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REVIEW

Immunotherapy in Combination with Well-Established Treatment Strategies in Pancreatic Cancer: Current Insights

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer and fourth most common cause of death in developed countries. Despite improved survival rates after resection combined with adjuvant chemotherapy or neoadjuvant chemotherapy, recurrence still occurs in a high percentage of patients within the first 2 years after resection. Immunotherapy aims to improve antitumor immune responses and reduce toxicity providing a more specific, targeted therapy compared to chemotherapy and has been proved an efficient therapeutic tool for many solid tumors. In this work, we present the latest advances in PDAC treatment using a combination of immunotherapy with other interventions such as chemotherapy and/or radiation both at neoadjuvant and adjuvant setting. Moreover, we outline the role of the tumor microenvironment as a key barrier to immunotherapy efficacy and examine how immunotherapy biomarkers may be used to detect immunotherapy's response.

Keywords: pancreatic cancer, immunotherapy, immune checkpoint inhibitors, cancer vaccines, adoptive cellular immunotherapy, microsatellite instability

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer accounting for more than 90% of cases[1] (commonly referred to as pancreatic cancer), other types being cystadenocarcinoma and acinar cell carcinoma.[2] PDAC represents a substantial health problem as presented on GLOBOCAN 2020 with as many deaths (466,000) as cases (496,000), affecting both sexes equally and rating pancreatic cancer as the seventh leading cause of cancer death globally.[3] Furthermore, especially in developed countries, PDAC is the fourth most common cause of death, however, the disease is predicted to reach second place within the next decade.[4] PDAC is associated with an extremely poor prognosis with less than 5% of the patients reaching 5-year overall survival (OS)[5,6] due to late diagnosis, rapid tumor progression and limited available treatments.[7]

Novel approaches, such as immunotherapy, aim to improve antitumor immune responses providing a more specific targeted therapy compared to chemotherapy. In recent years, immunotherapy has established its role in the treatment of various solid tumors including PDAC.[8–10] Immune checkpoint inhibitors (ICIs) are monoclonal antibodies used to block extracellular proteins expressed by the tumour or tumor-associated lymphocytes resulting in the suppression of antitumor immune response.[11] Examples of such extracellular proteins which prevent the T cells from recognizing and eliminating cancer cells are, the programmed cell death protein-1 (PD-1), and its ligand PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).[12] PD-1 binds to PD-L1 and PD-L2 ligands therefore preventing T-cell activity in peripheral tissues.[13] CTLA-4 is another inhibitory receptor that modulates the initial stages of T-cell activation and prevents immune hyperactivation by competitively inhibiting the binding of B7 ligands to the co-stimulatory receptor Cluster Differentiation 28 (CD-28).[13–16] Both PD-L1 and CTLA-4 are overexpressed in a subset of PDACs and are associated with worse survival,[17] therefore consisting of

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a promising therapeutic target. Furthermore, other strategies such as cancer vaccines use tumor-associated antigens (TAAs) to trigger immunization by activating the cytotoxic T-lymphocytes (CTLs). Tumor-associated antigens are derived either from whole-cell tumor lysates, recombinant tumor peptides or recombinant viruses.[18–20] On the other hand, adoptive cell transfer (ACT) includes genetically engendered autologous immune cells from patients' peripheral blood. These cells bind to specific cancer antigens leading to the immune destruction of tumor cells (Figure 1).[21] In addition, the chemokine system, a key regulator for inflammatory responses and leukocyte trafficking with chemokine receptor 2 (CCR2) and chemokine receptor 5 (CCR5), is playing an important role in this process;[22,23] CCR2 expression is relatively restricted to certain cell types, monocytes, NK and T lymphocytes, and it is shown to have a strong proinflammatory function, predominantly expressed by monocytes/macrophages, while when expressed in tumor microenvironments, it can be strongly immunosuppressive.[24] Therefore, targeting the recruitment of immunosuppressive monocytes/macrophages in tumors by CCR2 antagonism is used as a strategy to modify the tumor microenvironment and enhance anti-tumor immunity.[25] Despite the robust results in certain malignancies, neither immune checkpoint inhibitors nor vaccines or adoptive cell transfer have yet shown promising clinical efficacy in PDAC when used as single agent in most phases I and II clinical trials.[9,26,27] On the other hand a combination of immunotherapy with chemoradiation regimens have shown encouraging results. The aim of our work is to present a state-of-the-art review of the latest advances in PDAC treatment using a combination of immunotherapy with other strategies such as chemotherapy and radiation therapy both in the neoadjuvant and adjuvant setting.

Neoadjuvant Therapy

The majority of patients with PDAC are diagnosed in late stage disease with the tumour being either unresectable or metastatic. Only 15% to 20% are candidates for immediate tumor resection.[28] Adjuvant chemotherapy is considered the

