Immunologic Strategies in Pancreatic Cancer: Making Cold Tumors Hot
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The rising incidence and persistent dismal 5-year overall survival of pancreatic ductal adenocarcinoma (PDAC) highlight the need for new effective systemic therapies. Immunotherapy has shown significant benefits in solid organ tumors, but has thus far been disappointing in the treatment of PDAC. There have been several promising preclinical studies, but translation into the clinic has proved to be challenging. This is likely a result of PDAC’s complex immunosuppressive tumor microenvironment that acts to insulate the tumor against an effective cytotoxic immune response. Here, we summarize the mechanisms of immunosuppression within the PDAC tumor microenvironment and provide an up-to-date review of completed and ongoing clinical trials using various immunotherapy strategies.

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KEY POINTS
• Pancreatic adenocarcinoma possesses several intrinsic and extrinsic properties that insulate malignant cells from an effective adaptive immune response.
• Thus far, no single immunotherapy strategy has proved to be effective, warranting investigation of combination approaches to improve efficacy.
• Ongoing clinical trials evaluating combination immunotherapy strategies will demonstrate the role of immunotherapy in the treatment of pancreatic adenocarcinoma.

INTRODUCTION
Pancreatic ductal adenocarcinoma (PDAC) is projected to become the second leading cause of cancer-related mortality by 2030.1 Despite modest advances in conventional systemic therapies, the 5-year overall survival (OS) for PDAC remains a dismal 11%,2 in part because of its advanced stage at presentation precluding curative-intent resection and a high propensity for recurrence. Traditional fluorouracil- or gemcitabine-based chemotherapies, with or without radiation, are standard of care for patients with unresectable disease,3 however, development of more effective systemic therapies remains a significant unmet clinical need.

Advances in immunotherapies, specifically immune checkpoint blockade (ICB), have improved treatment options for some historically chemotherapy-refractory malignancies. In the past 10 years, ICB has shown efficacy in metastatic melanoma, renal cell carcinoma, colorectal cancers with microsatellite instability, non–small-cell lung cancer, Hodgkin’s lymphoma, and various other cancers.4-7 Anti–programmed death-1 (anti–PD-1) with or without anti–cytotoxic T-cell lymphocyte-4 therapy is now the standard of care for patients with advanced melanoma.8 Despite the successes of ICB, PDAC has been largely refractory to ICB monotherapy.9 Studies of single-agent ICB and dual-agent ICB with anti–PD-1 and anti–cytotoxic T-cell lymphocyte-4 antibodies have resulted in overall response rates (ORRs) of 0%10-12 and 3%, respectively.12 These disappointing results, contrasted with the marked effectiveness of ICB in other solid tumors, have influenced a body of research to identify and harness immunologic pathways that could be key to unlocking immunotherapy as a viable treatment option for the typically immunologically cold pancreatic cancer. Here, we summarize the mechanisms of immunosuppression within the PDAC tumor...
microenvironment (TME) and provide an up-to-date review of promising immunotherapy strategies.

**PDAC-INTRINSIC PROPERTIES LEADING TO IMMUNE EVASION**

PDAC possesses several intrinsic properties that result in evasion of an effective immune response (Fig 1). In general, tumor-specific antigens (TSAs) are expressed only on malignant cells, thus providing excellent specificity for antitumor T-cell cytotoxicity, with antigen strength correlating with the level of antitumor immune response.13-17 Retrospective data of surgically resected specimens suggest a survival advantage in the minority of patients whose tumors exhibit high levels of both TSAs and CD8+ T-cell infiltrate.18 Despite this association, CD8+ T cells demonstrate decreased interferon-gamma and other activation markers, indicating other immunosuppressive factors at play.19

PDAC oncogenes and their downstream effects contribute to the immunosuppressive TME. Mutated KRAS, resulting in constitutive activation, is found in 92% of pancreatic cancer20 and is associated with several downstream effects including production of granulocyte-macrophage colony-stimulating factor (GM-CSF), leading to recruitment of immunosuppressive myeloid cells21; promotion, formation, and maintenance of the fibroinflammatory stroma22; upregulation of programmed death ligand-1 (PD-L1) expression through mRNA stabilization23; increased CD73 expression leading to elevated immunosuppressive extracellular adenosine24; downregulation of major histocompatibility complex-1 and increasing regulatory T cells (Tregs)25; and induction of immunosuppressive Th17 and gamma-delta T cells.26

In addition to immunosuppressive oncogenes, PDAC cells possess variable mechanisms that impair antigen presentation and cytotoxic lymphocyte (CTL) function. PDAC cells selectively target major histocompatibility complex-1 molecules for lysosomal degradation through an autophagy-dependent mechanism.27 Preclinical inhibition of autophagy with hydroxychloroquine resulted in decreased tumor growth28 and synergized with dual ICB to enhance antitumor immune response.27 In addition, PDAC cells contain a high proportion of CD47 that prevents phagocytosis and antigen presentation by antigen-presenting cells (APCs).29 Anti-CD47 antibody-mediated phagocytosis of cancer cells by macrophages results in increased priming of CD8+ T cells and reduced immunosuppressive Tregs.30 PDAC cells also produce indoleamine 2,3-dioxygenase (IDO) to catalyze the degradation of tryptophan, a necessary component of cytotoxic T-cell survival and activation, thereby inducing T-cell apoptosis and anergy.31 Furthermore, PDAC cells downregulate the expression of human leukocyte antigen-DR isotype and CD40, resulting in immature dendritic cells (DCs) capable of directly suppressing effector CD8+ T cells.32 Overall, PDAC’s intrinsic immunosuppressive properties afford several mechanisms to subvert the normal host immune response, posing unique challenges to immunotherapeutic drug development in this tumor type.

