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# The Achilles' Heel of Pancreatic Cancer: Targeting pancreatic cancer's unique immunologic characteristics and metabolic dependencies in clinical trials

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## Introduction:

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis, with the 5-year survival ranging from 37.4% for local disease to 2.9% for distant disease. [1] The incidence of pancreatic cancer continues to rise and it is projected to become the second leading cause of cancer-related death by 2030.[2] Despite ongoing efforts to improve early detection, almost all PDAC is diagnosed at a stage that requires systemic therapy. Systemic therapy is being increasingly used in the neoadjuvant and adjuvant setting with the goal of improving potential surgical cure rates. Current chemotherapy options are limited and there is a crucial need to develop new treatments.

The goal of systemic chemotherapy for pancreatic cancer patients with metastatic disease is to control tumor burden, palliate clinical symptoms and prolong survival. Historically, the nucleoside analogue, gemcitabine, was approved for this role based on modest improvements in survival and clinical benefit compared to 5-FU.[3] In recent years, the MPACT and PRODIGE trials demonstrated an improvement in overall survival by using combination therapy with either nab-paclitaxel and gemcitabine or FOLFIRINOX regimens, compared to gemcitabine alone.[4,5] Even with these advances in first line chemotherapy, the median time to progression remains approximately 6 months. As patients progress beyond first line therapy, subsequent treatment options become limited due to cumulative therapeutic toxicity, declining performance status, and few FDA approved regimens. Less than 50% of patients proceed to receive second line treatment.[6]

In recent decades, cancer therapy in general has expanded beyond traditional cytotoxic chemotherapy. We now have extensive insights into tumor biology which can guide the use of targeted therapies or immunotherapy in many cancers. These treatments have been slow to impact care in the majority of patients with PDAC, but in recent years there have been notable successes. In the recently reported Phase III POLO trial, maintenance therapy with olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, significantly delayed disease progression compared to placebo in metastatic pancreatic cancer patients with a germline BRCA mutation who had responded to first line platinum based therapy.[7] Immune

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checkpoint blockade with pembrolizumab can result in durable responses in chemotherapy refractory patients with microsatellite unstable tumors and is now FDA approved for this indication.[8]

Although successful systemic therapy remains elusive for most patients with PDAC, clinical investigators working with basic scientists have made a concerted effort to increase our knowledge of the molecular and genetic properties of this cancer by expanding the number of ongoing translational clinical trials exploring novel therapies beyond cytotoxic chemotherapy. In this review, we will highlight preclinical development and clinical trials seeking to capitalize on the unique molecular profile, metabolic dependencies, and immune microenvironment of PDAC.

## Biology of pancreatic cancer

Targeted therapies rely on identifying unique and actionable vulnerabilities in tumor cells. Sequencing studies for PDAC have revealed the most common genomic alterations occur in *KRAS, CDKN2A, TP53,* and *SMAD4* genes. [9] However, at this time, these common mutations are considered undruggable, with only rare exceptions. Extensive in-depth sequencing studies have sought to find additional therapeutic targets. The Comprehensive Molecular Characterization of Advanced Pancreatic Ductal Adenocarcinoma for Better Treatment Selection (COMPASS) trial, investigated 63 tumors using RNAseq and whole genome sequencing. These investigators identified potentially actionable genetic alterations in 30% of patients, including activating mutations in *PIK3CA* and *ERBB2*, or *HER2* amplification.[10] Aguirre and colleagues also performed sequencing of tumor RNA in 71 patients with PDAC and found therapeutically relevant genomic alterations in 48% (34/71) of tumors.[11] Actionable examples include a diversity of alterations in *BRAF* (point mutation, in-frame deletion), ROS1 (fusion), and FGFR1 (amplification), mostly observed in tumors harboring wild-type *KRAS* genes.[11]

Another focus has been on therapeutically targeting tumors with deficiencies in DNA damage repair (DDR) pathways, as they may be sensitive to platinum-based chemotherapy or PARP inhibitors. Germline DDR mutations will be identified in approximately 4–7% of patients with pancreatic cancer.[12,13] This observation has led to recommendations for universal testing of PDAC patients for germline variants in established risk genes, as identification of inherited germline mutations may influence therapeutic decision making for patients and also screening choices for their relatives.[13] It is estimated that 17–20% of PDAC patients will have somatic mutations in DDR pathway genes, including *BRCA1/2, PALB2, ATM, ATR, ATRX, BAP1, BARD1, BRIP1, CHEK1/2, and RAD50/51/51B.*[14,15] The Know Your Tumor (KYT) initiative, a collaboration between Perthera Inc. and the Pancreatic Cancer Action Network (PanCAN), sequenced tumor samples from 640 patients. [14] In those with advanced PDAC, 87 patients were DDR deficient and 428 patients were DDR proficient. DDR deficient patients with advanced cancer demonstrated improved median overall survival when treated with platinum based chemotherapy, compared with patients who had DDR proficiency (2.37 versus 1.45 years; $p < 0.0001$).[16] However, in the absence of platinum-based therapy, there was no overall survival difference observed in DDR mutant versus DDR proficient patients, suggesting that DDR status has no pure

prognostic value.[16] An ongoing randomized phase II trial is prospectively evaluating cisplatin and gemcitabine with and without veliparib, a PARP inhibitor, for germline *BRCA* mutated patients (NCT01585805).[17] Further prospective studies will be needed to elucidate the role of specific DDR mutations and other genetic signatures to guide existing and novel therapies.