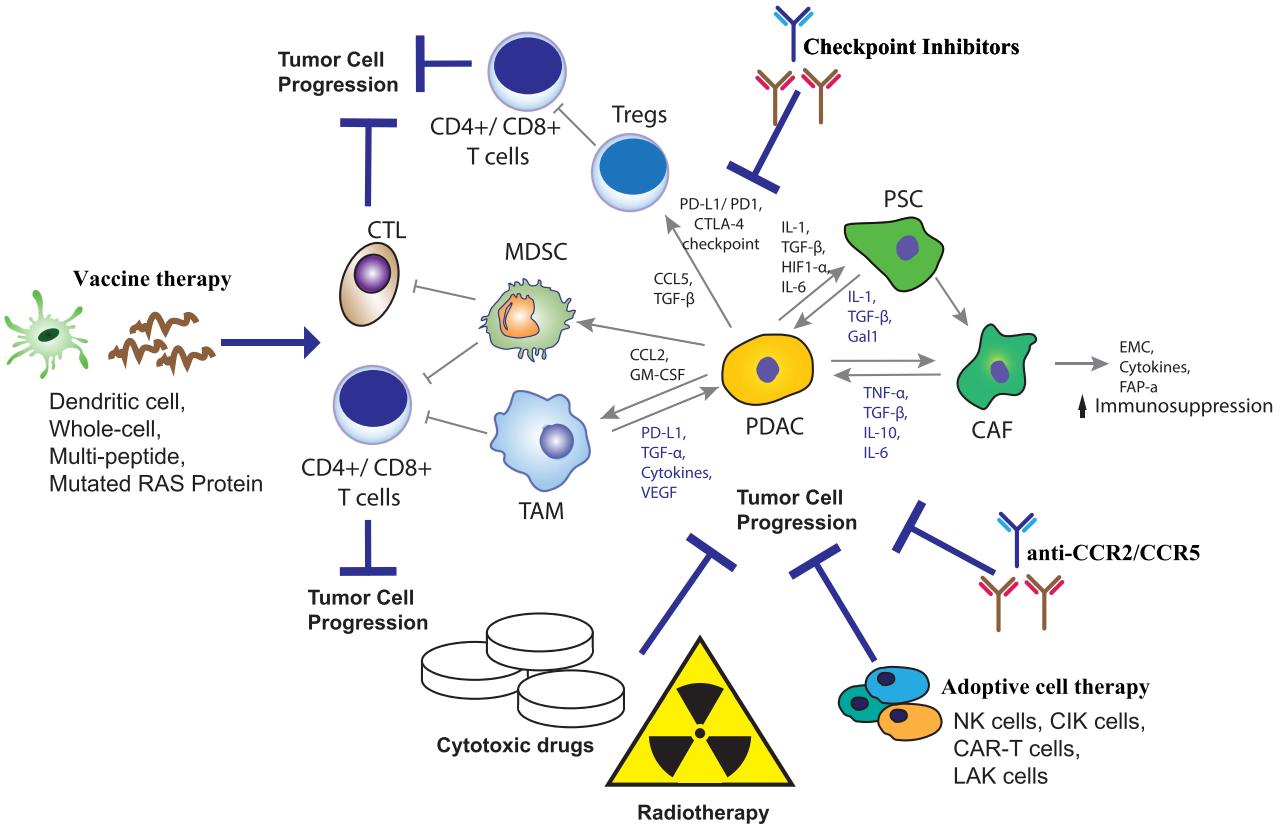

Figure 1 Therapeutic strategies target components of the tumor microenvironment in PDAC. Tumor microenvironment creates a barrier for immunotherapy and cytotoxic drugs in pancreatic cancer. Inhibition of the resistance mechanisms in pancreatic cancer by vaccine therapy and checkpoint inhibitors lead in activation of T-cells and tumor cell destruction. Adoptive cell transfer (ACT) lead to immune destruction of tumor cells while cytotoxic drugs and radiotherapy improve the efficacy of anticancer therapy. Adapted with permission from Schizas D, Charalampakis N, Kole C, et al. Immunotherapy for pancreatic cancer: a 2020 update. *Cancer Treat Rev.* 2020;86:102016.[9]
Abbreviations: ECM, extracellular matrix; PDAC, pancreatic adenocarcinoma; CAF, carcinoma- associated fibroblasts; MDSC, myeloid-derived suppressive cells; TAM, tumor-associated macrophages; CTL, cytotoxic T-lymphocytes; PSC, pancreatic stellate cells; CCL2/CCR2, C-C motif chemokine ligand/receptor.

current standard-of-care after surgical resection of PDAC.[29] However, recurrence still occurs in more than 75% of patients within the first 2 years after resection probably due to micrometastases,[30] increasing the need for optimization of neoadjuvant strategies and the development of new drug targets.[28] Neoadjuvant therapy is a systemic treatment prior to definitive surgical therapy which is supposed to provide an improved local and distant control.[31] According to the current clinical practice guidelines for pancreatic cancer,[29] neoadjuvant therapy is indicated for patients with borderline resectable and locally advanced PDAC, whereas its role for resectable PDAC is still under investigation. Immunotherapy was associated with tumor regression and improved OS in preclinical studies of PDAC when used in combination with other treatments.[32] However, there was no significant difference in the median OS for neoadjuvant or adjuvant immunotherapy. Nevertheless, in the neoadjuvant subset analysis, immunotherapy was associated with significantly improved OS compared to no immunotherapy.[33] Moreover, neoadjuvant immunotherapy may increase the presence of TILs in the PC microenvironment[34] and reduce the immunosuppressive effects of surgery by systemic release of glucocorticoids which induce apoptosis of naïve T cells and suppression of T-cell proliferation.[35,36] Together these limit the probability of recurrence.[34] Several clinical trials using a combination of immunotherapy and chemotherapy or chemoradiotherapy in the neoadjuvant setting are currently ongoing (Table 1). In a retrospective analysis studying the impact of neoadjuvant and adjuvant immunotherapy in the survival of pancreatic cancer patients, no significant difference in OS between neoadjuvant and adjuvant immunotherapy was found (HR: 1.06, 95% confidence interval (CI): 0.79–1.41; $p < 0.714$). However, multivariable Cox regression analysis revealed that neoadjuvant immunotherapy was associated with significantly improved OS (HR: 0.86, 95% CI: 0.74–0.99; $p < 0.04$) compared to no immunotherapy only in patients with a high-level of education, but not in patients with a low-level of education.[33] This difference between populations may be due to the fact that high-level of education patients are more prone to stick to the therapeutic plan and follow doctor instructions compared to low-level of education patients.

In phase Ib/II trial (NCT02305186), Rahma et al reported that pembrolizumab, an immune checkpoint inhibitor (anti-PD-1 IgG4 antibody), in combination with capecitabine and radiation as neoadjuvant regimen resulted in increased median recurrence free survival (RFS), 18.2 vs 14.1 months ($p = 0.41$), and overall survival (OS), 27.8 vs 24.3 months ($p = 0.68$), compared to chemoradiation alone (Table 1).[37] Moreover, the authors reported that 70% of the patients treated with pembrolizumab plus chemoradiation compared to 53% receiving chemoradiation alone underwent surgery.[37] This study is currently enrolling 25 more patients who will receive FOLFIRINOX prior to randomization to CRT± pembrolizumab, which will help to further investigate the immune modulatory effect of chemotherapy followed by CRT. FOLFIRINOX is also used as a neoadjuvant chemotherapy backbone in the NCT03983057 phase 3 trial in patients with locally advanced or borderline resectable PDAC. Contrary to the previous trial, this study evaluates chemoimmunotherapy without the addition of preoperative radiation.[38]

Immunotherapy agents have been successfully combined with other targeted therapies in several cancer types. Preclinical data suggest the existence of a synergistic effect between immunotherapy and certain targeted agents such as antiangiogenic factors and TKIs.[39] An ongoing phase II study examines the efficacy of the focal adhesion kinase (FAK) inhibitor defactinib in combination with pembrolizumab in patients with PDAC in the perioperative setting. FAK is a protein tyrosine kinase which is frequently overexpressed in various malignancies. FAK inhibition affects several intracellular pathways associated with cell survival and is involved in the immunomodulation of tumor microenvironment,[40] thus representing a promising therapeutic partner for immunotherapy regimens. Accordingly, a phase I safety trial in patients with various solid tumors, including PDAC has also produced encouraging safety and efficacy results when defactinib was combined with pembrolizumab.[41]

Likewise, treatment options have been significantly expanded with the addition of cancer vaccines and adoptive cell therapy, which use either cancer related antigens to sensitize the host's immune system against tumor cells, or in-vitro enhance patient's lymphocytes to identify and target tumor cells.[42] Since the efficacy of checkpoint inhibitors in PDAC seems limited, at least based on available results from completed clinical trials, attention has partially shifted towards the development of effective cancer vaccines. GVAX is a whole tumor cell vaccine genetically engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF).[43] The efficacy of GVAX in combination with CY has been studied as neoadjuvant therapy in stage I/II (resectable or borderline resectable) pancreatic cancer (Table 1).[44] Combination with CY resulted in lower disease free survival (DFS) and OS compared to GVAX monotherapy; ie 8.54