**THE IMMUNOSUPPRESSIVE PDAC MICROENVIRONMENT**

**Stromal Components—Cancer-Associated Fibroblasts and the Desmoplastic Reaction**

Although PDAC cells have intrinsic properties leading to immune evasion, their interaction with the surrounding TME poses a larger, more complex barrier to effective immunotherapy strategies (Fig 2). The histologic hallmark of PDAC is a heavily desmoplastic microenvironment that accounts for approximately 70% of tumor tissue, with increased fibrosis shown to be an independent prognostic factor.33,34 Pancreatic stellate cells (PSCs; activated PSCs have been referred to as cancer-associated fibroblasts [CAFs]) produce this fibrotic environment and exhibit several factors that promote tumorigenesis and abrogate antitumor immunity.35
The marked desmoplasia results in elevated interstitial fluid pressure limiting perfusion and diffusion of small molecule therapies secondary to intratumoral small vessel collapse. The associated hypoperfusion produces an overall hypoxic environment resulting in a Treg-mediated CD8+ T-cell inhibition. Preclinical work targeting hyaluronic acid (HA) through enzymatic degradation resulted in normalization of interstitial fluid pressure and permanent remodeling of the TME, leading to doubled OS when paired with chemotherapy. Beyond the physical barrier, CAFs appear to limit the migration of CTLs to the juxtatumoral stromal compartments through hyperactivation of focal adhesion kinase (FAK) and overproduction of C-X-C Motif Chemokine Ligand 12 (CXCL12), a ligand of C-X-C Motif Chemokine Receptor 4 (CXCR4), overall inhibiting T-cell priming. Preclinical models of FAK inhibition limited tumor progression, doubled survival, decreased immunosuppressive cells, and synergized with ICB therapy. In addition, the use of a CXCR4 antagonist increased CD8+ T-cell accumulation and acted synergistically with anti–PD-L1 antibody to decrease tumor burden in preclinical models. CAFs are capable of diminishing CTL function through secretion of soluble substances such as interleukin-10 (IL-10), transforming growth factor-β, vascular endothelial growth factor, prostaglandin E1, IDO, arginase, and expression of PD-L1. In addition to their interaction with CTLs, CAFs interact with immunosuppressive myeloid cells through secretion of inflammatory cytokines such GM-CSF, IL-6, vascular endothelial growth factor, prostaglandin E1, IDO, arginase, and expression of PD-L1. In addition to their interaction with CTLs, CAFs interact with immunosuppressive myeloid cells through secretion of inflammatory cytokines such GM-CSF, IL-6, vascular endothelial growth factor, prostaglandin E1, IDO, arginase, and expression of PD-L1. In addition to their interaction with CTLs, CAFs interact with immunosuppressive myeloid cells through secretion of inflammatory cytokines such GM-CSF, IL-6, vascular endothelial growth factor, prostaglandin E1, IDO, arginase, and expression of PD-L1. In addition to their interaction with CTLs, CAFs interact with immunosuppressive myeloid cells through secretion of inflammatory cytokines such GM-CSF, IL-6, vascular endothelial growth factor, prostaglandin E1, IDO, arginase, and expression of PD-L1. In addition to their interaction with CTLs, CAFs interact with immunosuppressive myeloid cells through secretion of inflammatory cytokines such GM-CSF, IL-6, vascular endothelial growth factor, prostaglandin E1, IDO, arginase, and expression of PD-L1.
FIG 2. The highly immunosuppressive tumor microenvironment of pancreatic ductal adenocarcinoma. Pancreatic tumor cells, myeloid cells (Mo-MDSCs, TAMs, and Gr-MDSCs), and fibroblasts within the tumor microenvironment interact through various ligands, cytokines, and chemokines that disrupt antitumor immunity. CAF, cancer-associated fibroblasts; GM-CSF, granulocyte-macrophage colony-stimulating factor; Gr-MDSC, granulocytic MDSC; IL, interleukin; MDSC, myeloid-derived suppressor cell; Mo-MDSC, monocytic MDSC; PD-L1, programmed death ligand-1; PDAC, pancreatic ductal adenocarcinoma; TAM, tumor-associated macrophage; TGF, transforming growth factor; Treg, regulatory T-cell; VEGF, vascular endothelial growth factor.
phenotype. This complex interaction between tumor cells, CAFs, T cells, and myeloid cells underscores the intertwined protumor mechanisms within the various components of the TME.