## Targeted therapies in Pancreatic cancer

Historically, targeted therapies have not been successful in pancreatic cancer. A recent meta-analysis of nine randomized phase III trials comprising a total of 4,564 patients comparing gemcitabine monotherapy versus gemcitabine plus a targeted agent in first-line treatment of advanced pancreatic cancer showed no significant improvements in survival when adding a targeted drug.[18] These targeted therapies included erlotinib, cetuximab, rigosertib, elpamotide, bevacizumab, aflibercept, axitinib, masitinib and ganitumab, targeting pathways such as EGFR, VEGF, IGFR.[18] However, advanced sequencing and metabolic studies are setting the stage for possible implementation of novel targeted therapies. As *KRAS* is the most commonly mutated gene in PDAC, with mutations seen in 90–95% of all patients, there have been efforts to target this gene and its downstream effectors.[9] The SWOG S1115 study evaluated combination therapy with a MEK inhibitor and AKT inhibitor as second line treatment for advanced pancreatic cancer patients.[19] The combination was not beneficial, with no significant overall survival benefit compared to the second line chemotherapy regimen, FOLFOX (3.9 vs 6.7 months; HR, 1.37; 95% CI, 0.90–2.08; P = 0.15).[20] Although, two different small molecule inhibitors of *KRAS* (AMG 510 and MRTX849) are garnering attention for preliminary efficacy data in lung cancer patients with $KRAS^{G12C}$ mutations,[21] this mutation is not frequently observed in PDAC, which is largely driven by $KRAS^{G12D}$ mutations. As *KRAS* inhibitors are characterized in the clinic it is hoped that this will lead to agents with the potential to benefit a larger subset of PDAC patients.

Another receptor tyrosine kinase, Axl, is currently being explored in PDAC. Axl, a member of the TAM (Tyro3, Axl, MerTK) subfamily of RTKs, participates in various cellular processes, including cell survival, proliferation, migration, epithelial plasticity, and the regulation of innate immune responses.[22] It is estimated to be active in 70% of human PDAC, where it is associated with an adverse clinical prognosis.[22] Bemcentinib is a first-in-class, highly selective, Axl tyrosine kinase inhibitor that exhibited decreases in tumor growth and increases in survival when combined with chemotherapy in both patient-derived xenografts (PDX) and genetically engineered mouse models.[22] These findings led to a multicenter, randomized, phase Ib/II clinical trial of nab-paclitaxel/gemcitabine/cisplatin with or without bemcentinib is in progress in patients with metastatic PDAC. The primary objective is to determine complete response rate with secondary endpoints being overall response rate, progression free survival (PFS) and adverse events.[23] An accompanying parallel biomarker study will analyze blood and tissue samples for Axl pathway activity, tumor proliferation rate and predictive biomarkers of response.[23]

Another avenue towards targeted therapy in PDAC is based on identifying vulnerabilities related to the unique metabolic mechanisms which PDAC employs to grow and thrive. PDAC features abnormal mitochondrial metabolism and enhanced glycolysis, which alters

glutamine and lipid metabolism.[24] Demivistat (CPI-613) is a lipoate analog that inhibits pyruvate dehydrogenase and a-ketoglutarate dehydrogenase, two key enzymes in the tricarboxylic acid cycle.[25] Inhibition of these enzymes substantially reduces the mitochondrial export of anabolic intermediates, including those essential to nucleotide synthesis, which is expected to substantially interfere with the efficiency of the DNA damage response.[25] Demivistat should hypothetically synergize with FOLFIRINOX, which is comprised of DNA damaging agents. A single-center, open-label, dose-escalation, phase I trial of Demivistat with FOLFIRINOX was conducted in treatment naïve metastatic pancreatic cancer patients.[25] For the 18 patients given the maximum tolerated dose, the drug combination was well tolerated with the most common grade 3–4 adverse events reported as hyperglycemia (55%), hypokalemia (33%), peripheral sensory neuropathy (28%) and neutropenia (28%).[25] A 61% objective response rate was observed including a 17% complete response (CR) rate.[25] These results propelled the initiation of a phase III, global, prospective, open label, multicenter, randomized, two-arm trial comparing Demivistat in combination with modified FOLFIRINOX versus modified FOLFIRINOX alone in treatment naïve patients with metastatic cancer, which is currently in progress.[26]

Further examinations of the nutritional dependencies of PDAC has turned attention to asparagine, an essential amino acid for cell growth and survival. A study of 471 resected PDAC specimens demonstrated low asparagine synthetase expression by immunohistochemistry in 70% of cases, suggesting that most pancreatic cancer cannot synthesize its own asparagine and must use circulating plasmacytic asparagine.[27] Eryaspase, a formulation of *E. coli* L-asparaginase encapsulated in erythrocytes, hydrolyses asparagine, cutting off the cancer's supply, leading to inhibition of protein synthesis and apoptosis.[27] An open label, multicenter phase II randomized study in patients with second-line metastatic pancreatic cancer examined eryaspase in combination with either gemcitabine or FOLFOX chemotherapy regimens.[28] Of the 141 pts enrolled, an overall survival of 26.1 weeks was observed for the patients receiving eryaspase and chemotherapy compared with 19 weeks for the patients who received chemotherapy alone (HR, 0.57; P = .03).[28] Building on this data, TRYbeCA-1, an international, randomized, open-label Phase III trial is currently recruiting 500 patients to test eryaspase combined with chemotherapy in the second line setting for patients with advanced pancreatic cancer.[29] Patients are randomized in a 1:1 ratio to receive chemotherapy (gemcitabine/nab-paclitaxel or FOLFIRI or liposomal irinotecan with 5-fluorouracil/leucovorin) with or without eryaspase with a primary endpoint of overall survival. Key secondary endpoints will include progression free survival and objective response rate.[29]

