and on-treatment biopsies found that the combination of motixafortide and pembrolizumab resulted in increased tumor infiltration of T-cells ($CD3^+$, $CD4^+$ and $CD8^+$) and activated $CD8^+$ granzyme B^+ cytotoxic T-cells, and decreased granulocyte-like MDSCs and decreased tumor cell density. These results raise optimism that the combination of CXCL4 inhibitor and chemotherapy can expand the applicability of CIs for treatment of PDAC after failure of first line therapy.

CI with poly ADP-ribose polymerases (PARP) inhibitors

PARP are a family of proteins that participate in DNA break repair and apoptosis (33). PARP inhibitors compete with NAD^+ at the active site on PARP thus trapping inactivated PARP1 on the stalled replication fork at the site of DNA damage preventing repair, and resulting in the death of vulnerable tumor cells with homologous recombination repair deficiency, such as BRCA-deficient cancer cells (33,34). In murine models of BRCA-deficient ovarian cancer, combination therapy of PARP inhibitors with CI induced a synergistic T-cell mediated anti-tumor effect (34). The effectiveness of combination CI and PARP inhibitor has thus also been explored in platinum-sensitive advanced PDAC. In an open label, phase 1b/2 study, 91 patients with locally advanced or mPDAC with known platinum sensitivity were randomized to receive maintenance therapy with niraparib (PARP inhibitor) and either nivolumab or ipilimumab (35). The niraparib and ipilimumab combination had superior 6-month PFS of 59.6% (95% CI: 44.3–74.9%, P=0.045) compared to that of niraparib with nivolumab (PFS of 20.6%, 95% CI: 8.3–32.9%, P=0.0002). Combination of CI and PARP inhibitor is a promising tolerable and effective maintenance therapy for individuals with platinum-sensitive advanced PDAC.

Because radiation can introduce DNA breaks, investigators assessed if radiation therapy could make tumors more vulnerable to the combination of PARP inhibitor and CI. In a single-arm, open-label, phase II trial, fifteen patients with microsatellite stable (MSS) PDAC were treated with a combination of niraparib, dostarlimab (anti-PD-1 antibody), and radiation therapy, yielding a disappointing 0% DCR (36).

Ongoing investigations are exploring other CI and PARP inhibitor combinations. An open-label, single-arm phase II trial is currently recruiting patients with mPDAC with mutations in DNA damage repair genes who benefited from first line platinum-based therapy to determine if they may have improved outcomes with olaparib and durvalumab combination therapy (37).

CI with TKI

Transforming growth factor beta (TGFβ) is a cytokine which participates in cell cycle regulation by crosslinking TGFβ receptor to phosphorylated SMAD proteins, causing downstream transcription of cyclin-dependent kinase inhibitors, thereby halting cell-cycle progression from G1 to S phase (38). TGFβ can inhibit activity of cytotoxic T-cells, leading to decreased production of cytokines including IFN-γ and cytolytic molecules such as perforin1 and granzyme B.

Galunisertib, an oral small molecule inhibitor of TGFβ receptor 1 (TGFβR1), was found in *in vitro* models to rescue TGFβ1-exposed $CD8^+$ T cells (39). In murine models of triple negative breast cancer, galunisertib resulted in dose-dependent tumor volume regression. Furthermore, combination therapy of galunisertib and anti-PD-L1 checkpoint blockade lowered NIH3T3 fibroblast activity and reversed the suppression of IFN-γ and granzyme B secretion in murine and human NK and $CD8^+$ T-cells (40). In light of these promising pre-clinical studies, an international, multicenter study assessed the combination of durvalumab and galunisertib for 79 patients with recurrent or refractory

mPDAC (41). This combination achieved a DCR of 25% and median OS of 5.72 months (95% CI: 4.01 to 8.83). Tumor PD-L1 immunohistochemistry scores did not correlate with clinical outcome. This study was limited by lack of a comparison arm and small sample size.

CI with electroporation

Mechanical disruption of tumor cells through electroporation is also under investigation as a method to improve response to CIs. Irreversible electroporation induces tumor cell apoptosis and release of tumor antigens, eliciting heightened cytotoxic $CD8^+$ T-cell response. A pilot, single-arm phase II trial is recruiting patients with mPDAC to undergo irreversible electroporation of a liver metastasis followed by nivolumab administration (42). PANFIRE-3, a randomized phase I trial, is similarly evaluating the combination of irreversible electroporation with nivolumab for mPDAC, with the addition of a toll-like receptor 9 (CpG) ligand (43). An overview of clinical trials evaluating immune CI treatments for PDAC can be found in *Table 2*.