**Cellular Components**

**Myeloid cells.** The PDAC TME is characterized by a robust immune infiltrate, which comprises nearly 50% of its cellular component and is largely composed of CD45+ bone marrow–derived immune cells.16,22,45 PDAC induces an altered state of myelopoiesis, recruitment, and repolarization of these cells to promote their accumulation and immunosuppressive properties within the TME.46,47 These intratumoral MDSCs are composed of myeloid progenitors and immature mononuclear cells, referred to as granulocytic MDSC (Gr-MDSCs) and monocytic MDSC, respectively. Tumor-associated macrophages (TAMs), in contrast to MDSCs, are mature cells derived from either the bone marrow or resident tissue macrophages.48,49 Elevated peripheral and intratumoral levels of inflammatory myeloid cells have been associated with poor clinical outcomes.50-52

TAMs are dominated by an M2 phenotype, virtually eliminating an M1 (antitumor phenotype) response. M2 TAMs produce IL-10 that maintains functional Treg populations and drive the development of Th2 cells, which secrete IL-4 and potentiate the development of additional TAMs.53 Inhibiting IL-10 resulted in increased IL-12 secretion from DCs and led to improved CTL infiltration and response to chemotherapy.54 TAMs can also directly induce T-cell apoptosis through their expression of PD-L154 and Dectin-1/galectin-9 axis55 and inhibit CTLs through production of arginase-1–depriving cytotoxic effector T cells of L-arginine, a key nutrient to support viability and expansion.51

Similar to TAMs, MDSCs deplete micronutrients through arginase-1–dependent consumption and L-cysteine sequestration to downregulate the T-cell receptor complex (TCR) and cause proliferative arrest of antigen-activated T cells.47 Furthermore, MDSCs are potent generators of reactive oxygen and nitrogen species that impair TCR activity and interfere with IL-2, a potent proinflammatory cytokine.51 In addition to TCR disruption, MDSCs have the ability to cause T-cell apoptosis, inhibit natural killer cells, and increase the activation and expansion of Tregs. Genetic ablation of CXCR2, a chemokine receptor found predominantly on Gr-MDSCs, led to increased T-cell infiltration into the tumor stroma.56 In an orthotopic model, inhibition of MDSCs via CXCR2 blockade led to decreased MDSCs within the TME, decreased fibrosis, and acted synergistically with ICB.57

Preclinical studies have identified a potential mechanism of resistance to TAM-targeted therapy by a compensatory increase in CXCR2+ Gr-MDSCs; dual inhibition of both TAMs and Gr-MDSCs demonstrated increased survival.58 Modulation of the myeloid receptor CD11b reduced intratumoral TAMs and MDSCs, repolarized M2 TAMs to an antitumor M1 phenotype, and increased infiltration of activated CD8+ T cells in preclinical models. When combined with anti–PD-1 antibody or chemotherapy, these immunomodulatory effects translated into potent antitumor effects and prolonged survival in orthotopic PDAC murine models.59 It is evident through a variety of mechanisms that PDAC co-opts myeloid cell pathways to render a cytotoxic T-cell response ineffective and thus requires consideration when developing immunotherapy strategies for this disease.

**Dendritic cells.** Conventional dendritic cells (cDCs) are professional APCs adept at presenting exogenous and/or endogenous antigens to T cells. Recruitment, retention, and spatial positioning of cDCs within the TME are limited by PDAC-derived proinflammatory cytokines and resulting immunosuppressive myeloid infiltrate.60 Reduced cDC concentrations appear to be influenced by high levels of cyclooxygenase 1 and 2 and decreased levels of locally available cDC growth factors such as the natural killer cell–producing fms-like tyrosine kinase 3 ligand (FLT3L).61 Soluble inhibitory factors not only work to exclude cDCs but also to limit their function as APCs. TAM- and Treg-generated IL-10 suppresses cDC production of IL-12, a costimulatory molecule necessary to mount an adaptive immune response.62 cDCs are also subject to increasing apoptosis secondary to increased levels of IL-6.63 Combination therapy with a CD40 agonist (a stimulatory ligand for T-cell activation) and FLT3L restored cDC abundance, improved tumor infiltration, and resulted in superior control of tumor outgrowth in a preclinical model.64

**B cells.** Recent studies have linked B cells to PDAC as reselenium human PDAC exhibited increased CD20 and Ig expression relative to normal pancreas,65 whereas depletion of B cells with anti-CD20 monoclonal antibodies inhibited progression of pancreatic intraepithelial neoplasia preclinically.53