## Immunotherapy for Pancreatic Cancer

PDAC is traditionally considered a 'non-immunogenic' tumor with preclinical studies supporting the notion that pancreatic tumors can employ multiple means of immune evasion.[30] To this end, the immune landscape of PDAC is a diverse environment comprised of many different cells acting in concert to help tumors evade immune recognition.[30–32] Detailed preclinical studies have provided the basis for modulating individual immune subsets for therapeutic effect. However, translating these findings for clinical benefit in patients has been a difficult task. For a small subset of patients with MMR protein deficiency (estimated

at 0.5–2%) there is clear benefit from treatment with checkpoint blockade and one agent (pembrolizumab) is approved for advanced patients refractory to first line therapy.[8] However, there is currently no role for PD1/PDL1 monotherapy in patients who have microsatellite stable PDAC. To date, chemotherapy combinations with PD1 inhibition have also failed to yield any benefit.[33] For example, a Phase I/II study of nivolumab in addition to nab-paclitaxel/gemcitabine did not show substantial benefits compared to chemotherapy alone.[34] Novel strategies targeting unique biological aspects of the tumor immune microenvironment are the focus of many ongoing clinical trials.[35]

## Vaccines:

As with other cancers, there have been efforts to develop an effective vaccine for PDAC patients. The most advanced vaccination program in PDAC utilizes a treatment combination consisting of an irradiated GM-CSF secreting PDAC cell line named GVAX, and CRS-207, a recombinant live-attenuated strain of *Listeria* engineered to secrete human mesothelin. In order to prompt a robust immune response, this therapy is preceded by treatment with low dose cyclophosphamide, which inhibits regulatory T cells. Phase I studies showed this regimen induced CD8+ T cells activity specific to the induced tumor associated antigen, mesothelin. A Phase II multicenter randomized trial comparing the triplet combination of cyclophosphamide, GVAX and CRS-207 to cyclophosphomide/GVAX (Cy/GVAX) alone reported an overall survival benefit of 9.7 versus 4.6 months (HR, 0.53; $P = .02$) for patients who received the triplet combination.[36] Moreover, enhanced mesothelin-specific CD8 T-cell responses were associated with longer overall survival, regardless of treatment arm.[36] A subsequent randomized three arm Phase IIb trial (ECLIPSE) compared Cy/GVAX and CRS-207, with CRS-207 alone or physician's choice of single-agent chemotherapy in metastatic PDAC patients who had received ≧2 prior lines of therapy.[37] Unfortunately, final results of this study did not demonstrate benefit from treatment with either Cy/GVAX and CRS-207 or CRS-207 alone compared to single agent chemotherapy in this population.[37,38] Current vaccine strategies are aimed at priming tumor antigen-specific T cells while simultaneously blocking PD1 checkpoints. A phase II study of the safety, efficacy, and immune response of Cy/GVAX and CRS-207 with or without nivolumab in patients with previously treated metastatic pancreatic adenocarcinoma (STELLAR) is currently in progress.[39]

Chimeric antigen receptor T cells (CAR-T) are genetically engineered T cells that can specifically kill tumor cells without major histocompatibility complex restriction and have been successful in treating hematological malignancies.[40] CAR-T cells are genetically modified to acquire specificity to a tumor antigen, while also providing an activation signal needed for T cell activation. Mesothelin is the most widely studied target for CAR-T therapy based on its high expression in PDAC cells. A phase 1 study evaluating the safety and efficacy of autologous mesothelin-specific CAR T cells was conducted in 6 chemotherapy-refractory metastatic PDAC patients.[41] There were no dose limiting toxicities and disease stabilization was achieved in 2 patients, with progression-free survival times of 3.8 and 5.4 months.[41] Further studies will clarify the potential role of CAR-T cells in pancreatic cancer.

### CSF1R blockade:

Due to the robust intratumoral infiltration by tumor-associated macrophages (TAMs) in both human PDAC and autochthonous genetically engineered mouse models,[42] multiple groups have reported efforts to target colony-stimulating factor 1 receptor (CSF-1R) signaling, which supports the recruitment, differentiation, and maintenance of immunosuppressive macrophages.[43] In preclinical mouse models, combination therapy with gemcitabine, CSF1R blockade and either anti-CTLA4 or anti-PD1 therapy resulted in a synergistic response that was further enhanced with co-blockade of both PD-1 and CTLA-4 with complete tumor regression in 30% of animals and an average tumor regression of 85%.[32,44] Small molecule inhibitors and monoclonal antibodies inhibiting CSF1R have been developed and are in Phase I or Phase II clinical trials in combination with immunotherapy and/or cytotoxic chemotherapy.[45] Cabiraluzimab, a humanized IgG4 monoclonal antibody, binds to CSF-1R and blocks its signaling, a key determinant of TAM activation and survival. By reducing TAMs, a proinflammatory microenvironment may be formed that can stimulate T-cell responses, sensitizing PDAC to therapy with anti−PD-1 checkpoint therapies. A Phase Ia/b study of cabiraluzimab and nivolumab showed that the combination was tolerable, with preliminary evidence of on-target tumor immune modulation and durable clinical benefit in heavily pretreated patients with advanced PDAC.[46] Elevations in creatinine phosphokinase (14%) and AST (5%) were among the most common grade 3 adverse events and were reversible without significant clinical sequelae.[46] Among the 31 participants, there were three confirmed partial responses and one patient with stable disease, comprising a 6-month disease control rate of 13%, and objective response rate of 10%.[46] A randomized, open-label, phase 2 study evaluating the safety and efficacy of cabiraluzimab + nivolumab ± chemo in advanced PDAC is currently in progress though preliminary results suggest that there is no clinical benefit from the combination. [43,47] An alternative strategy employs PLX-3397 (Pexidartinib), a small molecule inhibitor of CSF-1R. PLX-3397 is being evaluated in combination with durvalumab (anti-PDL1 antibody) in advanced pancreatic cancer patients. In a Phase I trial, the most frequent grade 3 adverse events reported were fatigue, elevations in AST/ALT or alkaline phosphatase, or decreases in neutrophils or white blood cell count. Preliminary efficacy data revealed a clinical benefit rate of 2 months in 21% of patients (4 out of 19 patients had stable disease). [48]