CD40 agonist monoclonal antibodies

CD40 is a member of the tumor necrosis factor (TNF) receptor superfamily expressed on APCs and nonhematopoietic tissue. CD40 ligation on naïve B-cells activates B-cells and induces immunoglobulin isotype switching (44). CD40 ligand binding to dendritic cells induces maturation and upregulates signaling cascades leading to antigen presentation and release of cytokines interleukin-12 (IL-12) and p70, resulting in an increased $CD8^+$ T-cell immune response (45). CD40 activated monocytes and macrophages switch to M1 phenotype with resulting cytotoxic effects on tumor cells and degradation of extracellular stroma. Due to its potential anti-tumor activity, efforts are underway to enhance CD40 activity in patients with PDAC.

An open-label, multicenter phase I trial evaluated the benefit of neoadjuvant and adjuvant selicrelumab, a CD40 agonist monoclonal antibody, with or without chemotherapy in patients with resectable PDAC (46). Sixteen patients were randomized to receive selicrelumab single agent or in combination with gemcitabine and nab-paclitaxel preoperatively. The 1-year disease-free survival rate was 49.9% for patients treated with selicrelumab monotherapy compared to 75.0% for patients treated with selicrelumab with chemotherapy. Histologic examination suggested that selicrelumab induced changes in the tumor microenvironment. Resected tumor specimens from patients treated with selicrelumab had half the extent of fibrosis compared to control patients who did not receive selicrelumab. Patients treated with selicrelumab also had statistically higher densities of mature dendritic cells, $CD8^+$ T-cells and $CD4^+$ T-cells compared to controls not treated with selicrelumab. Based on CD163 expression on macrophages and monocytes, there was less M2 macrophage activation state noted in those treated with selicrelumab. Higher levels of inflammatory cytokines CXCL10 and CCL22 were also identified in patients treated with selicrelumab. Expanded T-cell clones were seen in the tumor specimens from selicrelumab treated patients. Higher expression of PD-1 on $CD4^+$ and $CD8^+$ T-cells was noted in selicrelumab-treated tumors, suggesting that selicrelumab may increase potency of PD-1 blocking agents. Selicrelumab, by increasing T-cell-enrichment and infiltration, may be able to convert a "cold" to "hot" tumor, thus increasing its vulnerability to cytotoxic T-cell therapies.

Similarly, the PRINCE trial compared outcomes of multimodal therapy. The PRINCE trial was a randomized, open-label phase II study of 99 mPDAC patients treated with chemotherapy combined with either nivolumab, sotigalimab (CD40 agonist antibody) or both as first line therapy (47). The primary endpoint of one year OS rate was highest for patients treated with nivolumab with chemotherapy (75.7%, P=0.006), compared to sotigalimab with chemotherapy (48.1%, P=0.062), or both with chemotherapy (41.4%, one sided P=0.23). These results were compared to historical control of 35%. $CD4^+$ T-cell, B-cell and dendritic cell subsets in circulation and tumor were predictive of longer OS in patients who were treated with both sotigalimab and chemotherapy while antigen-experienced type-1 CD4 T-cells and T follicular helper cells ($CD4^+PD\text{-}1^+CXCR5^+$) were predictive of longer survival than those treated with nivolumab and chemotherapy, illustrating that surrogate biomarkers correlating to treatment response may vary with the therapeutic agent.

The REVOLUTION trial, an open-label, non-randomized 2-stage study, is the successor of the PRINCE trial, and is recruiting treatment-naive patients with mPDAC to evaluate chemotherapy (gemcitabine and nab-paclitaxel) with combinations of nivolumab, ipilimumab, hydroxychloroquine or NG350A (an oncolytic adenoviral vector-expressing anti-CD40 antibody) (48).

Mitazalimab, a human immunoglobulin G (IgG)

Table 2 Clinical trials evaluating immune checkpoint inhibitor treatments for PDAC