**T cells.** Although a relative minor component of the PDAC immune infiltrate, the T-cell infiltrate exhibits both anti- and protumor immunologic effects and includes effector CD8+, CD4+ (both Th1 and Th2 helper cells), FoxP3+ Tregs, Th17+, and γδ T cells. There is a relative paucity of cytotoxic effector CD8+ T cells within the TME, comprising <7% of the total leukocyte infiltrate.64 In addition to their limited presence, these effector cells are often functionally deficient as they express various coinhibitory molecules.64 CD4+ helper T cells are found with greater frequency within the TME relative to CD8+ T cells and display a tumor-promoting Th2 phenotype.65 Although less frequent than Th2 cells, Treg density increases with disease progression and has been found to correlate with lymph node metastases and poor survival.66,67 PDAC cells produce a host of cytokines that are associated with Treg migration and accumulation including CCL5,68 transforming growth factor-β, and IL-10.69 These immunosuppressive T cells possess several protumor immunologic effects including restraint of
tumor-associated DC expansion and suppression of the costimulatory ligands CD86 and CD40, which are necessary for CD8+ T-cell activation\(^{32}\) and promotion of local immune suppression.\(^{70,71}\) Eliminating Tregs in a preclinical model allowed DCs to induce a potent antitumor immune response that was CD8+ dependent.\(^{52}\) However, Treg depletion in a spontaneous murine model did not affect CD8 T-cell recruitment, suggesting that Treg elimination alone is insufficient to restore productive T-cell immunity.\(^{72}\)

The complex T-cell populations, composed of both pro- and anti-tumor cells, require selective stimulatory and inhibitory strategies to elicit an effective adaptive immune response. Although an effective CD8+ T-cell response is the final pathway of most immunotherapy regimens, PDAC possesses several mechanisms to subvert activation of adaptive immunity through ICB alone. Combination therapies are likely required to garner an effective immunotherapy regimen.

**CURRENT STRATEGIES FOR IMMUNOTHERAPY**

**Stromal Targeting**

Strategies disrupting components of the desmoplastic PDAC stroma have been met with variable results. Despite preclinical success of enzymatic degradation of HA using pegvoryluronicidase (PEGPH20), its addition to gemcitabine/nab-paclitaxel was evaluated in the phase III HALO 109-301 trial of patients with HA-high PDAC and demonstrated a slight increase in ORR, 47% versus 36% (ORR ratio, 1.29 [95% CI, 1.03 to 1.63]), but no change in OS (hazard ratio [HR], 1.00; 95% CI, 0.80 to 1.27; \(P = .97\)) or progression-free survival (PFS; HR, 0.97; 95% CI, 0.75 to 1.26).\(^{73}\) These disappointing results of HA-targeted therapy have led to pairing PEGPH20 with other immunotherapies, and investigations of combining PEGPH20 with ICB are ongoing (Table 1).

Another recent stromal-associated strategy includes CXCR4/CXCL12 axis disruption. The phase Iia COMBAT trial evaluated BL-8040, a CXCR4 inhibitor, in combination with anti–PD-1 therapy with or without chemotherapy in previously treated patients with metastatic PDAC. Treatment with BL-8040 resulted in decreased suppressive cell types within the TME and promotion of T-cell infiltration. The cohort treated with BL-8040 plus ICB and chemotherapy demonstrated encouraging outcomes with an ORR of 32% and a disease control rate (DCR) of 77%.\(^{74}\)

Contrasting the encouraging results of the COMBAT trial, other studies evaluating CXCR4 inhibition have resulted in poorer treatment responses. A best overall response of stable disease (SD) in three of eight patients was found with combination treatment of LY2510924 (a CXCR4 peptide antagonist) and anti–PD-L1 in patients with advanced refractory PDAC, similar to responses seen with ICB alone.\(^{75}\)

Two other stromal-targeting strategies include inhibition of FAK and the upstream Janus kinase–signal transducers and activators of transcription (JAK-STAT) signaling pathway. A phase I trial pairing defactinib, a small molecule inhibitor of FAK, and anti–PD-1 therapy with gemcitabine showed modest results with 2 of 27 and 14 of 27 patients with PDAC showing partial response (PR) or SD, respectively. Paired biopsies demonstrated increased CD8+ T-cell infiltration and proliferation, whereas Tregs, macrophages, and stromal density decreased with treatment.\(^{76}\)

The JAK-STAT pathway plays a key role in activation of PSCs.\(^{77}\) Unfortunately, the JANUS1 and JANUS 2 trials combining ruxolitinib and capcitabine showed no difference in OS (JANUS 1: HR, 0.969; 95% CI, 0.74 to 1.2; JANUS 2 HR, 1.58; 95% CI, 0.89 to 2.83) or PFS (JANUS 1: HR, 1.06; 95% CI, 0.82 to 1.35; JANUS 2: HR, 1.17; 95% CI, 0.69 to 1.98).\(^{78}\)

The ongoing phase Ib/II Morpheus trial in metastatic PDAC seeks to combine several immunotherapies in a variety of treatment settings. The trial is enrolling both pretreated and treatment-naive patients with metastatic PDAC and randomly assigns them to a variety of treatment arms including pairing atezolizumab (anti–PD-L1) with PEGPH20 or BL-8040 as second-line treatment. Of note, one arm of this trial that combined atezolizumab with cobimetinib (a MEK inhibitor) in 14 patients with refractory PDAC showed no objective responses.\(^{79}\) Although translation of stromal-targeting strategies has thus far been met with challenges, correlative studies have been insightful. Further results are pending from the Morpheus trial, which will shed light on combining stromal- and immune cell–targeting therapies.