### CCL2/CCR2 axis:

Another strategy for inhibiting tumor associated macrophages is to block the CCL2/CCR2 chemokine axis. CCR2+ monocytes from the bone marrow migrate to pancreatic tumors rich in CCL2 chemokines and become immunosuppressive tumor associated macrophages.[49] A phase IB trial of a CCR2 specific oral antagonist CCX872 was used in combination with FOLFIRINOX to treat PDAC patients with locally advanced or metastatic pancreatic cancer in a multi-center study. Among 50 subjects, the combination therapy achieved an overall survival of 29% at 18 months without clear safety issues. This compares favorably to historical data in which 18 months survival was 18.6% for FOLFIRINOX regimen alone.[4] Though circulating monocytes were reduced by treatment, curiously, better overall survival was associated with lower peripheral blood monocyte counts at baseline. [50] Another oral small molecule CCR2 inhibitor, PF-04136309, tested in combination with FOLFIRINOX in a phase Ib trial with the same study population, yielded an objective tumor response in 16 of

33 patients (49%), which was encouraging compared to expected results with FOLFIRINOX alone.[51] The combination was also considered safe and tolerable with 18% of patients having grade 3 febrile neutropenia or hypokalemia, 15% having diarrhea and 69% of patients having neutropenia.[51] A subsequent Phase Ib study evaluated PF-04136309 in combination with nab-paclitaxel and gemcitabine in patients with metastatic PDAC. In this multi-center study, there was no clear indication of benefit with objective response seen in 5 of 21 subjects (24%). Furthermore, there was a concerning safety signal with 5 cases of pulmonary toxicity.[52] These results reflect the potential importance of using different combination chemotherapy regimens and the need to completely define the benefit and toxicity prior to any subsequent clinical development.

### CD40 targeting:

Rather than inhibit accumulation of a specific immune cell population, another approach is to repair insufficient T cell priming to make T cells more responsive to checkpoint inhibition. CD40 is a cell-surface member of the TNF receptor superfamily that is expressed on antigen presenting cells, such as dendritic cells, B cells, and myeloid cells. Based on preclinical evidence, anti-CD40 agonist therapy appears to work in conjunction with chemotherapy by activating antigen presenting cells to present tumor antigens to T cells.[53] Subsequent studies using subcutaneous xenograft implanted and genetically engineered mouse models showed combination therapy with gemcitabine, nab-paclitaxel, CD40 antibody and PD-1 antibody further extended the activity and durability of response to combination chemotherapy with CD40 alone.[54] Results from a phase Ib trial of patients with newly diagnosed metastatic pancreatic cancer, treated with chemotherapy and APX005 (a humanized rabbit IgG1 antibody to CD40), with or without nivolumab, showed an encouraging ORR of 54% (n = 24 patients).[55] A randomized phase II study of gemcitabine/nab-paclitaxel with or without APX005M, and with or without nivolumab, in first-line untreated metastatic pancreatic cancer is ongoing.[55] Similarly, selicrelumab, an anti-CD40 compound made by Roche, is also under investigation in combination with chemotherapy or immunotherapy. A Phase I study (NCT02588443) investigating the combination of selicrelumab with gemcitabine/nab-paclitaxel in a neoadjuvant and adjuvant setting in pancreatic adenocarcinoma has been completed in November 2018, with results pending.[56] The large Phase Ib/II MORPHEUS trial is ongoing and evaluating several immunotherapy combinations including selicrelumab.[57] This trial has incorporated multiple experimental cohorts, that compare combinations of chemotherapy, PD1 therapy, CD40 therapy or drugs that affect the tumor associated stroma (PEGPH20).

### Myeloid-derived suppressor cells:

Myeloid-derived suppressor cells (MDSCs) are a heterogenous group of immature immune cells originating from the myeloid lineage.[58] They are typically classified as being monocytic or granulocytic based on mouse model data, though due to the differences in immune markers between mice and humans as well as within different mouse model systems, exactclassification remains difficult.[58] A hallmark of MDSCs is their ability to suppress the functions of T and NK cells through the production of immunosuppressive cytokines that shield the tumor from the patient's immune system.[59] Due to these suppressive functions, MDSCs are increasingly recognized as a barrier to effective

immunotherapy.[60] MDSCs are difficult to target due to their heterogeneity and there are limited agents that interfere with their function. Approaches using a TLR8 agonist, which induces cell death in monocytic MDSCs, failed in head and neck cancer, [61] and subsequent clinical trials in pancreatic cancer were terminated.[62] HuMax-IL8 (BMS-986253), a human monoclonal antibody that inhibits interleukin-8 (IL-8), a chemokine that promotes recruitment of myeloid-derived suppressor cells was deemed safe and well tolerated in a Phase I trial of 15 patients with metastatic or unresectable locally advanced solid tumors.[63] It is currently in Phase II trials in liver cancer, but has not been tested in clinical trials for PDAC patients yet and much remains to be discovered regarding MDSC targeting.

### CXCR2- tumor associated neutrophils:

The role of tumor associated neutrophils (TANs) in pancreatic cancer is progressing. Human PDAC have significant elevation of TAN-related genes which are associated with poor prognosis. [64] The chemokine receptor CXCR2 attracts TANs into tumors and CXCR2 inhibitors represents a tractable therapeutic target.[64] TANs inhibit T cell function through multiple mechanisms and combined inhibition of CXCR2 and PD1 in preclinical mouse models with established disease demonstrated significant extension of survival.[64] Similarly, dual targeting of $CCR2^{+}$ macrophages and $CXCR2^{+}$ neutrophils in mice improved antitumour immunity and chemotherapeutic response in PDAC compared with either strategy alone.[65] An early clinical trial evaluated the combination of the PDL1 antibody, durvalumab and an oral CXCR2 inhibitor (AZD5069) in previously treated pancreatic cancer patients. Among the 18 subjects enrolled, there was a low response rate (1 of 18 responders) and median PFS of only 1.6 months.[66] Further studies are needed to determine if additional combinations or targets in this pathway may provide greater benefit.