Study NCT number	Date of NCT entry	Phase	Experimental arm	Control arm	Primary endpoint	Primary endpoint result
NCT00729664	August 7, 2008	I	Nivolumab	None	Safety and tolerability	91% of patients experienced AE, mostly low grade. Grade 3 or treatment-related AE occurred in 9% of patients. None of the patients with pancreatic cancer had objective response (complete response or partial response) to therapy
NCT00112580	June 3, 2005	II	Ipilimumab	None	Percentage of participants reaching CR or PR	0% of patients in the locally advanced and 0% of patients in metastatic disease cohort achieved complete response or partial response
NCT02558894	September 24, 2015	II	Durvalumab + tremelimumab ×4 cycles, followed by durvalumab monotherapy	Durvalumab monotherapy	ORR	3.1% RR for patients in experimental arm, and 0% RR for patient in control arm
NCT02879318	August 25, 2016	II	Gemcitabine + nab-paclitaxel + durvalumab + tremelimumab	Gemcitabine + nab-paclitaxel	OS	No significant difference in OS (median OS =9.8 months in chemo + CI *vs.* 8.8 months chemo alone HR =0.94, with 90% CI: 0.71–1.25, P=0.72)
NCT04674956	December 19, 2020	III	Camrelizumab + nab-paclitaxel + gemcitabine	albumin-bound paclitaxel + gemcitabine	PFS at 3 years	Recruiting
NCT05630183	November 29, 2022	II	Botensilimab + gemcitabine + nab-paclitaxel	gemcitabine + nab-paclitaxel	PFS at 2 years	Recruiting
NCT04229004	January 14, 2020	II/III	Pamrevlumab + gemcitabine + nab-paclitaxel, canakinumab + spartalizumab + gemcitabine + nab-paclitaxel, SM-88	Gemcitabine + nab-paclitaxel, mFOLFIRINOX	OS	Active, not recruiting
NCT02311361	December 8, 2014	I/II	Durvalumab + tremelimumab + RT	Durvalumab + RT	Safety and tolerability	The most common treated related was lymphopenia. No dose limiting toxicity noted
NCT02866383	August 15, 2016	II	SBRT + nivolumab + ipilimumab	SBRT + nivolumab	Clinical benefit rate (stable disease or complete response or partial response)	CBR was 37.2% (24.0–52.1%) *vs.* 17.1% (8.0–30.6%) for SBRT + nivolumab + ipilimumab *vs.* SBRT + nivolumab
NCT04247165	January 29, 2020	I/II	Gemcitabine + nab-paclitaxel + nivolumab + ipilimumab + SBRT	None	Safety and tolerability	Recruiting

Table 2 *(continued)*

Table 2 *(continued)*

Study NCT number	Date of NCT entry	Phase	Experimental arm	Control arm	Primary endpoint	Primary endpoint result
NCT02179970	July 2, 2014	I	Plerixafor	None	Safety and tolerability	No drug limiting toxicity at the 20, 40 or 80 μg/kg/h dose
NCT02826486	July 11, 2016	II	Cohort 1: BL-8040 + pembrolizumab. Cohort 2: BL-8040 + pembrolizumab + liposomal irinotecan + fluorouracil + leucovorin	None	Overall response rate	32% ORR with BL-8040 + pembrolizumab + liposomal irinotecan + fluorouracil + leucovorin
NCT03404960	January 19, 2018	I/II	Arm A: niraparib + nivolumab. Arm B: niraparib + ipilimumab	Null hypothesis	PFS at 6 months, safety and tolerability	6-month PFS was 20.6% (95% CI: 8.3–32.9%, P=0.0002) for niraparib + nivolumab, 6-month PFS was 59.6% (44.3–74.9%, P=0.045) for niraparib + ipilimumab
NCT04409002	July 23, 2020	II	Niraparib + dostarlimab + radiation	None	Disease control rate	Disease control rate was 0/15 (95% CI: 0–22%)
NCT05659914	December 21, 2022	II	Olaparib + durvalumab	None	Overall response rate	Recruiting
NCT02734160	April 12, 2016	Ib	Galunisertib + durvalumab	None	Safety and tolerability	No DLT recorded. 69.0% of patients had grade 3+ AE
NCT04212026	December 26, 2019	II	Irreversible electroporation + nivolumab	None	Overall response rate	Terminated
NCT04612530	November 3, 2020	I	Irreversible electroporation + nivolumab + toll-like receptor 9	Nivolumab	Safety and tolerability	Completed

PDAC, pancreatic ductal adenocarcinoma; NCT, National Clinical Trial; AE, adverse event; CR, complete remission; PR, partial remission; ORR, overall response rate; RR, risk ratio; OS, overall survival; chemo + CI, chemotherapy + checkpoint inhibitor; HR, hazard ratio; PFS, progression-free survival; RT, radiotherapy; SBRT, stereotactic body radiation therapy; CBR, clinical benefit rate; DLT, dose-limiting toxicity.

monoclonal anti-CD40 antibody is currently under investigation in different trials, with chemotherapy in OPTIMIZE-1, and in combination with MesoPher, a dendritic cell vaccine in REACtiVe-2 (49,50). An overview of clinical trials evaluating CD40 agonist monoclonal antibody treatments for PDAC can be found in *Table 3*.

Vaccines

Dendritic cell vaccines

Dendritic cells are antigen-presenting cells that help direct innate and adaptive immune response by promoting T-cell, NK cell and memory B-cell activity. The PDAC tumor microenvironment is deficient in dendritic cells, due in part to tumor-derived cytokines and exosomes which attenuate dendritic cell activity and increase levels of MDSCs, creating a tumor-tolerant environment (51). Certain $CD11b^+$ dendritic cells promote Tregs and suppress $CD8^+$ T-cells. Dendritic cells seize, process, and present antigens on MHC class I and II molecules, which are then recognized by $CD8^+$ and $CD4^+$ T-cells, promoting their activity and proliferation (52).