**Myeloid Suppression/Reprogramming**

The CCL2-CCR2 chemokine axis, which plays a role in recruiting TAMs into the TME, has been a molecular pathway targeted by investigators. In a phase I study of locally advanced PDAC, the combination of PF-04136309 (an oral CCR2 inhibitor) and 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) resulted in a 49% ORR and a 97% DCR.\(^{80}\) However, an additional phase I/II study pairing the same oral CCR2 inhibitor with gemcitabine/nab-paclitaxel was terminated early because of lack of efficacy.\(^{81}\) A combinatorial CCR2/CCR5 inhibitor with or without chemotherapy and anti–PD-1 therapy trial in metastatic colorectal and PDAC has finished enrollment with awaiting results (ClinicalTrials.gov identifier: NCT03184870).

Similar to CCR2 inhibition, CSF1-R inhibition leads to disruption of TAM recruitment and repolarization to promote antigen presentation, thus increasing T-cell activation through synergizing with ICB.\(^{82}\) Unfortunately, a randomized phase II study of cabiralizumab (anti–CSF-1R) + anti–PD-1 therapy with or without chemotherapy in advanced PDAC did not meet its primary end point of increasing PFS (ClinicalTrials.gov identifier: NCT03336216). However, several studies using CSF1-R inhibitors with various combinations of chemotherapy and immunotherapy are ongoing (Table 1).
Contrasting TAM-targeted therapy, a phase I study evaluating SX-682, a CXCR2 inhibitor targeting Gr-MDSCs, in combination with anti-PD1 therapy as maintenance therapy in patients with stable unresectable PDAC after first-line chemotherapy is currently ongoing (ClinicalTrials.gov identifier: NCT04477343). In addition, dual inhibition of both TAM and G-MDSC populations through CD11b modulation in combination with anti–PD-1 therapy and chemotherapy is currently being explored with minimal adverse effects reported.88 With many ongoing studies, myeloid cell targeting represents a promising component of immunotherapy strategies to mitigate the potent immunosuppressive TME.

B-Cell Targeting

B cells were recently implicated as contributors to the PDAC immunosuppressive TME and were targeted in a phase III trial evaluating ibrutinib, a Bruton’s tyrosine kinase inhibitor, in combination with chemotherapy. Ibrutinib, used in the treatment of various hematologic malignancies, had demonstrated reduced stromal fibrosis and decreased tumor progression in preclinical PDAC models.84 However, the phase III RESOLVE study examining treatment-naïve patients with metastatic PDAC found that the combination of gemcitabine/nab-paclitaxel with ibrutinib resulted in no improvement in median OS (9.7 v 10.8 months; \( P = .3225 \)) and reduced PFS (5.3 v 6.0 months; \( P < .0001 \)) and ORR (29% v 42%; \( P = .0058 \)) when compared with standard chemotherapy.85

**INCREASED T-CELL ACTIVATION BEYOND ICB**

CD40 Agonist

In addition to targeting the immunosuppressive components of the TME, a complementary strategy is to enhance the cytotoxic capabilities of the adaptive immune system. CD8+ T cells express both coinhibitory and costimulatory receptors, and activating the latter may be able to compensate for the intrinsic and environmentally poor antigen quality and presentation. Agonistic antibodies to these costimulatory receptors, namely, anti-CD40, have shown promise in PDAC.86

Correlative work from phase I studies of isolated CD40 agonism demonstrated CD8+ T-cell enrichment, increased mature DCs, reduced M2 TAMs, and increased B-cell expression of costimulatory molecules.87,88 The increasing T-cell response seen with CD40 agonists was associated with increased expression of PD-L1 within the PDAC TME, suggesting that pairing ICB with CD40 agonists may be a valuable strategy.89 The phase Ib PRINCE trial combining gemcitabine/nab-paclitaxel and the CD40 agonist APX005M with or without anti-PD1 antibody in untreated metastatic PDAC demonstrated an overall 58% response rate among all treated patients, while showing a tolerable safety profile.90 In the phase II PRINCE trial, chemotherapy plus anti-PD1 antibody and APX005M did not show an improvement in OS when compared with historical controls (\( P = .236 \)). Interestingly, chemotherapy combined with either anti-PD1 antibody or APX005M resulted in improved 1-year OS when compared with historical controls (57% [\( P = .007 \)] and 51% [\( P = .029 \)], respectively v 35% in historical controls).91 Correlative studies are ongoing to identify potential biomarkers and resistant mechanisms of therapies. Building on the findings of the PRINCE trial, the Revolution Platform study (ClinicalTrials.gov identifier: NCT04787991) will combine gemcitabine/nab-paclitaxel with nivolumab plus ipilimumab or hydroxychloroquine plus ipilimumab as first-line treatment for metastatic adenocarcinoma. This trial is currently enrolling.