### B cell targeted therapy:

An overabundance of B cells in human pancreatic intraepithelial neoplasia (PanIN) and PDAC lesions as well as in oncogenic K-Ras-driven murine pancreatic neoplasms has suggested the potential significance of B cells as a therapeutic target.[67] Inhibitors against Bruton tyrosine kinase (BTK), a key B-cell and macrophage kinase are already in use in hematological cancers. Preclinical data showed BTK inhibitors restored T cell-dependent antitumor immune responses, thereby inhibiting PDAC growth.[68,69] Because of this, clinical trials explored the use of BTK inhibitors with PD1 inhibitors or chemotherapy in PDAC. A Phase II multicenter, open-label, randomized study (NCT02362048) evaluated the BTK inhibitor, acalabrutinib alone or in combination with pembrolizumab in PDAC.[70] Limited efficacy results are available, the treatment did not lead to substantial activity with no responses among 29 evaluable subjects in the monotherapy arm and 11% response rate (3 of 27) in the combination arm.[71] Another BTK inhibitor, ibrutinib, was evaluated in a Phase III study in combination with nab-paclitaxel and gemcitabine for the first-line treatment of patients with metastatic pancreatic cancer (RESOLVE study). This study randomized 424 subjects to receive ibrutinib or placebo plus chemotherapy, final results have recently been reported without benefit in overall survival from adding ibrutinib.[72] These negative studies demonstrate the challenge of finding therapeutic immune targets in PDAC but will inform future clinical development of these and related pathways. In addition to the studies

reviewed here, many other targeted agents and immunotherapies have been evaluated in recently completed or ongoing studies including many listed in Table 1.

## Current Outlook

Over the past several years, significant resources have been dedicated to understanding the genetic and molecular mechanisms driving PDAC, which has enabled clinical investigators to design early phase translational clinical trials targeting specific elements in PDAC biology. Single agent targeted therapy is not curative, and resistance mechanisms are common. Targeted therapeutics exploiting nutritional dependencies of pancreatic cancer remain promising but will likely require combinations with our currently approved therapeutics.

Modulating the immune microenvironment is a delicate task as disruption of one population is often associated with a compensatory response in a related population.[65] Combination trials using different immunotherapeutic agents with or without chemotherapy are necessary for therapeutic effectiveness. However, finding the correct combination remains difficult as few preclinical studies incorporate combinations and there is uncertainty regarding which preclinical model has the best predictive potential for patients. Ultimately, promising therapies will have to prove efficacy in advanced clinical trials and correlative studies are critical for interpreting results that diverge from preclinical predictions. As discussed in this review, despite targeting pathways with strong rationale, several early and late stage trials have failed to show benefit in PDAC. These include a large Phase III study of pegylated IL-10 which was tested in combination with FOLFOX chemotherapy, but failed to improve overall survival compared to chemotherapy alone.[73,74] Understanding the immune effects of currently approved chemotherapy may help guide these combinations, as will aggressive preclinical modeling and correlative studies. Despite the failure of PD1 inhibitors alone, there remains intense interest in exploring combination therapy with potential relevance to the many other PD1 refractory cancers.

Despite these challenges, it is notable that the FDA has approved a targeted agent (PARP inhibitors in *BRCA* mutated patients) and an immunotherapy drug (pembrolizumab in MSI-high tumors) in PDAC patients. Clinical trials are needed to refine and expand on these successes, while simultaneously exploring novel therapeutic pathways as summarized in this review. Several promising targets have failed in recent late clinical trials and ongoing preclinical investigation is critical to determine the most promising strategies and combinations. There is room for optimism that these ongoing efforts will yield clinically meaningful options and change outcomes for patients with pancreatic cancer.

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**Table 1:**

Clinical Trials in Progress

| Title | Start Date | Therapy Target | Primary Endpoint | Number Enrolled | Status | Clinical Trial Registry Number |
|---|---|---|---|---|---|---|
| 5-fluorouracil, oxaliplatin and dasatinib (FOLFOX-D) for previously untreated metastatic pancreatic adenocarcinoma. | 2012 | BCR-ABL, SRC | PFS | 44 | Active, not recruiting | NCT01652976 |
| A Phase 1, Open-Label Dose Escalation First-in-Human Study to Evaluate the Tolerability, Safety, Maximum Tolerated Dose, Preliminary Clinical Activity and Pharmacokinetics of AM0010 in Patients With Advanced Solid Tumors | 2013 | IL-10 | Safety and tolerability as measured by incidence of adverse events | 350 | Active, not recruiting | NCT02009449 |
| Phase I study of veliparib with gemcitabine and radiation therapy in patients with borderline resectable and locally advanced unresectable pancreatic cancer. | 2013 | PARP | MTD | 34 | Active, not recruiting | NCT01908478 |
| A phase I trial with cohort expansion of BYL719 in combination with gemcitabine and nab-paclitaxel in locally advanced and metastatic pancreatic cancer. | 2014 | PIK3CA | MTD | 15 | Active, not recruiting | NCT02155088 |
| A Phase 1/II Study of the Safety, Immunopharmacodynamics and Anti-tumor Activity of Ibrutinib Combined With Gemcitabine and Nab-Paclitaxel in Patients With Metastatic Pancreatic Adenocarcinoma | 2015 | IL-10 | MTD | 18 | Active, not recruiting | NCT02562898 |
| A pilot study of immune checkpoint inhibition (tremelimumab and/or MEDI4736) in combination with radiation therapy in patients with unresectable pancreatic cancer. | 2015 | PD1, CTLA4 | Safety, tolerability, and efficacy | 61 | Active, not recruiting | NCT02311361 |
| Phase I/IB multicenter study of afatinib in combination with capecitabine in patients (pts) with refractory solid tumors and pancreatico-biliary cancers. | 2015 | BCR-ABL, SRC | Safety and RP2D | Estimated 48 | Recruiting | NCT02451553 |
| A Phase 1/2 Feasibility, Safety, and Activity Study of PSCA-Specific Chimeric Antigen Receptor Engineered T Cells (BPX-601) in Subjects With Previously Treated Advanced Solid Tumors | 2016 | CAR-T | Dose limiting toxicity, and adverse events | Estimated 151 | Recruiting | NCT02744287 |
| Phase I study of defactinib combined with pembrolizumab and gemcitabine in advanced cancer. | 2016 | FAK, PYK2 | RP2D | 43 | Active, not recruiting | NCT02546531 |
| A phase II pilot trial of nivolumab + albumin bound paclitaxel + paricalcitol + cisplatin + gemcitabine (NAPPCG) in patients (pts) with previously untreated metastatic pancreatic ductal adenocarcinoma. | 2016 | PD1, Vitamin D | CR, ORR, PFS, and OS | Estimated 10 | Recruiting | NCT02754726 |
| A pilot study to assess the efficacy, safety, and pharmacodynamic effects of pembrolizumab and BL-8040 in patients with metastatic pancreatic cancer. | 2016 | CXCR4 | ORR | Estimated 23 | Active, not recruiting | NCT02907099 |
| Phase II Randomized Trial of mFOLFIRINOX +/− Ramucirumab in Advanced Pancreatic Cancer | 2016 | VEGF | PFS | Estimated 95 | Active, not recruiting | NCT02581215 |
| Phase I Study of Human Chimeric Antigen Receptor Modified T Cells (CAR T Cells) in Patients With Pancreatic Cancer | 2017 | CAR-T | Incidence of treatment-related | Estimated 18 | Recruiting | NCT03323944 |