Wilms tumor gene 1 (WT1) antigen is an attractive antigenic candidate because it is highly expressed in PDAC, but not observed in normal pancreatic ductal cells (53). *In vitro* exposure of five human pancreatic cancer cell lines to WT1 antisense oligomers resulted in growth inhibition,

Table 3 Clinical trials evaluating CD40 agonist monoclonal antibody treatments for PDAC

NCT number	Date of NCT entry	Phase	Experimental arm	Control arm	Primary endpoint	Primary endpoint result
NCT02588443	October 27, 2015	I	Arm I: selicrelumab. Arm II: selicrelumab + nab-paclitaxel + gemcitabine	None	Safety and tolerability	Most AE attributed to selicrelumab neoadjuvant therapy were mild
NCT03214250	July 11, 2017	I/II	Nivolumab + gemcitabine + nab-paclitaxel *vs.* sotigalimab + gemcitabine + nab-paclitaxel *vs.* nivolumab + sotigalimab + gemcitabine + nab-paclitaxel	Historical 1 year OS of 35% for gemcitabine-nab-paclitaxel	1-year overall survival	1 year OS nivo/chemo 5.7% *vs.* sotiga/chemo 48.1% *vs.* sotiga/nivo/chemo 31.3%
NCT04787991	March 9, 2021	I	Arm A: nivolumab + ipilimumab + nab-paclitaxel + gemcitabine. Arm B: hydroxychloroquine + ipilimumab + nab-paclitaxel + gemcitabine. Arm C: ipilimumab + nab-paclitaxel + gemcitabine + NG350A	None	Safety and tolerability	Recruiting
NCT04888312	May 17, 2021	I/II	Mitazalimab + mFOLFIRINOX	None	Part 1: safety and tolerability. Part 2: ORR	Active, not recruiting
NCT05650918	August 30, 2021	I	Mitazalimab + mFOLFIRINOX + MesoPher	None	Safety and tolerability	Completed

PDAC, pancreatic ductal adenocarcinoma; NCT, National Clinical Trial; AE, adverse event; OS, overall survival; nivo, nivolumab; chemo, chemotherapy; sotiga, sotigalimab; ORR, overall response rate.

suggesting that WT1 antigen is a tumorigenic target for inhibition. A randomized phase II study in Japan evaluated the combination of intradermal WT1 vaccine with gemcitabine compared to gemcitabine alone in 85 patients with advanced PDAC and found that combination therapy resulted in longer PFS [5.2 *vs.* 3.3 months, hazard ratio (HR) =0.66, P=0.08], although there was no significant difference in median OS (54). Delayed type hypersensitivity (DTH) to WT1 was associated with longer PFS and increased WT1-cytotoxic T-cells, and longer PFS (P<0.0001), suggesting that WT1 specific immune responses were required for prolonging PFS.

Histologic evaluations have found that dendritic cell vaccines can alter the tumor microenvironment. In an unblinded phase I trial, a WT1 pulsed dendritic cell vaccine was studied in combination with adjuvant chemotherapy in eight human leukocyte antigen (HLA)-class II -compatible patients with WT1 expressing resectable PDAC (55). OK-432, picibanil, a streptococcal preparation known to induce cytokines which promote dendritic cell, macrophage, NK cell and type 1 helper T-cells and cytotoxic T-cell activity, was also administered (56). The OS rate at 2 years post-surgery with dendritic cell (DC) vaccination was 62.5%. ELISpot assay found a statistically significant rise in WT1-specific cytotoxic T-cell population from pre- to post-vaccination (P=0.02), however by tetramer assay of five patients, no significant difference was found. The 2-year post-surgical OS was significantly better for patients who had WT1-specific cytotoxic T-cell response compared to those who did not (71.4% *vs.* 0.0%, P=0.008). This study suggests that with careful selection of a tumor-associated antigen, dendritic cell vaccines can orchestrate an immunomodulatory response directed at PDAC that is safe and tolerable.

MUC1 (CD227) is also a target for vaccine therapy. Over-expressed in 90% of PDAC, this glycosylated type I transmembrane protein increases tumor invasion and angiogenesis (57,58). An open label phase I/IIa study assessed the safety and efficacy of WT1 peptide and MUC1-pulsed dendritic cell vaccine with chemotherapy as adjuvant treatment for patients with resectable PDAC expressing both WT1 and HLA-ABC (58). Although 90% of patients experienced an adverse event, none exceeded grade 1, and this combination was well tolerated overall. Median OS was

46.4 months and median relapse-free survival (RFS) was 17.7 months from time of surgical resection. Neither the quantity of cytotoxic T-cells as detected by tetramer assay, cytoplasmic WT1 staining intensity, nor tumor-infiltrating mononuclear cell immunophenotype correlated to OS or RFS; however results were limited by low sample size. Increased infiltration of $CD3^+$, $CD4^+$, $CD8^+$ mononuclear cells was associated with induction of WT1 specific cytotoxic T-cells, but did not meet statistical significance, emphasizing the need for larger clinical trials to determine the immunomodulatory effect on the tumor microenvironment.