Table 1 Adjuvant Immunotherapy in Surgically Resected Pancreatic Adenocarcinoma

Intervention		Cancer Stage	Clinical Phase/ Identifier	Outcomes: Disease Free Survival (Months) (95% CI)	Outcomes: Median Overall Survival (Months) (95% CI)	Reference
GVAX/5-FU/ radiation	Whole-cell vaccine, Cytotoxic drugs	Resected stage I or II pancreatic adenocarcinoma	Phase II, NCT00084383	17.3 (14.6–22.8)	24.8 (21.2–31.6)	Lutz et al 2011[60]
GVAX/ Chemoradiation	Whole-cell vaccine, Cytotoxic drugs	Stage II or III Positive/ nevative margins	Phase I	13	20	Jaffee et al 2001[61]
Algenpantucel-L/ Chemoradiation	Multi-peptide vaccine, Chemoradiation	Surgically Resected Pancreatic Cancer	Phase II, NCT00569387	62% 12-month DFS	86% 12-month OS	Hardacre, Mulcahy et al 2013[62]
Algenpantucel-L, Gemcitabine/5-FU/ Rradiation	Multi-peptide vaccine, Cytotoxic drugs, radiation	Surgically resected pancreatic cancer	Phase III, NCT01072981	Completed No results posted	Completed No results posted	McCormick et al 2016[64]
K-Ras vaccine/GM-CSF	Peptide vaccine, Costimulatory molecule	Surgically resected and advanced disease patients	Phase I/II CTNRAS95002 CTNRAS97004	No results posted	25.6 (10–39) for Res 10.2 (3–28) for NonRes	Gjertsen et al 2001[66]
Ras-peptide/GM-CSF/Chemotherapy	Peptide vaccine, Costimulatory molecules, chemotherapy	Resected KRAS mutant pancreatic cancer	NA	No results posted	20.3 (95% CI, 11.6–45.3)	Abou-Alfa et al 2011[67]
TG01/GM-CSF /Gemcitabine	Vaccine, Costimulatory molecules, chemotherapy	Resected pancreatic cancer	Phase I/II NCT02261714	16.1 (11.1–19.6)	33.3 (24.0–40.0)	ASA 2012[68]
GI-4000/ Gemcitabine Placebo/ Gemcitabine	Mutated RAS Protein vaccine, Cytotoxic drugs	Resected pancreatic cancer/ KRAS mutant	Phase II	9.4 8.3	17.22 14.5	Muscarella et al 2012[69]
Nivolumab/GVAX/ CRS-207/CY GVAX/CRS-207/CY	PD-1 inhibitor, Whole-cell vaccine, Listeria vaccine, Cytotoxic drugs	Previously treated metastatic pancreatic adenocarcinoma	Phase II, NCT02243371	2.23 (2.14–2.33) 2.17 (2.00–2.30)	5.88 (4.73–8.64) 6.11 (3.52–7.00)	Hopkins et al 2015[77]
KIF20A/VEGFR1/ VEGFR2/ Gemcitabine	Peptide cocktail vaccine, Cytotoxic drugs	Resected pancreatic cancer patients	Phase II	15.8 (11.1–20.6)	NR	Miyazawa et al 2017[70]
Nivolumab, MS-813160, GVAX	PD-1 inhibitor, CCR2/ CCR5 dual antagonist, Whole-cell vaccine	Locally advanced pancreatic cancer	Phase I/II, NCT03767582	Recruiting	Recruiting	Hopkins 2019[71]
Nivolumab, MS-813160, Gemcitabine, Nab-paclitaxel	PD-1 inhibitor, CCR2/ CCR5 dual antagonist, Cytotoxic drugs	Resectable and locally advanced pancreatic cancer	Phase I/II, NCT03496662	Recruiting	Recruiting	Medicine WUSo et al 2018[72]

Abbreviations: 5-FU, fluorouracil; GM-CSF, granulocyte-macrophage colony-stimulating factor; CY, cyclophosphamide; KIF20A, kinesin family member 20A; VEGFR1/R2, vascular endothelial growth factor receptor ½; CI, confidence interval; Res, resected; NonRes, non-resected; NR, not reached; NA, not applicable.

months (95% CI, 2.66–17.1) compared to 18.92 months (95% CI, 13.87–34.1). OS was also lower, 15.4 months (95% CI, 13.2–26.5) compared to 34.2 months (95% CI, 21.6–45.7) respectively.[44] Another ongoing phase 2 study combined GVAX with pembrolizumab and SBRT in 58 patients with locally advanced PDAC. Among them, 35 patients underwent surgery and the median distant metastases free for the entire cohort reached 9.7 months,[45] while a phase 2 study in a similar population combines GVAX with pembrolizumab, cyclophosphamide and SBRT[46] with results still pending. The NCT03153410 early Phase 1 trial adds IMC CS4, a monoclonal antibody blocking the colony-stimulating factor receptor, to the aforementioned combination in patients with borderline resectable PDAC.[47] Additional strategies have

been employed including a combination of cancer vaccines, checkpoint inhibitors and chemoradiation to increase the efficacy of neoadjuvant therapy, however, no results have been reported so far.[48–54] On the other hand, the safety and efficacy of CCX872-B, a CCR2 Inhibitor, is currently evaluated in patients with histologically or cytologically confirmed non-resectable pancreatic adenocarcinoma with or without metastases also receiving FOLFIRINOX (NCT02345408).[55] Another phase 1b trial (NCT03778879) was designed to evaluate the efficacy of CCX872-B in combination with stereotactic body radiotherapy for preoperative treatment of resectable pancreatic cancer, however, the study was discontinued due to an insufficient quantity of the CCX872-B drug to conduct the study.[56] Furthermore, another phase I trial (NCT01413022)[57] studies the side effects and optimal dose of PF-04136309 (a CCR2 inhibitor) in combination with chemotherapy (FOLFIRINOX) in patients with locally advanced or borderline resectable pancreatic cancer, who are not candidates for surgical resection. During this study, no treatment-related deaths occurred while grade 3 or higher adverse events were reported in at least 10% of the patients receiving PF-04136309. Six out of 33 (49%) patients receiving FOLFIRINOX plus PF-04136309 who had undergone repeat imaging achieved an objective tumor response, while in the FOLFIRINOX alone group, none of the five patients with repeat imaging achieved an objective response.[58]

Adjuvant Therapy

Since surgery alone is associated with short-term survival and early tumor relapse, the implementation of systemic therapy is needed in the majority of patients.[59] A phase II clinical study in resected, stage I or II pancreatic adenocarcinoma patients, showed an increased DFS of 17.3 months (95% CI, 14.6–22.8), and OS of 24.8 (95% CI, 21.2–31.6) when patients were treated with whole-cell vaccine GIVAX in combination with chemoradiation in an adjuvant setting (Table 2).[60] (Table 2) These findings were also supported by Jaffee et al, although this was a phase I trial performed in stage II or III pancreatic cancer patients with both positive and negative resection margins, and so was not designed to test clinical benefit.[61] A phase 2 multi-institutional trial, evaluated the use of algenpantucel-L immunotherapy in addition to chemotherapy and chemoradiotherapy in the adjuvant setting for resected pancreatic

Table 2 Neoadjuvant Immunotherapy in Resectable or Borderline Resectable Pancreatic Adenocarcinoma

Intervention		Cancer Stage	Clinical Phase/ Identifier	Outcomes: Disease Free Survival (Months) (95% CI)	Outcomes: Median Overall Survival (Months) (95% CI)	Reference
Pembrolizumab/ Capecitabine/Radiation Capecitabine/Radiation	PD-1 inhibitor, Cytotoxic drugs,	Resectable or Borderline Resectable Adenocarcinoma	Phase Ib/II, NCT02305186	18.2 14.1 (p 0.41)	27.8 24.3 (p 0.68)	Rahma et al. 2021[37]
Pembrolizumab/ Defactinib	PD-1 inhibitor, Kinase inhibitor	Resectable Adenocarcinoma	Phase II, NCT03727880	Recruiting	Recruiting	Hopkins et al 2019[41]
Pembrolizumab/GVAX/ IMC-CS4/CY	PD-1 inhibitor, Whole-cell vaccine, Antineoplastic agent, Cytotoxic drug	Borderline Resectable Adenocarcinoma	Early Phase I, NCT03153410	Active, not recruiting	Active, not recruiting	Hopkins et al 2018[47]
GVAX/CY GVAX	Whole-cell vaccine, Cytotoxic drugs	Resectable or Borderline Resectable Adenocarcinoma	Phase II, NCT00727441	8.54 (2.66–17.1) 18.92 (13.87–34.1)	15.4 (13.2–26.5) 34.2 (21.6–45.7)	Hopkins 2008[44]
Nivolumab/GVAX/CY/ Urelumab	PD-1 inhibitor, Whole-cell vaccine, Cytotoxic drugs, Antineoplastic agent	Resectable Adenocarcinoma	Phase I, II, NCT02451982	Recruiting	Recruiting	Hopkins et al 2016[51]

(*Continued*)

Table 2 (Continued).