| Title | Start Date | Therapy Target | Primary Endpoint | Number Enrolled | Status | Clinical Trial Registry Number |
|---|---|---|---|---|---|---|
| | | | adverse events | | | |
| Phase Ib Trial of CAR-T Hepatic Artery Infusions or Pancreatic Venous Infusions Delivered With the Surefire Infusion System (SIS) for CEA-Expressing Liver Metastases or Pancreas Cancer | 2017 | CAR-T | Safety | Estimated 5 | Active, not recruiting | NCT02850536 |
| A Phase I/II Study Administering Peripheral Blood Lymphocytes Transduced With a CD70-Binding Chimeric Antigen Receptor to Patients With CD70 Expressing Cancers | 2017 | CAR-T | MTD and ORR | Estimated 113 | Recruiting | NCT02830724 |
| Randomized Phase III Study of AM0010 in Combination With FOLFOX Compared to FOLFOX Alone as Second-line Tx in Pts With Meta Pancreatic Cancer That Has Progressed During or Following a First-Line Gemcitabine Containing Regimen | 2017 | IL-10 | OS | Estimated 566 | Active, not recruiting | NCT02923921 |
| A randomized phase II study of cabiralizumab (cabira) + nivolumab (nivo) ± chemotherapy (chemo) in advanced pancreatic ductal adenocarcinoma (PDAC). | 2017 | CSFR2, PD1 | Median PFS | Estimated 160 | Recruiting | NCT03336216 |
| An open-label, phase II study of intravenous anetumab ravtansine, an anti-mesothelin antibody drug conjugate, in pretreated mesothelin-expressing advanced pancreatic cancer | 2017 | Mesothelin | ORR | Estimated 18 | Active, not recruiting | NCT03023722 |
| A phase 1b (open-label)/phase 2 (randomized, double-blinded) study evaluating nab-paclitaxel and gemcitabine with or without olaratumab in first-line treatment of metastatic pancreatic cancer | 2017 | PDGFRa | OS | Estimated 186 | Recruiting | NCT03086369 |
| MORPHEUS: A Phase Ib/II study platform evaluating the safety and clinical efficacy of cancer immunotherapy (CIT)–based combinations in gastrointestinal (GI) cancers. | 2017 | Various | Safety and ORR | Estimated 205 | Recruiting | NCT03193190 |
| Phase II open-label, single-center study evaluating safety and efficacy of pembrolizumab following induction with the hypomethylating agent azacitidine in patients with advanced pancreatic cancer after failure of first-line therapy. | 2017 | PD1, DNA methyltransferase | PFS | Estimated 31 | Recruiting | NCT03264404 |
| A single arm phase II study of rucaparib maintenance in patients with advanced pancreatic adenocarcinoma and a known deleterious BRCA1, BRCA2 or PALB2 mutation who have achieved stability on platinum therapy. | 2017 | PARP | PFS at 6 months | Estimated 42 | Recruiting | NCT03140670 |
| Immunotherapy for Peritoneal Carcinomatosis (IPC) - A Phase I Study of the Safety and Efficacy of Anti-CEA CAR-T Cell Intraperitoneal Infusions for Treatment of CEA-Expressing Adenocarcinoma Peritoneal Metastases or Malignant Ascites | 2018 | CAR-T | Safety | Estimated 18 | Active, not recruiting | NCT03682744 |
| NANT cancer vaccine an orchestration of immunogenic cell death by overcoming immune suppression and activating NK and T cell therapy in patients with third line or greater metastatic pancreatic cancer. | 2018 | NK, T cells | Incidence of treatment-related adverse events | Estimated 173 | Active, not recruiting | NCT03586869 |