Autologous dendritic vaccines produced from mutant KRAS peptide antigens and vaccines produced from tumor lysate are under investigation with ongoing clinical trials (59,60).

Peptide vaccines

Peptide vaccines aim to introduce HLA restricted tumor-specific antigens to antigen-presenting cells, which in turn induce cytotoxic T-cell activity to eliminate cancer cells that express those antigens. A multicenter, non-randomized, single-arm phase II trial evaluated the combination of two HLA-A*2402 restricted peptide vaccines against VEGFR1, VEGFR2 and KIF20A peptide with gemcitabine in 68 chemotherapy-naïve patients with unresectable PDAC (61). VEGF1 and VEGF2 promote tumor vascularization, while KIL20A is involved in intracellular trafficking of molecules and organelles. The 1-year OS rates for HLA-matched and HLA-unmatched groups were similar, 27.0% and 34.5% respectively (P=0.66), and median PFS was 4.7 months and 5.2 months respectively (P=0.275). Patients who developed a peptide specific cytotoxic T-lymphocyte response had better outcomes compared to those who did not (P=0.02, P=0.009 respectively), however this did not hold true for VEGFR2 (P=0.31).

Another randomized, placebo-controlled phase I dose escalation study evaluated VXM01, an antigen vaccine developed using live attenuated Salmonella typhi harboring a VEGFR2-encoding plasmid in the treatment of 26 patients with locally advanced, inoperable or stage IV pancreatic cancer (62). Patients were concurrently treated with gemcitabine. The VEGFR2 cytotoxic T-cell response, as measured by IFN-γ ELISpot analysis was significantly higher in the higher dose VXM01 group compared to the placebo and lower dose VXM01 group, however there was no statistically significant difference in outcomes between the placebo and VXM01 patients.

To eliminate the concern of a target antigen not being present on the tumor, efforts are underway to develop personalized vaccines. A phase II retrospective study evaluated neoantigen-based peptide vaccine, iNeo-Vac-P01 in 7 patients with advanced PDAC who had progression or intolerance after initial therapy (63). Patient tissue and blood samples were evaluated via whole exome sequencing and bioinformatics studies to synthesize the 15–35 HLA classes I and II neoantigen peptide personalized vaccines. Patients were also provided with granulocyte-macrophage colony-stimulating factor (GM-CSF), concurrently with chemotherapy or CI therapy. Mean OS was 24.1 months (11 to 31.4 months). Patients with longer OS were found to have a higher IFN-γ titer after vaccination, compared to those who had shorter OS, suggesting that IFN-γ titer may be a surrogate marker for treatment efficacy. All patients had higher proportions of $CD4^+$ CTLA-4^+ and $CD8^+$ CTLA-4^+ T-cells in peripheral blood during vaccination and patients with longer OS had more effector memory T-cells compared to central memory T-cells. None of the patients developed a serious adverse event, suggesting that personalized vaccines may have safety benefits in addition to their anti-tumor effect.

GVAX

GVAX is a vaccine technology using either allogeneic pancreatic cancer cells or autologous pancreatic cancer cells transgenically modified to express GM-CSF, which promotes DC maturation. Combination therapies with GVAX aim to reduce Treg activity while promoting antigen presentation, cytotoxic T-cell activity and innate immunity. In one multicenter, open-label trial, 93 patients with mPDAC who had received one previous line of therapy were randomized to receive cyclophosphamide and GVAX vaccine, followed by either CRS-207 (*Listeria monocytogenes*-expressing mesothelin) and nivolumab (arm A) or CRS-207 alone (arm B) (64). *Listeria monocytogenes*, when phagocytosed, introduces mesothelin to APCs which then process and present the peptides on the cell surface bound to MHC. Median OS was not statistically different at 5.9 months for arm A *vs.* 6.1 months for arm B, with HR 0.86. Arm A patients with longer OS had notably greater densities of lymphoid cells, NK cells and $CD8^+$ T-cells and increased myeloid PD-L1 expression compared to those with short OS. The combination therapy was able to induce modifications in the tumor microenvironment, and further exploration is necessary to improve clinical outcomes.

Other studies have evaluated GVAX in combination with different CIs. A phase Ib open-label study randomized 30 patients with previously treated locally advanced or mPDAC to receive either ipilimumab alone or in combination with GVAX (65). Median OS between the treatment arms were not statistically significant (5.7 months for combination therapy *vs.* 3.6 months for ipilimumab alone, HR =0.51, P=0.07), however combination therapy had a higher 1-year OS rate (27% *vs.* 7%). An OS exceeding 4.3 months was associated with greater mesothelin-specific T-cell responses (P=0.01) and larger mesothelin-specific T-cell repertoire size (P=0.009). These outcomes are again suggestive that multimodal induction of greater T-cell activity may lead to better clinical outcomes.