Intervention		Cancer Stage	Clinical Phase/ Identifier	Outcomes: Disease Free Survival (Months) (95% CI)	Outcomes: Median Overall Survival (Months) (95% CI)	Reference
Nivolumab/FOLFRINOX (FFX)	PD-1 inhibitor, chemotherapy regimen	Borderline Resectable Adenocarcinoma	Phase 1/2, NCT03970252	Recruiting	Recruiting	Center, Squibb et al 2019[52]
Nivolumab/GVAX/BMS-813160/SBRT	PD-1 inhibitor, Whole-cell vaccine, Antineoplastic agent, Radiation	Locally Advanced Adenocarcinoma	Phase 1/2, NCT03767582	Recruiting	Recruiting	Hopkins 2019[54]
GMCI/Chemotherapy/ Radiation	Adenoviral vector, Chemoradiation	Advanced Non-Metastatic Pancreatic Adenocarcinoma	Phase 1/2, NCT02446093	Recruiting	Recruiting	Candel Therapeutics and University 2015[53]
M7824/ M9241/ SBRT	PD-L1 inhibitor, Immunocytokine	Advanced Pancreas Cancer	Phase ½, NCT04327986	Recruiting	Recruiting	Institute and Center 2021[48]
Algenpantucel-L/ FOLFRINOX/ Gemcitabine/5-FU	Multi-peptide vaccine, Cytotoxic drugs	Borderline resectable pancreatic cancer	Phase II, NCT02405585	Study terminated No results posted	Study terminated No results posted	Corporation and Pharma 2015[49]
Algenpantucel-L/ FOLFRINOX/ Gemcitabine/Nab-paclitaxel/Capecitabine/ 5-FU	Multi-peptide vaccine, Cytotoxic drugs	Resectable (stage II), Unresectable (stage III)	Phase III, NCT01836432	Study terminated No results posted	Study terminated No results posted	Corporation and Pharma 2013[50]
CCX872-B/FOLFIRINOX	CCR2 Inhibitor, Cytotoxic drugs	Patients With Pancreatic Adenocarcinoma	Phase 1b, NCT02345408	Active, not recruiting	No results posted	ChemoCentryx[55]
CCX872-B/SBRT	CCR2 Inhibitor, Radiation	Resectable pancreatic cancer	Phase 1b, NCT03778879	Withdrawn No results posted	No results posted	Katz and Rochester 2019[56]
PF-04136309/ FOLFIRINOX	CCR2 Inhibitor, Cytotoxic drugs	Borderline resectable and locally advanced pancreatic cancer	Phase 1, NCT01413022	CCR2-targeted therapy plus FOLFIRINOX is safe and tolerable		Nywening et al 2016[58] Medicine, W. U. S. o., and Institute, N. C.[57]

Abbreviations: CY, cyclophosphamide; FOLFIRINOX (FFX), oxaliplatin, leucovorin, irinotecan, 5-fluorouracil; SBRT, stereotactic body radiation; GMCI, gene mediated cytotoxic immunotherapy (aglatimagene besadenovec plus valacyclovir); 5-FU, fluorouracil; CI, confidence interval.

cancer, resulted in 62% 12-month disease-free survival and 86% 12-month overall survival.[62] However, encouraging results from this phase II trial did not translate into clinical benefit in the phase III IMPRESS clinical trial, where the addition of algenpantucel-L to chemotherapy did not improve OS in patients with resected PDAC. Algenpantucel-L has also failed to prove its effectiveness in the treatment of locally advanced PDAC in the PILLAR phase III trial,[63] Nevertheless, phase III trial assessing overall survival after treatment with Algenpantucel-L, chemotherapy and radiation is completed however no results have been reported so far.[64]

The majority of pancreatic adenocarcinoma patients have mutations in KRAS oncogene.[65] In order to enhance the immune response, synthetic mutant RAS peptides plus GM-CSF were used as adjuvant treatment in a phase I/II trial, leading in peptide-specific immunity induction in 58% of the patients.[66] Patients that responded to the peptide vaccine

had higher OS (4.9 months) compared to non-responders (2 months). Another study, however, yielded low immune response (1 out of 9 patients) and a median OS of 20.3 months.[67] TG01 is injectable antigen-specific cancer immunotherapy which induces RAS-mutant-specific T-cell responses, enhanced by co-administration of GM-CSF. Patients with stage I or II pancreatic adenocarcinoma (R0 or R1) receiving adjuvant gemcitabine with TG01/GM-CSF presented a median OS of 33.1 (95% CI 24.0–40.0) months, and median DFS of 16.1 months (95% CI, 11.1−19.6)[68] (Table 2). Improved outcomes are also observed after an inactivated recombinant saccharomyces cerevisiae expressing mutant RAS protein (GI-4000) combined with gemcitabine in an adjuvant setting.[69] The phase II clinical study showed improvement in survival in R1 subjects with Ras mutant positive pancreas cancer and a significantly higher rate of mutation specific T cell response. The median OS was reported at 17.2 and 14.5 months and RFS at 9.4 and 8.3 months for GI-4000 group and placebo group respectively.[69] In addition, peptide cocktail vaccine (OCV-C01) plus gemcitabine in patients with resected pancreatic cancer presented a median DFS at 15.8 (95% CI, 11.1–20.6) months with OS while OS at 18 months was 69% (95% CI, 48.8–82.5).[70] In addition, all four patients who underwent R0 resection with KIF20A expression had no recurrence of pancreatic cancer with KIF20A-specific CTL responses.[70] Concerning CCL2/CCR2 Axis, a phase I/II study (NCT03767582) was established to evaluate the combination of nivolumab and a CCR2/CCR5 dual antagonist (BMS-813160) with GVAX in patients with locally advanced pancreatic cancer (LAPC) who have received chemotherapy and radiotherapy. Safety profile is checked as well as whether this combination therapy enhances the infiltration of CD8+CD137+ cells in PDACs.[71] Another phase I/II study (NCT03496662) which is currently under recruitment status evaluates the tolerability and efficacy of bms-813160 with nivolumab, gemcitabine and nab-paclitaxel in borderline resectable and locally advanced PDAC.[72]