PDAC Vaccines

Similar to other immunotherapy strategies for PDAC, vaccination has been met with varying success. GVAX, an irradiated allogeneic whole-tumor cell vaccine in which PDAC cells are engineered to express GM-CSF, induces T-cell infiltration when administered before resection.92 In patients with previously treated PDAC, a phase II study of cyclophosphamide and GVAX with or without CRS-207, a bacterium-based vaccine, found that those receiving CRS-207 experienced improved OS when compared with second-line chemotherapy (6.1 months v 3.9 months [HR], 0.59; \( P = .02 \)).93 Although this study appeared to enhance CD8+ T-cell response, the larger Phase Ib ECLIPSE study examining the combination of cyclophosphamide/GVAX/CRS-207 failed to show a difference in OS compared with single-agent chemotherapy (\( P = \) not significant; HR, 1.17; 95% CI, 0.84 to 1.64).94 The addition of anti–PD-1 therapy to GVAX/cyclophosphamide/CRS-207 yielded an OS and a PFS of 5.88 months and 2.23 months, respectively, not significantly different from GVAX/cyclophosphamide/CRS-207 alone.95

Vaccine therapy has been deployed in the adjuvant setting with mixed results. Algenpantucel-L, a whole-cell vaccine genetically engineered to facilitate complement and antibody-dependent cytotoxicity, was added to adjuvant standard-of-care chemotherapy in a phase II study. This single-arm study demonstrated favorable results finding the 1-year disease-free survival (DFS) and OS to be 62% and 86%, respectively.96 Unfortunately, the randomized phase III IMPRESS study examining this approach failed to demonstrate a survival advantage compared with controls (ClinicalTrials.gov identifier: NCT01072981). Algenpantucel-L was also evaluated in borderline resectable disease, but again did not improve median OS (HR, 1.02; 95% CI, 0.66 to 1.58; \( P = .98 \)) nor PFS (HR, 1.33; 95% CI, 0.72 to 1.78; \( P = .59 \)) when compared with standard therapy.97

Another targetable antigen for vaccine therapy is Mucin-1 (MUC-1). MUC-1 is a transmembrane protein involved in oncogenic signaling to increase invasion, angiogenesis, and metastasis.98 A phase I study of resected PDAC using MUC-1 peptide has shown that mucin vaccination increased intratumoral and peripheral blood CD8+ T cells, with low but detectable mucin-specific T-cell response.99
| Therapeutic Mechanism | ID                | Phase | Patient Population                          | Chemotherapy, RT | ICB                                    | Treatment (target)                                                                 | Recruitment Status       |
|-----------------------|-------------------|-------|---------------------------------------------|------------------|----------------------------------------|--------------------------------------------------------------------------------|--------------------------|
| **Targeting stromal elements** |                  |       |                                             |                  |                                        |                                                                                |                          |
|                       | NCT02907099       | IIb   | Previously treated metastatic PDAC          | NA               | Pembrolizumab                          | BL-8040 (CXCR4)                                                               | Active, not recruiting   |
|                       | NCT03634332       | II    | Previously treated, HA-high, metastatic PDAC| NA               | Pembrolizumab                          | PEGPH20 (HA)                                                               | Recruiting               |
|                       | MORPHEUS NCT03193190 | Ib/II | Untreated and previously treated metastatic PDAC | Nab-paclitaxel and gemcitabine/FOLFIRINOX | Atezolizumab/ | Cobimetinib (MEK)/PEGPH20 (HA)/BL-8040 (CXCR4)/selicrelumab (CD40)/AB928 (adenosine receptor)/tocilizumab (IL-6)/tiragolumab (TIZIT) | Recruiting               |
| **Inhibiting immunosuppressive myeloid cells** |                  | Ib2   | Untreated advanced or metastatic tumors including PDAC | Nab-paclitaxel and gemcitabine/FOLFIRI | Nivolumab                             | BMS-813160 (CCR2/CCR5)                                                                 | Completed enrollment—awaiting results |
|                       | NCT02526017       | I     | Previously treated advanced or metastatic tumors including PDAC | NA               | Nivolumab                             | Cabiralizumab (CSF1-R)                                                                 | Completed enrollment—awaiting results |
|                       | NCT02777710       | I     | Previously treated advanced or metastatic tumors including PDAC | NA               | Durvalumab                             | Pexidartinib (CSF1-R)                                                                 | Completed enrollment—awaiting results |
|                       | NCT03153410       | I     | Borderline resectable or locally advanced PDAC | Cyclophosphamide | GVAX, pembrolizumab                    | LY3022855 (CSF1-R)                                                                 | Active, not recruiting    |
|                       | NCT04060342       | I/II  | Untreated advanced or metastatic tumors including PDAC | Nab-paclitaxel/gemcitabine | Pembrolizumab                          | GB1275 (CD11b modulator)                                                                 | Active, not recruiting    |
|                       | NCT04477343       | I     | Previously treated advanced and metastatic PDAC | NA               | Nivolumab                             | SX-682 (CXCR1/2i)                                                                 | Recruiting               |
| **CD40 agonism**      | PRINCE NCT03214250 | I/II  | Untreated metastatic PDAC                    | Nab-paclitaxel/gemcitabine | Nivolumab                             | APX005M (CD40)                                                                 | Active, not recruiting    |
|                       | REVOLUTION NCT04787991  | I    | Untreated metastatic PDAC                    | Nab-paclitaxel/gemcitabine | Nivolumab, ipilimumab                  | Hydroxychloroquine (tumor cell autophagy)                                     | Recruiting               |
|                       | NCT03329950       | I     | Previously treated advanced or metastatic tumors including PDAC | Nab-paclitaxel/gemcitabine | NA                                     | CDX-1140 (CD40) and CDX-301 (rhFLT3L)                                        | Recruiting               |