A phase II multicenter trial of 80 individuals with PDAC found that combination therapy of GVAX with ipilimumab was inferior to FOLFIRINOX (median OS 9.38 *vs.* 14.7 months, respectively, HR =1.74, P=0.02) (66).

mRNA vaccines

mRNA vaccines introduce neoantigens into a patient to stimulate both humoral and cell-mediated targeted anti-tumor responses. Because they are personalized, non-infectious, manufacturable, and do not insert into the host genome, mRNA vaccines are a popular treatment modality under investigation for cold tumors like PDAC (67).

A phase I trial evaluated the ability of autogene cevumeran, a personalized mRNA neoantigen vaccine, to promote T-cell activity in patients with surgically resected PDAC (68). The study enrolled 32 patients of whom 16 patients underwent surgery and received treatment with atezolizumab (anti PD-L1 antibody), autogene cevumeran, and the chemotherapy regimen mFOLFIRINOX (including 5-fluorouracil, folinic acid, oxaliplatin and irinotecan). Eight out of 16 (50%) patients who received autogene cevumeran had increased T-cell activity directed against at least one vaccine neoantigen. Furthermore, patients with measurable T-cell response, responders, had substantially expanded *de novo* polyclonal neoantigen-specific CD8 cells in the tumors that remained functional and durable for up to 2 years post-surgery. Responders had a longer median RFS compared to nonresponders, with a median RFS that was not reached compared to median RFS of 13.4 months (HR =0.08, P=0.003). Further studies are needed to optimize the process of neoantigen screening and improvise mRNA vaccine potency.

There is continued interest in the applicability of mRNA vaccines in PDAC and other KRAS mutated solid tumors, and results of a phase I trial evaluating the safety and tolerability of the combination of mRNA-5671/V941 monotherapy compared to combination therapy with pembrolizumab are pending (69). An overview of clinical trials evaluating vaccine treatments for PDAC can be found in *Table 4*.

CAR T-cell therapy

CAR T-cells are generated by procuring patient's T-cells via leukapheresis of peripheral blood, then genetically modifying the T-cell receptor (using viral vectors) to recognize a specific tumor antigen target, thereby directing its anti-tumor immune response. CAR T-cells can modify the immunosuppressive tumor microenvironment by producing cytokines that improve T-cell infiltration into the tumor (70). To improve CAR T-cells' likelihood of engraftment and expansion, patients receive conditioning chemotherapy to cause lymphodepletion prior to CAR T-cell infusion. Although approved for several hematological malignancies, CAR T-cell therapy is not yet approved for treatment of solid tumors. There are ongoing efforts to identify pancreatic cancer tumor antigenic targets for CAR T-cell development.

Mesothelin is a glycoprotein that is highly expressed in PDAC, pleural mesothelioma, and ovarian adenocarcinoma, but also present in lower levels on pleural, pericardial, peritoneal, tracheal and tonsillar tissues (71). In a phase-I study, two of six patients with chemotherapy-refractory mPDAC who were treated with CAR-T-targeting mesothelin (CART-meso) cells achieved stable disease, with PFS of 3.8 to 5.4 months (72). The levels of reactive IgG doubled from baseline in five of the six patients studied. While CAR transcripts were noted in the blood after each infusion, they were not detected in the few available post-treatment biopsies, suggesting that CART-meso cell infusion caused transient changes in the tumor microenvironment or that the CART-meso durability was limited. This study was limited in that biopsies were not obtained to confirm tumor cell surface expression of mesothelin prior to initiation of therapy.

CART-meso cells feature a two-pronged approach to antitumor effect. Through binding to mesothelin, CART-meso cells induce tumor cell death and trigger the release of tumor antigens and inflammatory cytokines. CART-meso furthermore expresses CD40L which binds to CD40 on dendritic cell and macrophages, activating them to uptake