Advanced Metastatic

The majority of patients with PDAC are diagnosed at late stages with the tumor being either unresectable or metastatic.[28] For patients with locally advanced and metastatic pancreatic cancer the treatment of choice is palliative chemotherapy, although very few improvements are seen in survival.[29,59] However, recent combination therapies including immunotherapy have shown some promising outcomes (Table 3). A phase Ib clinical trial in unresectable (Stage III) or metastatic pancreatic cancer patients treated with CTLA-4 inhibitor, ipilimumab, showed improved outcomes when ipilimumab was combined with gemcitabine.[73] Patients who received ipilimumab at 6 mg/kg in weeks 1, 4, 7 and 10 and gemcitabine hydrochloride at 1, mg/m^2 in weeks 1–7 and 9–11, showed 3.86 months (95% CI, 0.75 to 22.41) and 8.99 months (95% CI, 0.75–30.04) of progression free survival (PFS) and OS respectively.[73] In another study, a combination of ipilimumab with a PD-1 inhibitor, nivolumab, and MEK inhibitor, cobimetinib (arm 2), reported improved objective response rate (ORR) compared to ipilimumab plus nivolumab (arm 1), at 6.7 (95% CI, 0.8–22.1) versus 0.0 (95% CI, 0.0–18.5) months respectively.[74] Nevertheless, patients in arm 2 were treated at 3 mg/kg nivolumab plus cobimetinib, compared to arm 1 where nivolumab was used at 1 mg/kg.[75] Ipilimumab also improved OS when combined with GVAX, administrated in locally advanced or metastatic pancreatic cancer, resulting in OS of 5.7 months (95% CI, 4.3–14.7) compared to 3.6 months (95% CI, 2.5–9.2) when used as monotherapy.[76] On the other hand, a combination of nivolumab and GIVAX, listeria vaccine CRS-207 and CY, resulted in no survival differences compared to GIVAX/CRS-207/CY in patients with previously treated metastatic pancreatic adenocarcinoma.[77] These poor results may be due to the increased progression of metastatic pancreatic adenocarcinoma and therefore failure of treatment.

The use of tremelimumab, another CTLA-4 inhibitor in combination with PD-1 inhibitor, durvalumab, or gemcitabine showed modest but higher OS and DFS compared to tremelimumab or durvalumab monotherapy in advanced/metastatic tumors (Table 3).[27,78] However, no differences were observed when tremelimumab plus durvalumab were used in metastatic adenocarcinoma patients with progression after fluoropyrimidine or gemcitabine first-line chemotherapy.[27] Another study performed in advanced or metastatic pancreatic cancer patients treated with pembrolizumab plus gemcitabine and Nab-paclitaxel resulted in improved PFS and OS at 9.1 months (95% CI, 4.9–13/3) and 15.0 months (95% CI, 6.8–22.6) respectively.[79,80] Further clinical trials using PD-1 inhibitors in combination with chemotherapies are currently ongoing. The NCT03977272 trial uses the anti-PD-1 immune checkpoint inhibitor camrelizumab in combination with FOLFIRINOX in patients with metastatic PDAC that have received either no previous treatment or only gemcitabine-based first-line chemotherapy.[81] Another single arm study evaluated the safety and efficacy of camrelizumab

Table 3 Clinical Trials in Locally Advanced or Metastatic Pancreatic Adenocarcinoma

Intervention		Cancer Stage	Clinical Phase/ Identifier	Outcomes: Disease Free Survival (Months) (95% CI)	Outcomes: Median Overall Survival (Months) (95% CI)	Reference
Ipilimumab/ Gemcitabine	CTLA-4 inhibitor, Cytotoxic drugs	Unresectable (Stage III/ IV) or metastatic pancreatic cancer	Phase Ib, NCT01473940	3.8 (0.7–22.4)	8.9 (0.7–30.0)	University and Center 2012[73]
Ipilimumab/ Nivolumab/ Cobimetinib	CTLA-4 inhibitor, PD-1 inhibitor, MEK inhibitor	Advanced/metastatic Tumor	Phase I/II, NCT01928394	ORR 6.7 (95% CI 0.8–22.1) months		Squibb 2013[75]
Ipilimumab/ GVAX Ipilimumab	CTLA-4 inhibitor, Whole-cell vaccine	Locally advanced, unresectable or metastatic pancreatic	Phase I, NCT00836407	No results posted	5.7 (4.3–14.7) 3.6 (2.5–9.2)	Le et al 2013[76]
Tremelimumab/ Durvalumab Tremelimumab Durvalumab	CTLA-4 inhibitor, PD-1 inhibitor	Advanced/Metastatic Tumor	Phase II, NCT02527434	2.86 (1.87–3.52) 1.77 (1.38–2.92) 1.84 (1.84–1.84)	7.18 (3.98–18.76) 3.98 (2.83–5.13) 4.14 (NA–NA)	AstraZeneca 2015[27]
Tremelimumab/ Durvalumab Durvalumab	CTLA-4 inhibitor, PD-1 inhibitor	Metastatic adenocarcinoma/ progression after fluoropyrimidine or gemcitabine first-line chemotherapy	Phase II, NCT02558894	1.5 (1.2–1.5) 1.5 (1.3–1.5)	3.1 (2.2–6.1) 3.6 (2.7–6.1)	AstraZeneca 2015[27]
Tremelimumab/ Gemcitabine	CTLA-4 inhibitor, Cytotoxic drugs	Advanced Metastatic Pancreatic Cancer	Phase I, NCT00556023	No results posted	7.4 (5.8–9.4)	Aglietta et al 2014[78]
Pembrolizumab/ Gemcitabine/ Nab-paclitaxel	PD-1 inhibitor, Cytotoxic drugs	Advanced Metastatic Pancreatic Cancer	Phase Ib/II, NCT02331251	9.1 (4.9–13/3)	15.0 (6.8–22.6)	Weiss et al 2019[79] Weiss et al 2018[80]
Nivolumab/ OSE2101/ FOLFIRI	PD-1 inhibitor, multi-neoepitope vaccine, Cytotoxic drugs	Locally Advanced or Metastatic	Phase 2, NCT03806309	Recruiting	Recruiting	Group, Immunotherapeutics et al 2019[148]
Atezolizumab, KY1044	PD-L1 inhibitor, Inducible T cell co-stimulator	Advanced Metastatic Pancreatic Cancer	Phase I/II, NCT03829501	Recruiting	Recruiting	Limited and Sanofi 2019[149]
GVAX/CRS-207/CY GVAX/CY	Whole-cell vaccine, Listeria vaccine, Cytotoxic drugs	Metastatic pancreatic adenocarcinoma	Phase 2a, NCT01417000	No results posted	6.28 (4.47–9.40) 4.07 (3.32–5.42)	Whiting et al 2015[91]
GVAX/CRS-207/CY CRS-207 CY	Whole-cell vaccine, Listeria vaccine, Cytotoxic drugs	Previously treated metastatic pancreatic adenocarcinoma	Phase IIb, NCT02004262	No results posted	3.7 (2.9–5.3) 5.4 (4.2–6.4) 4.6 (4.2–5.7)	Le et al 2019[92]
KIF20A-66 BSC	Peptide vaccine	Metastatic pancreatic adenocarcinoma, previously treated with gemcitabine	Phase I/II, UMIN000004919	No results posted	4.7 ± 0.8 2.7 ± 1.1	Asahara et al 2013[93]
KIF20A/ VEGFR1/ VEGFR2/ Gemcitabine	Peptide vaccine, Peptide vaccine, Peptide vaccine, Cytotoxic drugs	Advanced and/or metastatic pancreatic cancer	Phase II, UMIN000008082	4.7, HLA-matched 5.2, HLA-unmatched	9.0, HLA-matched 10.0, HLA-unmatched	Suzuki et al 2017[94]

(*Continued*)

Table 3 (Continued).