(continued on following page)
| Therapeutic Mechanism | ID          | Phase | Patient Population                                                                 | Chemotherapy, RT | ICB                          | Treatment (target)                                                                 | Recruitment Status |
|-----------------------|-------------|-------|-------------------------------------------------------------------------------------|------------------|------------------------------|----------------------------------------------------------------------------------|--------------------|
| Cancer vaccines       | NCT03592888| I     | Resected PDAC                                                                       | Cyclophosphamide | NA                           | mDC3/8 (mature dendritic cell primer and booster)                                   | Recruiting         |
|                       | NCT04117087| I     | Resected PDAC, MSS CRC                                                              | NA               | Ipilimumab plus nivolumab    | Poly-ICLC (KRAS peptide)                                                           | Recruiting         |
| Adoptive cell transfer| NCT03054298| I     | Untreated advanced or metastatic tumors including PDAC                              | Cyclophosphamide | NA                           | Mesothelin CAR T cells                                                            | Recruiting         |
|                       | NCT02706782| I     | Previously treated advanced and metastatic PDAC                                    | NA               | NA                           | Mesothelin CAR T cells                                                            | Unknown            |
|                       | NCT01935843| I/II  | Previously treated advanced or metastatic HER2-positive solid tumors including PDAC | NA               | NA                           | CART-HER-2                                                                      | Unknown            |
|                       | NCT02159716| I     | Previously treated metastatic tumors including PDAC                                 | NA               | NA                           | Mesothelin CAR T cells                                                            | Completed enrollment—awaiting results |
|                       | NCT02587689| I/II  | Resected PDAC                                                                       | NA               | NA                           | MUC-1 CAR T cells                                                                | Unknown            |
|                       | NCT02349724| I     | Previously treated advanced or metastatic solid tumors including PDAC              | NA               | NA                           | CEA CAR T cells                                                                  | Unknown            |
|                       | NCT02744287| I/II  | Previously treated advanced or metastatic solid tumors including PDAC              | Rimiducid        | NA                           | BPX-601 (PSCA CAR-T cell)                                                         | Recruiting         |
| Tumor-targeted         | NCT04104672| I     | Previously untreated advanced or metastatic PDAC                                    | Nab-paclitaxel/ gemcitabine | Zimberelimab (anti–PD-1) | AB680 (CD73 inhibitor)                                                            | Recruiting         |
| immunotherapies       | NCT04548752| II    | Previously treated BRCA PDAC patients with SD                                       | NA               | Pembrolizumab                | Olaparib (PARP inhibitor)                                                          | Recruiting         |