Table 4 Clinical trials evaluating vaccine treatments for PDAC

NCT number	Date of NCT entry	Phase	Experimental arm	Control arm	Primary endpoint	Primary endpoint result
Dendritic cell vaccines						
NCT03592888	November 20, 2018	I	Mature dendritic cell (mDC3/8-KRAS) vaccine	None	Safety and tolerability	Active, not recruiting
NCT04157127	August 3, 2020	I	Autologous dendritic cell vaccine	None	Safety and tolerability	Active, recruiting
Peptide vaccines						
NCT03645148	August 24, 2018	I	iNeo-Vac-P01	None	Safety and tolerability	No severe vaccine-related adverse effects
GVAX vaccines						
NCT02243371	September 17, 2014	II	GVAX + CRS-207 + nivolumab	GVAX + CRS-207	Overall survival	Median OS was 5.9 months for GVAX + CRS-207 + nivolumab *vs*. 6.1 months for GVAX + CRS-207
NCT00836407	February 4, 2009	Ib	Ipilimumab + xGVAX	Ipilimumab	Safety and tolerability	20% of patients in either arm had grade 3–4 immune related adverse events
NCT01896869	July 11, 2013	II	Ipilimumab + GVAX	FOLFIRINOX	Overall survival	Median OS was 9.38 months for GVAX and ipilimumab *vs*. 14.7 months for FOLFIRINOX (HR 1.75, P=0.02)
mRNA vaccines						
NCT04161755	December 13, 2019	I	Atezolizumab + mFOLFIRINOX + autogene cevumeran	None	Safety and tolerability	6% of patients had grade 3 + adverse events (fever and hypertension)
NCT03948763	June 26, 2019	I	mRNA-5671/V941 + pembrolizumab	Pembrolizumab	Safety and tolerability	Pending

PDAC, pancreatic ductal adenocarcinoma; NCT, National Clinical Trial; OS, overall survival; HR, hazard ratio.

Table 5 Clinical trials evaluating CAR T-cell treatments for PDAC

NCT number	Date of NCT entry	Phase	Experimental arm	Control arm	Primary endpoint	Primary endpoint result
NCT02159716	June 10, 2014	I	CART-meso	None	Safety and tolerability	CART-meso is safe at doses up to 3×10^8 CAR T cells/m^2
NCT05650918	December 14,2022	I	MesoPher and mitazalimab	None	Safety and tolerability	Recruiting

CAR T, chimeric antigen receptor T; PDAC, pancreatic ductal adenocarcinoma; NCT, National Clinical Trial; CART-meso, CAR-T-targeting mesothelin.

tumor peptide antigens and present them via MHC to naïve T cells, promoting their maturation, thus broadening, and amplifying the immune response by a process called epitope spreading.

A phase I trial found that CART-meso cells had minimal tumor infiltration and limited durability on patients with mPDAC, thus further efforts are necessary to improve outcomes with this emerging therapy (73). An overview of clinical trials evaluating CAR T-cell treatments for PDAC can be found in *Table 5*.

Table 6 Clinical trials evaluating bispecific antibody treatments for PDAC

NCT number	Date of NCT entry	Phase	Experimental arm	Control arm	Primary endpoint	Primary endpoint result
NCT02912949	September 23, 2016	II	Zenocutuzumab	None	Overall response rate by RECIST 1.1	ORR among patients with pancreatic cancer was 39%
NCT05149326	December 8, 2021	III	KN046 + gemcitabine + nab-paclitaxel	Gemcitabine + nab-paclitaxel	Overall survival	Active, not recruiting
NCT04324307	March 27, 2020	I/II	Cohort 1: PD-L1/CTLA-4 bispecific antibody. Cohort 2: PD-L1/CTLA-4 bispecific antibody with gemcitabine with albumin-paclitaxel FOLFIRINOX. Cohort 3: PD-L1/CTLA-4 bispecific antibody with FOLFIRINOX	None	Objective response rate at 2 years	Recruiting

PDAC, pancreatic ductal adenocarcinoma; NCT, National Clinical Trial; ORR, overall response rate; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte associated protein 4.

Bispecific antibodies

Bispecific antibodies are an increasingly popular immunotherapy drug category because they can potentially achieve better tumor specificity, reduce on-target, off-tumor adverse effects and lower the risk of resistance by simultaneous alteration of two tumorigenic pathways (74). Zenocutuzumab is an antibody-dependent cellular cytotoxicity-enhanced anti-HER2xHER3 bispecific antibody designed for patients who harbor neuregulin 1 gene fusion (NRG1) rearrangements. NRG1 fusion rearrangements are driver mutations that occur in 1.5% of KRAS wild-type pancreatic cancers. NRG1 results in a mutant protein which binds members of the ERBB RTK family, triggering heterodimerization, activating the phosphoinositide-3 kinase pathway and promoting tumorigenesis (75). Zenocutuzumab functions by a "dock and block" approach; one Fab arm binds prevalent cell-surface-expressed HER2 protein ("docks"), while the other Fab arm blocks NRG1 interaction with HER3 ("blocks"), thereby inhibiting this stimulatory pathway. *In vitro* studies found that zenocutuzumab inhibited proliferation of lung adenocarcinoma and breast cancer cell lines expressing NRG1 fusion rearrangements.