Intervention		Cancer Stage	Clinical Phase/ Identifier	Outcomes: Disease Free Survival (Months) (95% CI)	Outcomes: Median Overall Survival (Months) (95% CI)	Reference
MUC1, HLA-A2, ICAM-1, LFA-3, GM-CSF	Vaccinia virus-tumor antigens, Costimulatory molecules	Unresectable or metastatic pancreatic cancer	Phase I	No results posted	15.3, anti CEA/ MUC-1 positive 3.9, anti CEA/ MUC-1 negative	Kaufman et al 2007[95]
w/ Poly-ICLC plus peptide-pulsed DC-CIK	Immunostimulant DC-CIK vaccination	Metastatic, unresectable pancreatic cancer	Phase I NCT01410968	No results posted	7.7 months	Mehrotra et al 2017[150]
DC-CIK /Chemotherapy S-1 DC-CIK Chemotherapy S-1 BSC	DC-CIK vaccination, Cytotoxic drugs	Metastatic, unresectable pancreatic cancer	Phase I /II, NCT01781520	4.5 2.8 3 1.4	7 4.2 4.7 1.73	Jiang et al 2017[97]
GV1001/ Gemcitabine/ Capecitabine Gemcitabine/ Capecitabine	Peptide vaccine, Cytotoxic drugs	Locally advanced or metastatic pancreatic cancer	Phase III, NCT02854072	No results posted	6.9 (6.4–7.6) 7.9 (7.1–8.8)	Middleton et al 2014[96]
MORAb-009, Gemcitabine Placebo/ Gemtacibine	Monoclonal antibody, Cytotoxic drugs	Unresectable (stage III or IV)	Phase II, NCT00570713	No results posted	6.5 (4.5–8.10) 6.9 (5.4–8.8)	Morphotek 2007[151]

Abbreviations: FOLFIRI, fluorouracil, leucovorin, irinotecan, and oxaliplatin; BSC, best supportive care; CY, cyclophosphamide; KIF20A, kinesin family member 20A; VEGFR1/R2, vascular endothelial growth factor receptor 1/2; MUC1, mucin 1; ICAM-1, intercellular adhesion molecule 1; LFA-3, lymphocyte function-associated antigen 3; GM-CSF, granulocyte-macrophage colony-stimulating factor; CI, confidence interval; ORR, objective response rate; NR, not reached.

in combination with gemcitabine and nab-paclitaxel in 20 patients with advanced PDAC. More than half of the study's population responded to the treatment regimen and almost all patients achieved disease control. Toripalimab is another anti PD-L1 antibody used as first line treatment in combination with nab-paclitaxel and gemcitabine as first-line treatment for advanced pancreatic adenocarcinoma in a phase Ib/II trial of 20 untreated patients with advanced PDAC. ORR was 35.3% and DCR 82.4% and PFS and OS reached 5 months and 14 months respectively.[82] Results from another early phase trial of the PD-1 inhibitor sintilimab showed a similar efficacy rate and a predictable toxicity profile.[83]

The development of monoclonal antibodies targeting immune checkpoints in order to counter the immunosuppression of tumor microenvironment represents a significant development in the treatment of solid tumors and has significantly augmented the therapeutic armamentarium. This notion is further advanced with the development of bispecific proteins that bind to multiple receptor simultaneously and link tumor cells to lymphocytes, facilitating lymphocyte-mediated tumor cell destruction.[84] Few trials are currently exploring bispecific molecules in patients with metastatic PDAC. Envafolimab is a bispecific PD-L1/CTLA-4 antibody currently tested in a phase II trial in combination with gemcitabine and nab-paclitaxel in the advanced setting. Preliminary results from 17 patients show a 55% ORR and 88.9% DCR, while around one-third of patients experienced grade 3 or higher treatment related adverse events, mainly hepatic toxicity and nausea.[85]

Another bispecific molecule tested in pretreated patients with mPDAC is the bispecific fusion protein targeting PD-L1 and the TGF-β receptor. An ongoing phase II trial combines this novel molecule with the multi-potent TKI famitinib in patients with pretreated PDAC and preliminary safety data have not reported grade 4 or 5 toxicities till now.[86]

Cytokines are molecules that regulate intercellular interaction and play a major role in orchestrating the immune response to infections as well as to tumor cells. Use of cytokines such as interferon-alpha and interleukin-2 have been one of the first attempts to sensitize the host's immune system to tumor cells to induce lymphocyte mediated cell lysis.[87] The optimal role of cytokines in cancer treatment is still being investigated in several clinical trials, especially in immunosensitive tumors such as melanoma and renal cell carcinoma. Since PDAC is relatively resistant to ICIs, attempts are being made to enhance their activity with the addition of cytokines in recent clinical trials. The phase II NCT04390763 study examines the safety and efficacy of the anti-TGF-β monoclonal antibody NIS793 with and without the PD-1 inhibitor spartalizumab in combination with nab-paclitaxel and gemcitabine versus chemotherapy alone in patients with untreated metastatic PDAC.[88] Similarly, nadunolimab, an interleukin-1 receptor accessory protein inhibitor, was combined with chemotherapy in 36 untreated patients with advanced PDAC. ORR and DCR were 27% and 57.6% respectively, while mPFS reached 7.8 months.[89] Unfortunately, the phase III SEQUOIA trial showed no benefit in OS or PFS with the addition of pegilodecakin, a pegylated IL-10 formation drug, to standard of care FOLFOX chemotherapy after progression on gemcitabine-based chemotherapy.[90]

Cancer vaccines have been used in several clinical studies (Table 3). The addition of listeria vaccine to GVAX plus CY resulted in improved OS compared to GVAX/CY regimen, 6.28 (95% CI, 4.47–9.40) and 4.07 (95% CI, 3.32–5.42) months respectively.[91] On the other hand, the combination of Cy/GVAX + CRS-207 did not improve survival over chemotherapy as presented by a phase IIb trial (NCT02004262).[92] A previously conducted phase I clinical trial combining the HLA-A*2402-restricted KIF20A-derived peptide vaccine with gemcitabine for advanced pancreatic cancer confirmed its safety and immunogenicity increasing the OS compared to best supportive care (BSC) (Table 3).[93] The VENUS-PC study, a single-armed, phase II trial used two antiangiogenic cancer vaccines targeting VEGFR1 and VEGFR2 in addition to the KIF20A peptide. In this study, authors evaluated the clinical benefit of the cancer vaccination in combination with gemcitabine.[94] No differences were observed either in median OS or in median PFS between the HLA-matched and HLA-unmatched group.[94] Nevertheless, patients in the HLA-matched group with peptide-specific CTL induction for KIF20A or VEGFR1 had a better prognosis compared to those without such induction.[94]

Ten patients with advanced pancreatic cancer were treated in a phase I clinical trial with vaccination regimen consisted of vaccinia virus expressing tumor antigens carcinoembryonic antigen (CEA) and mucin-1 (MUC-1) with three costimulatory molecules B7.1, ICAM-1 and LFA-3 (TRICOM) (PANVAC-V) and fowlpox virus expressing the same antigens and costimulatory molecules (PANVAC-F).[95] Median overall survival was reported at 6.3 months with a significant increase in overall survival noted in patients who generated anti CEA- and/or MUC-1-specific immune responses compared with those who did not (15.1 vs 3.9 months, respectively; $P = 0.002$). Moreover, antibody responses were observed in all 10 patients while 62.5% of the patients had antigen-specific T cell responses.[95] Another, open-label, randomised, phase 3 trial on locally advanced or metastatic pancreatic cancer patients using a combination of GV1001 peptide vaccine with gemcitabine and capecitabine failed to improve survival compared to chemotherapy alone.[96] 358 patients were allocated to the chemotherapy group, 350 to the sequential chemoimmunotherapy group, and 354 to the concurrent chemoimmunotherapy group. Median overall survival was reported at 7.9 months (95% CI, 7.1–8.8) for chemotherapy group, 6.9 months (95% CI, 6.4–7.6) for sequential chemoimmunotherapy group and 8.4 months (95% CI, 7.3–9.7) for concurrent chemoimmunotherapy group.[96]