| Title | Start Date | Therapy Target | Primary Endpoint | Number Enrolled | Status | Clinical Trial Registry Number |
|---|---|---|---|---|---|---|
| Phase 2 trial of durvalumab and radiation revaccination in patients with metastatic adenocarcinoma of the pancreas who have progressed through first-line chemotherapy. | 2018 | PD1 | PFS | Estimated 39 | Recruiting | NCT03490760 |
| Trybeca-1: A randomized, phase 3 study of eryaspase in combination with chemotherapy versus chemotherapy alone as second-line treatment in patients with pancreatic adenocarcinoma | 2018 | Asparagine | OS | Estimated 500 | Not Yet Recruiting | NCT03665441 |
| Avenger 500, a phase III open-label randomized trial of the combination of CPI-613 with modified FOLFIRINOX (mFFX) versus FOLFIRINOX (FFX) in patients with metastatic adenocarcinoma of the pancreas. | 2018 | Pyruvate dehydrogenase, A-ketoglutarate dehydrogenase. | ORR and PFS | Estimated 500 | Recruiting | NCT03504423 |
| A randomized clinical trial of chemotherapy with gemcitabine/cisplatin/nabpaclitaxel with or without the AXL inhibitor bemcentinib (BGB324) for patients with advanced pancreatic cancer. | 2019 | AXL | CR | Estimated 74 | Recruiting | NCT03649321 |
| Phase 1b Study of the Efficacy and Safety of CAR2 Anti-CEA CAR-T Cell Hepatic Infusions for Pancreatic Carcinoma Patients With CEA+ Liver Metastases Resistant to Standard Therapy Using the HITM Method and Pressure Enabled Delivery Device | 2019 | CAR-T | OS | Estimated 6 | Active, not recruiting | NCT03818165 |

Legend: PFS = Progression free survival, Maximum tolerated dose (MTD), ORR= overall response rate, CR= complete response, OS= overall survival, RP2D= recommended phase II dose

**Table 2:**

Completed Immunotherapy Trials

| Title | Start Date | Phase | Target | Primary Endpoint | Number Enrolled | Status | Clinical Trial Registry Number | Result |
|---|---|---|---|---|---|---|---|---|
| Vaccine Therapy Combined With Adjuvant Chemoradiotherapy in Treating Patients With Resected Stage I or Stage II Adenocarcinoma of the Pancreas | 2002 | II | GVAX | OS and DFS | 60 | Completed | NCT00084383 | Median DFS 17.3 months (95% CI, 14.6–22.8) [75] Median OS 24.8 months (95% CI, 21.2–31.6) |
| A Safety and Efficacy Trial of Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected With the GM-CSF Gene in Combination With Cetuximab for the Treatment of Advanced Pancreatic Adenocarcinoma | 2005 | II | GVAX + EGFR | Safety (Treatment-related Grade 3 or 4 Adverse Events Observed in Greater Than 5% of the Patient Population) | 60 | Completed | NCT00305760 | Serious Adverse events in 20% of participants [76] |
| A Phase 1 Dose Escalation Open Label Study Of CP-870,893 In Combination With Gemcitabine In Patients With Chemotherapy-Naïve Surgically Incurable Pancreatic Cancer | 2008 | I | CD40 | Number of Participants With Dose Limiting Toxicities | 22 | Completed | NCT00711191 | Serious Adverse events in 9/22 participants [36,77] |
| Safety and Efficacy of Combination Listeria/GVAX Immunotherapy in Pancreatic Cancer | 2011 | II | Cy/GVAX + CRS-207 | OS | 93 | Completed | NCT01417000 | OS 6.1 months[75] |
| Phase I/II Study of Metastatic Cancer Using Lymphodepleting Conditioning Followed by Infusion of Anti-mesothelin Gene Engineered Lymphocytes | 2012 | I | CAR-T: anti-mesothelin | ORR Serious and Non-serious Adverse Events | 15 | Terminated | NCT01583686 | ORR 0% Study did not proceed to Phase II. [78] |
| Phase IB Study of FOLFIRINOX Plus PF-04136309 in Patients With Borderline Resectable and Locally Advanced Pancreatic Adenocarcinoma | 2012 | Ib | CCR2 | RP2D and DLT | 47 | Completed | NCT01413022 | Combination was safe and tolerable |
| A Phase 2, Multicenter Study of FOLFIRINOX Followed by | 2013 | II | CTLA4+ GVAX | OS | 83 | Completed | NCT01896869 | No Results Posted-Completed 5/2019[79] |

| Title | Start Date | Phase | Target | Primary Endpoint | Number Enrolled | Status | Clinical Trial Registry Number | Result |
|---|---|---|---|---|---|---|---|---|
| Ipilimumab With Allogenic GM-CSF Transfected Pancreatic Tumor Vaccine in the Treatment of Metastatic Pancreatic Cancer | | | | | | | | |
| Phase I Clinical Trial of Autologous Mesothelin Re-directed T Cells in Patients With Chemotherapy Refractory Metastatic Pancreatic Cancer | 2013 | I | CAR-T: anti-mesothelin | Adverse Events as a Measure of Safety and Tolerability. | 16 | Completed | NCT01897415 | No Results Posted-Completed 3/2017[80] |
| A Phase IIB, Randomized, Controlled, Multicenter, Open-Label Study of the Efficacy and Immune Response of GVAX Pancreas Vaccine (With Cyclophosphamide) and CRS 207 Compared to Chemotherapy or to CRS-207 Alone in Adults With Previously-Treated Metastatic Pancreatic Adenocarcinoma | 2014 | IIB | GVAX/ CRS-207 | OS | 303 | Completed | NCT02004262 | The combination of Cy/GVAX + CRS-207 did not improve survival over chemotherapy. [37] |
| Phase I Study of Neo-adjuvant RO7009789 Alone or Neo-adjuvant RO7009789 Plus Nab-Paclitaxel and Gemcitabine Followed by Adjuvant RO7009789 Plus Nab-Paclitaxel and Gemcitabine for Patients With Newly Diagnosed Resectable Pancreatic Carcinoma | 2015 | I | CD40 | Adverse Events as a Measure of Safety and Tolerability | 10 | Completed | NCT02588443 | No Results Posted-Completed 11/2018[81] |
| A Multi-Center Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination With Durvalumab (MEDI4736), in Subjects With Relapsed or Refractory Solid Tumors | 2015 | I/II | BTK/PD1 | Adverse Events ORR | 44 | Completed | NCT02403271 | 2% ORR[82] |