In preclinical trials, zenocutuzumab prevented cell cycle progression and promoted apoptosis (75). Zenocutuzumab effectively shrank NRG1 fusion xenograft tumors by 63%±17% in murine models. Two mPDAC patients with *NRG1* gene fusion treated with zenocutuzumab had symptomatic improvement and reduction in tumor size for 11–14 months. These early successes raised interest in increased NRG1 fusion testing for patients with mPDAC. A phase I/II open-label clinical trial assessing zenocutuzumab for patients with solid tumors and NRG1 fusion mutation found that among patients with pancreatic cancer, the investigator-assessed ORR was 39% (76).

Other bispecific antibodies are also under investigation. KN046, a recombinant humanized bispecific antibody, is composed of a PD-L1 inhibitor and a CTLA-4 inhibitor. KN046 was assessed as single agent therapy in the second line setting for 21 patients with unresectable or mPDAC in a phase II trial, achieving an ORR of 11.1%, median PFS of 2.1 months and median OS of 7.5 months (77). In China, there are ongoing clinical trials evaluating KN046 and a PD-L1/CTLA-4 bispecific antibody (78,79).

There is persistent optimism that bispecific antibodies will help overcome exhaustion of tumor infiltrating lymphocytes and spur anti-tumor activity. An overview of clinical trials evaluating bispecific antibody treatments for PDAC can be found in *Table 6*.

Bispecific antibody armed activated T-cells (BATs)

Efforts to increase T-cell trafficking and T-cell binding to specific tumor antigen independent of MHC binding led

to the development of the BAT, an activated T-cell with one antibody arm that binds a tumor associated antigen and another that stimulates T-cell activity (80). An *in vitro* study found that BATs armed with anti-CD3/anti-EGFR or anti-CD3/anti-HER2 bispecific antibody had statistically greater cytotoxicity against cell lines resistant to cisplatin, gemcitabine or both compared to unarmed activated T cells (P<0.001) (81). Furthermore, sequential use of HER2-BATs followed by EGFR-BATs showed statistically higher cytotoxicity compared to BAT monotherapy (77% *vs.* 25%, P<0.05). Priming pancreatic tumor cells by exposing them to BATs prior to cisplatin resulted in increased cytotoxicity at lower concentrations of cisplatin compared to pancreatic tumor cells that were not primed. Priming is associated with downregulation of ABC transporters, regulators of small molecule transport across cell membranes, which may reduce the efflux of chemotherapy from pancreatic cancer cells, thereby improving cytotoxicity. As such, BATs may lower the effective dose of chemotherapy, thus reducing the risk of adverse events.

Discussion

Given that current systemic therapies for advanced PDAC have poor efficacy, there is an urgent need for improved treatment options (82,83). MSI-H PDAC appears to benefit from checkpoint inhibition. In the MSS population, ongoing investigations aim to modulate the tumor microenvironment to generate an enhanced anti-tumor response. While checkpoint inhibition alone is insufficient to elicit a clinically significant disease regression, synergistic combination therapies aim to increase tumor killing by augmenting antigen exposure and cytotoxic response. Many upcoming phase I and phase II trials are assessing such new classes of immuno-therapeutic agents.

Despite expansion of candidate drug molecules in the recent years as reviewed in this article, there remain several limitations to the studies. Several of these trials have low sample size, limiting the ability of the investigator to make determinations regarding the clinical efficacy of these novel therapies. Moreover, studies reviewed here did not investigate the expression pattern of the targets of drug candidates in each patient, making it further difficult to interpret the clinical efficacy. Most of the studies with CIs failed to indicate tumor mutational burden, MSI-status or mismatch repair (MMR) deficiency status routinely. Pre-intervention, few studies ascertained PD-L1 status, adequate expression of the molecular targets such as, mesothelin or VEGR. While a heterogeneous group of patients may not have a statistically significant response to the targeted intervention, it is possible that patients with tumor expressing the investigational target demonstrate superior outcomes, and thus should be the focus of the phase I trials.

Nonetheless, these studies serve as a valuable platform and indicate the potential for immunotherapy strategies as emerging landscape in PDAC treatment in the near future. These initial studies suggest most of the candidate drugs are safe and well tolerated. While the role of immunotherapies in PDAC treatment is evolving, further studies should personalize treatments, pairing therapeutic interventions with patients based on their molecular profiles, which in turn will help predict the response rate more accurately. Furthermore, there remain challenges to identify better biomarkers that accurately reflect measurable changes over time in the local tumor microenvironment for the purpose of monitoring durability of response.

Conclusions

Although pancreatic cancer has historically yielded poor responses to chemotherapy due to its immunosuppressive microenvironment, recent innovations in immunotherapy have introduced new tools to the arsenal against this devastating illness. These multimodal therapies aim to increase tumor antigen presentation, stimulate cytotoxic activity, and disrupt tumor proliferative signaling cascades. Ongoing clinical trials investigating targets identified through careful inspection of tumors' molecular profiles hold the potential to improve the treatment of pancreatic cancer.

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