On the other hand, immunostimulant DC-CIK vaccination in combination with the S-1 chemotherapy regimen in 47 patients with advanced pancreatic cancer resulted in favorable PFS and OS compared to monotherapy or best supportive care.[97] Moreover, analysis of peripheral blood demonstrated that the $CD3^+$, $CD3^+/CD4^+$, and $CD8^+/CD28^+$ T-cell subsets were significantly elevated, while the $CD3^+/CD8^+$, $CD3^+/CD16^+/CD56^+$and $CD4^+/CD25^+$ cell subsets were significantly decreased after DC-CIK cell therapy.

A recent breakthrough in adoptive cell therapy has been the development of chimeric antigen receptor (CAR) T-cells. These patient-derived lymphocytes have been genetically engineered and expanded ex-vivo to express receptors that target specific tumor antigens.[98]

When reinfused into patients, they cause tumor-cell destruction through multiple mechanisms, exploiting both the inhibition of tumor signaling pathways and the cytotoxic effect of T-cells. This new treatment modality has shown promising results, mainly in the treatment of hematologic malignancies.[21] Several trials are currently exploring the efficacy and safety of CAR-T cells with various chimeric receptors in PDAC binding to already known tumor antigens

such as Nectin4/FAP, mesothelin, HER2 and CEA, based on promising data from preclinical trial.[99] A few clinical trials have already produced some early safety and efficacy results.[100] A phase I trial of mesothelin targeting CAR-T cells tested in 6 patients with pretreated PDAC showed clinical benefit in 3 out of 6 patients NCT04037241, NCT03323944.[101]

Several novel molecules that target immune checkpoints have been developed and are being tested in the clinical setting. The combination of the novel CD40 agonist sotigalimab with gemcitabine and nab-paclitaxel with or without nivolumab produced some interesting results and showed promising efficacy in a phase 2 study. Interestingly though, the combination of sotigalimab and nivolumab led to worse outcomes than either of these drugs alone, suggesting a possible antagonistic effect among immunotherapy drugs.[102]

In addition to novel agents, other drugs that have been investigated or frequently used in different diseases have been employed in the treatment of PDAC. Masitinib is a TKI with activity against c-KIT, PDGFR and FGFR3 and has been investigated in the treatment of systemic mastocytosis due to its activity on mast cell and macrophage function, which may have an immunomodulatory effect on tumor microenvironment.[103]

The phase 3 AB12005 trial evaluated masitinib plus chemotherapy in 384 untreated patients with advanced or metastatic PDAC which suffered from cancer pain. Addition of masitinib improved PFS and OS in patients with locally advanced PDAC but not in the overall study population.[104] The hypomethylating agent azacitidine is being investigated in a phase II trial NCT03264404 in combination with pembrolizumab in patients with pretreated PDAC. Finally, the phase I MEDIPLEX study is examining the TKI and colony-stimulating factor-1 receptor inhibitor pexidartinib, which is currently used for the treatment of tenosynovial giant cell tumor in combination with durvalumab in patients with advanced PDAC and colorectal cancer.[105]

The combination of chemotherapy and immunotherapy with local radiation has been explored as a preoperative approach in an attempt to downstage large invasive tumors and facilitate R0 resection. Exploiting the systemic biological synergy between immunotherapy and radiation, as suggested by several preclinical studies,[106] a few trials have incorporated radiotherapy combinations in the advanced and metastatic setting. For example, the phase II/III QUILT 88 combines standard of care chemotherapy with low-dose chemoradiation and immunotherapy which consists of an infusion of NK-cells with high affinity for PD-L1 and an IL-15 cytokine fusion protein.[107] Another phase II study uses camrelizumab in combination with chemotherapy and local ablation in patients with PDAC and liver metastases.[108]

Immunotherapy Biomarkers in PDAC

The tumor microenvironment (TME) acts as a physical barrier against effective delivery of systemic chemotherapy.[109–111] Moreover, immune-suppressing mechanisms induced by regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSC) and tumor-associated macrophages (TAM) accumulation, play a central role in suppressing antigen-presenting cells. Tregs lead in T-cell apoptosis and inhibit dendritic cell maturation and function,[112] moreover, immune tolerance is also due to CTLA-4 which is constantly expressed on Tregs (Figure 1).[113] On the other hand, MDSC inhibit both innate and adaptive antitumor immunity in pancreatic cancer[114] while TAMs prevent dendritic cell-mediated antitumor immune responses by secreting a variety of growth factors.[115,116] Moreover, the presence of regulatory (FOXP3+) T-cells prevents active T-cells through PD-1/ PD-L1 checkpoint inhibitor expression (Figure 1).[117] Understanding of tumor microenvironments may lead in the identification of subgroups of patients who will have better outcome from certain therapies.

Accumulation of somatic mutations leads to increased neoantigen formation therefore renders tumors susceptible to immunotherapy through inflammatory cytokines and T-cell activation.[118] The mismatch repair (MMR) system is a family of proteins (MLH1, MSH2, MSH3, MSH6, PMS1 and PMS2) playing an important role in error repair during DNA replication. Defects in this system (dMMR) leads to random mutations occurring in specific regions of short DNA sequences of repetitions (microsatellites), a mechanism known as microsatellite instability (MSI).[119–121] In the majority of pancreatic cancer patients neoantigen formation is caused, however, due to the immunosuppressive tumor microenvironment, as effective immune responses fail to be generated.[114] Despite the limited and inconsistent literature of mismatch repair deficiency/ microsatellite instability in pancreatic cancer, a comparatively better prognosis and significantly prolonged survival for microsatellite instability high (MSI-H) compared to low (MSI-L) pancreatic cancer patients has been demonstrated.[122–126] Several studies have evaluated the expression of PD-L1 in PDAC.[14,127–131] As presented in a meta-

analysis of nine studies, PD-L1 positive rate was found in 19% to 62.5% of PDAC patients.[132] Although an association between checkpoint inhibitors PD-L1 and dMMR/MSI-H as well as with tumor mutational load (TML) has not been extensively studied, PD-L1 expression was seen in 38.9% of dMMR tumors and 15.2% of MMR proficient tumors,[133,134] emerging with the potential role of MSI-H status as predictive of a response to immunotherapy. TML express the total number of somatic/acquired mutations per coding area of a tumor genome.[135] It is associated with increased sensitivity to immunotherapy[135] and MSI-H tumors.[133] The clinical benefit of anti-programmed death-1 therapy with pembrolizumab has been evaluated in dMMR/MSI-H previously treated unresectable or metastatic noncolorectal cancer patients.[136] Among 233 enrolled patients with MSI-H/dMMR, advanced pancreatic cancer has been the most common, followed by endometrial cancer, gastric cancer and cholangiocarcinoma. PFS and OS was evaluated at 2.1 (95% CI 1.9–3.4) and 4.0 (95% CI 2.1–9.8) months respectively.[136] Currently there are several clinical trials conducted in MSI-high pancreatic ductal adenocarcinoma patients in combination with chemotherapy or immunotherapy agents, nevertheless no result have been posted yet (Table 4).