| Title | Start Date | Phase | Target | Primary Endpoint | Number Enrolled | Status | Clinical Trial Registry Number | Result |
|---|---|---|---|---|---|---|---|---|
| Pilot Study of Autologous T-cells Redirected to Mesothelin and CD19 With a Chimeric Antigen Receptor in Patients With Metastatic Pancreatic Cancer | 2015 | I | CAR-T: anti-mesothelin, anti-CD19 | Safety | 4 | Terminated | NCT02465983 | Terminated. No results posted. [83] |
| Phase Ib Trial of CAR-T Hepatic Artery Infusions Followed by Selective Internal Radiation Therapy (SIRT) With Yttrium-90 Sir-Spheres for CEA-Expressing Liver Metastases | 2015 | I | Yttrium-90 Sir-Spheres with anti-CEA CAR-T | Safety as Measured by Number of Participants with AE | 8 | Completed | NCT02416466 | No Results Posted-Completed 6/2018[84] |
| Phase 1B/2 Study Of PF-04136309 In Combination With Gemcitabine and Nab-Paclitaxel in Patients with Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma | 2016 | Ib/II | CCR2 | Number of Participants with DLT, Number of Participants With Treatment-Emergent AE, PFS | 22 | Terminated | NCT02732938 | ORR of 23.8%. High incidence of pulmonary toxicity (24%), 3 of 17 subjects (17.6%) had DLT.[85] |
| A Dose Escalation Phase I Study With an Extension Part Evaluating the Safety and Activity of an Anti-PDL1 Antibody (Durvalumab) Combined With a Small Molecule CSF-1R Tyrosine Kinase Inhibitor (Pexidartinib) in Patients With Metastatic/Advanced Pancreatic or Colorectal Cancers | 2016 | I | PDL-1, CSF1R | DLT, ORR | 48 | Completed | NCT02777710 | No Results Posted-Completed 12/2019[86] |
| Phase IB Study Investigating the Tolerability, Immunomodulatory Impacts and, Therapeutic Correlates of the Novel Toll-like Receptor 8 Agonist Motolimod Plus Cyclophosphamide Treatment of Advanced Solid Tumors | 2016 | I | TLR-8, MDSC | Change in pharmacodynamics after drug administration | 4 | Terminated | NCT02650635 | Permanently closed per sponsor's request[87] |

Legend: PFS = Progression free survival, Maximum tolerated dose (MTD), ORR= overall response rate, CR= complete response, OS= overall survival, RP2D= recommended phase II dose, DFS= Disease Free survival, DLT= Dose limiting toxicity, AE= Adverse events

**Table 3:**

Completed Targeted Therapy Clinical Trials

| Title | Start Date | Phase | Therapy Target | Primary Endpoint | Number Enrolled | Status | Clinical Trial Registry Number | Result |
|---|---|---|---|---|---|---|---|---|
| A Novel Biomarker Panel Examining Response to Gemcitabine with or without Erlotinib for Pancreatic Cancer Therapy in NCIC Clinical Trials Group PA.3 | 2001 | III | EGFR | OS | 569 | Completed | NCT00040183 | **positive** mOS (control vs combo) of 5.91 vs 6.24 months (HR=0.82, p= 0.038); 1yr OS 17% vs 23%[88] |
| Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205 | 2004 | III | EGFR | OS | 745 | Completed | NCT00075686 | **negative** mOS (control vs combo) of 5.9 vs 6.3 months (HR= 1.06, p=0.23, one-sided)[89] |
| Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer | 2005 | III | VEGF-A EGFR | OS | 607 | Completed | NCT01214720 | **negative** mOS (control vs combo) was 7.1 vs 6.0 months (HR= 0.89, p= 0.2087)[90] |
| Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer | 2007 | III | VEGFR1 | OS | 546 | Terminated | NCT00574275 | **negative- stopped early for futility** mOS (control vs combo) was 7.8 vs 6.5 months (HR 1.165, p=0.2034).[91] |
| Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study | 2007 | III | VEGFR1VEGFR2 VEGFR3 | OS | 632 | Completed | NCT00471146 | **negative** mOS (control vs combo) of 8.5 vs 8.3 months (HR=1.014, p=0.5436, one sided)[92] |
| A randomized, placebo-controlled phase III trial of masitinib plus gemcitabine in the treatment of advanced pancreatic cancer | 2008 | III | c-Kit, PDGFR FGFR3 FAK | OS | 353 | Completed | NCT00789633 | **negative** mOS (control vs combo) of 7.7 vs 7.1 months (HR=0.89, p= 0.695)[93] |
| A phase II/III randomized study to compare the efficacy and safety of | 2011 | II/III | PLK1 PI3K | OS | 160 | Completed | NCT01360853 | **negative** mOS (control vs combo) of 6.1 vs 6.4 months |

| Title | Start Date | Phase | Therapy Target | Primary Endpoint | Number Enrolled | Status | Clinical Trial Registry Number | Result |
|---|---|---|---|---|---|---|---|---|
| rigosertib plus gemcitabine versus gemcitabine alone in patients with previously untreated metastatic pancreatic cancer | | | | | | | | (HR=1.24, p not reported)[94] |
| A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas: the GAMMA trial | 2011 | III | IGFR | OS | 640 | Terminated early | NCT01231347 | **negative** mOS (control vs combo) was 7.2 vs 7.0 months. (HR=1.00, p=0.494).[95] |
| A Phase III, Open Label, Multicentre Randomised Clinical Study comparing Acelarin (NUC-1031) With Gemcitabine in Patients With Metastatic Pancreatic Carcinoma | 2015 | II/III | dFdCTP | OS | 328 | Suspended | NCT03610100 | Suspended to recruitment following review on efficacy and toxicities[96] |

Legend: OS= overall survival, HR= Hazard ratio