Homologous recombination deficiency (HRD) represents a prominent new biomarker in metastatic PDAC. Patients with HRD positive tumors are characterized by deregulation of DNA repair enzymes which makes these tumors highly susceptible to DNA damaging chemotherapy drugs, such as platinum derivatives, alkylating agents, and mitomycin C.[137] Patients with HRD are also highly-sensitive to PARP inhibitors, as demonstrated by numerous trials in ovarian cancer,

Table 4 Clinical Trials in Pancreatic Cancer Patients with High Microsatellite Instability

Intervention		Cancer Stage	Clinical Phase/ Identifier	Outcomes: Disease Free Survival (Months) (95% CI)	Outcomes: Median Overall Survival (Months) (95% CI)	Reference
Pembrolizumab	PD-1 inhibitor	MSI High/advanced pancreatic cancer	Phase II, NCT02628067	Recruiting/2.1 (1.9–3.4)	1395 participants 4.0 (2.1–9.8)	Marabelle et al 2020[136]
Pembrolizumab/ Sonidegib	PD-1 inhibitor, Hh-pathway inhibitor	MSI High/ advanced pancreatic cancer	Phase I, NCT04007744	Recruiting	Recruiting	Clinic and Institute 2020[152]
Pembrolizumab/ DEBIO1143	PD-1 inhibitor, IAP inhibitor	Non-MSI-high/ advanced/metastatic	Phase I, NCT03871959	Recruiting	Recruiting	Berard et al 2019[153]
Pembrolizumab/ XmAb®22841	PD-1 inhibitor, CTLA-4/ LAG-3 inhibitor	MSI High/advanced or metastatic pancreatic cancer	Phase I, NCT03849469	Recruiting	Recruiting	Xencor and Research 2019[154]
Nivolumab/ Ipilimumab/Radiation	PD-1 inhibitor, CTLA-4 inhibitor, Radiation	MSI High/pancreatic adenocarcinoma	Phase II, NCT03104439	Recruiting	Recruiting	Hospital and Squibb 2017[155]
Nivolumab/ Pembrolizumab/ Atezolizumab/FT500/ CY/Fludarabine	PD-1 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, iPSC-NK cell, Cytotoxic drugs	MSI High/advanced pancreatic cancer	Phase I, NCT03841110	Recruiting	Recruiting	Therapeutics 2019[156]
LY3300054/ Ramucirumab/ Abemaciclib/ Merestinib/LY3321367	PD-1 inhibitor, VEGFR2 antagonist, CDK inhibitor, HGFR inhibitor, anti-TIM3	MSI High/pancreatic cancer	Phase I, NCT02791334	Recruiting	Recruiting	Lilly and Company 2016[157]
TIL Fludarabine/CY	Adoptive cell transfer Cytotoxic drugs	MSI High/advanced, recurrent, or metastatic pancreatic cancer	Phase II, NCT03935893	Recruiting	Recruiting	Kammula 2019[158]

Abbreviations: MSI, microsatellite instability; Hh-pathway, hedgehog signaling pathway; IAP, inhibitor of apoptosis proteins; VEGFR2, vascular endothelial growth factor receptor 2; CDK, cyclin-dependent kinase; HGFR, hepatocyte growth factor receptor; TIM3, T-cell immunoglobulin and mucin domain-3; TIL, tumor infiltrating lymphocytes; CY, Cyclophosphamide; iPSC-NK, induced pluripotent stem cells-derived Natural Killer cell.

and to a lesser extent in other solid tumors, such as breast and prostate cancer.[138] When it comes to PDAC, about 14–44% of patients carry mutations in at least one HRD gene, with BRCA and ATM being the most frequent[139] study. Moreover, the use of the PARP inhibitor olaparib as maintenance therapy after response to platinum-based chemotherapy in patients with BRCA-mutated metastatic PDAC has led to improved PFS over treatment with a placebo.[140] Similarly, rucaparib, another PARP inhibitor has shown promising results as maintenance treatment in patients with mutations in BRCA1, BRCA2 and PALB2 in a phase II trial.[141]

These promising results in a malignancy associated with poor prognosis and scarce therapeutic options led to the investigation of PARP-based combination treatments. The synergy of immunotherapy and PARP inhibitors has been the subject of many preclinical studies which have generated encouraging results that, in turn, formed the base for many ongoing clinical trials in solid tumors.[142] In PDAC, exploratory results from a Canadian phase II study showed improved clinical outcomes in patients with ATM mutated metastatic PDAC receiving a combination of durvalumab and tremelimumab with chemotherapy over those that received chemotherapy alone. The phase II POLAR trial is currently exploring the safety and efficacy of a combination of pembrolizumab and olaparib as maintenance treatment in patients with metastatic PDAC and HRD or major response to platinum-based chemotherapy NCT04666740. Another phase I/IIb trial is examining the combination of niraparib with either ipilimumab or nivolumab in a similar population NCT03404960.

Emerging molecular targets such as CXCR4, LAG-3 and TIGIT have been suggested as predictive biomarkers to immunotherapy response in preclinical studies and are currently explored in various solid tumors in combination with immunotherapy or other treatment modalities.[143] CXCR4 has been associated with higher pro-inflammatory cytokine expression and with improved OS, suggesting a possible benefit with immunotherapy in CXCR4 high patients.[144] There is also an ongoing phase II trial (NCT02826486) currently evaluating an CXCR4 inhibitor in metastatic PDAC. LAG-3 expression in tumor infiltrating T-cells was associated with worse DFS in a sample of 69 patients with resected PDAC.[145] Data from pre-clinical models link CD155/TIGIT activity with immune evasion of pancreatic tumor cells.[146] Finally, experimental immune checkpoints such as IDO, VISTA, TIM3 represent potential targets for novel checkpoint inhibitors and may lead to advancements in the barren field of pancreatic cancer immunotherapy.[147]

Conclusion

Regardless of recent advances in cancer treatment, pancreatic duct adenocarcinoma is associated with extremely poor prognosis, still remaining a challenging disease to treat. So far, surgical resection in combination with either adjuvant or neoadjuvant chemotherapy, depending on stage of the disease, offers modest improvement in survival rates. Nevertheless, the overall prognosis for patients of all stages combined remains poor. Although advances in immunotherapy have provided an effective and safe treatment regimen in several cancer types, results of clinical trials for pancreatic cancer treatment have uniformly been disappointing for the majority of these regimens when used as monotherapy. On the other hand, both neoadjuvant and adjuvant immunotherapy have shown promising results, so far, when combined with cytotoxic drugs and/or radiotherapy. It seems that neoadjuvant immunotherapy increases the presence of TILs in the PC microenvironment and reduces the apoptosis of naïve T cells as well as the suppression of T-cell proliferation caused by surgical stress. Moreover, tremendous improvements in our knowledge, concerning the complex molecular and cellular microenvironment of pancreatic cancer cells, have occurred during the last decade. This knowledge will probably lead to the identification of subgroups of patients who will gain more benefit from specific therapies, in accordance with the concept of personalized treatment. Identification of valid biomarkers may guide treatment options in a pathway of targeted therapies which, in combination with immunotherapy, may reduce toxicity and improve outcomes. Further clinical studies are important in order to overcome microenvironment resistance and enhance effective treatment.

Disclosure

The authors report no conflicts of interest in this work.

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