Abbreviations: CAR-T cell, chimeric antigen receptor T cell; CEA, carcinoembryonic antigen; FLT3L, fms-like tyrosine kinase 3 ligand; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFIRINOX, 5-fluorouracil, irinotecan, and oxaliplatin; HA, hyaluronic acid; ICB, immune checkpoint blockade; IL, interleukin; MUC-1, Mucin-1; NA, not available; PARP, poly (ADP-ribose) polymerase; PD-1, programmed death-1; PDAC, pancreatic adenocarcinoma; PEGPH2O, pegvorhyaluronidase; PSCA, prostate stem cell antigen; SD, stable disease.
| Therapeutic Mechanism                        | ID         | Phase | Patient Population        | Chemotherapy, RT                  | ICB              | Treatment (target)                              | Significant Results                                                                 |
|---------------------------------------------|------------|-------|---------------------------|-----------------------------------|------------------|-----------------------------------------------|------------------------------------------------------------------------------------|
| Targeting stromal elements                  | NCT01839487| II     | Untreated metastatic PDAC  | Nab-paclitaxel/gemcitabine        | NA               | PEGPH20 (HA)                                  | No improvement in ORR (HR, 0.96; 95% CI, 0.57 to 1.61) or OS (HR, 0.96; 95% CI, 0.57 to 1.61). Did improve PFS (HR, 0.73; 95% CI, 0.53 to 1.00; P = .049) |
|                                            | NCT01959139| I/II   | Untreated metastatic PDAC  | mFOLFIRINOX                       | NA               | PEGPH20 (HA)                                  | Terminated early for clinical futility and AE                                      |
|                                            | NCT02715804| III    | Untreated, hyaluronan-high, metastatic PDAC | Nab-paclitaxel/gemcitabine | NA               | PEGPH20 (HA)                                  | No improvement in OS (HR, 1.00; 95% CI, 0.80 to 1.27; P = .97) or PFS (HR, 0.97; 95% CI, 0.75 to 1.26). The confirmed ORR was 34% v 27% |
|                                            | NCT02826486| I/IIa  | Previously treated metastatic PDAC | FOLFIRI                          | Pembrolizumab    | BL-8040                                       | 32% ORR and 77% DCR                                                               |
|                                            | NCT02737072| I      | Previously treated advanced or metastatic tumors including PDAC | NA                                | Durvalumab       | LY2510924 (CXCR4)                             | DCR 37.5%                                                                         |
|                                            | NCT02472977| I/II   | Previously treated advanced or metastatic tumors including PDAC | NA                                | Nivolumab        | Ulocuplumab (CXCR4)                           | Terminated early for clinical futility                                            |
|                                            | NCT02546531| I      | Previously treated advanced or metastatic tumors including PDAC | Gemcitabine                       | Pembrolizumab    | Defactinib (FAK)                              | No PR or CRs observed. Increased CD8+ infiltration                                |
|                                            | NCT02117479| III    | Previously treated advanced or metastatic PDAC                     | Capecitabine                      | NA               | Ruxolitinib (JAK-STAT)                        | OS: HR, 0.969, 95% CI, 0.74 to 1.2; PFS HR, 1.06; 95% CI, 0.82 to 1.35            |
|                                            | NCT02119663| III    | Previously treated advanced or metastatic tumors including PDAC    | Capecitabine                      | NA               | Ruxolitinib (JAK-STAT)                        | OS HR, 1.58; 95% CI, 0.89 to 2.83; PFS HR, 1.17, 95% CI, 0.69 to 1.98           |
| Inhibiting immunosuppressive myeloid cells  | NCT01413022| Ib     | Borderline resectable or locally advanced PDAC                     | FOLFIRINOX                        | NA               | PF-04136309 (CCR2)                            | 49% ORR, 97% DCR compared with 0% ORR and 80% in the FOLFIRINOX arm              |
|                                            | NCT02732938| I      | Untreated metastatic PDAC                                          | Nab-paclitaxel and gemcitabine    | NA               | PF-04136309 (CCR2)                            | Terminated because of toxicity and lack of efficacy                              |
|                                            | NCT03336216| II     | Previously treated advanced or metastatic PDAC                     | Nab-paclitaxel and gemcitabine    | Nivolumab        | Cabiralizumab (CSF1-R)                        | No increase in PFS                                                                |
|                                            | NCT02583477| Ib/II  | Previously treated metastatic PDAC                                  | NA                                | Durvalumab       | AZD5069 (CXCR2)                               | Safe and well tolerated. Awaiting results                                         |

(continued on following page)
| Therapeutic Mechanism | ID         | Phase | Patient Population | Chemotherapy, RT | IC8 | Treatment (target) | Significant Results |
|-----------------------|------------|-------|--------------------|------------------|-----|-------------------|---------------------|
| B-cell inhibition     | NCT02436668 | III   | Untreated metastatic PDAC | Nab-paclitaxel/gemcitabine | NA  | Ibrutinib (BTK)   | No improvement in median OS (9.7 v 10.8 months; \( P = .3225 \)) and reduced PFS (5.3 v 6.0 months; \( P < .0001 \)) and ORR (29% v 42%; \( P = .0058 \)) when compared with standard chemotherapy |
| CD40 agonism          | NCT00711191 | I     | Previously untreated advanced or metastatic PDAC | Nab-paclitaxel/gemcitabine | NA  | CP-870,893 (CD40) | OS 23.4 months. Increased T-cell infiltration. Decreased fibrosis and M2 macrophages. More mature DCs |
|                       | NCT02588443 | I     | Untreated resectable PDAC | Nab-paclitaxel/gemcitabine | NA  | R07009789, selicrelumab (CD40) | ORR 58% DCR 83.3% |
|                       | NCT03214250 | I/II  | Untreated metastatic PDAC | Nab-paclitaxel/gemcitabine | Nivolumab | APX005M, sotigalimab (CD40) | OS 23.4 months. Increased T-cell infiltration. Decreased fibrosis and M2 macrophages. More mature DCs |
| Cancer vaccines        | NCT00084383 | II    | Resected PDAC | FU-based | NA  | GVAX               | Median DFS 17.3 months Median OS 24.8 months |
|                       | NCT01417000 | II    | Previously treated metastatic PDAC | Cyclophosphamide | NA  | GVAX ± CRS-207    | Triple therapy OS 6.1 months GVAX + Cy OS 3.9 months Enhanced mesothelin-specific CD8 T cells |
|                       | NCT02004262 | IIb   | Previously treated metastatic PDAC | Cyclophosphamide, gemcitabine, or FU-based | NA  | GVAX + CRS-207    | No significant improvement in OS for Cy/GVAX + CRS-207 v chemotherapy |
|                       | NCT02243371 | II    | Previously treated metastatic PDAC | Cyclophosphamide | Nivolumab | GVAX + CRS-207 | No significant difference seen with addition of nivo |
|                       | NCT00836407 | Ib    | Previously treated metastatic PDAC | Cyclophosphamide | Ipilimumab | GVAX              | Combination of CTLA-4 and GVAX had an improved 1-year OS of 27% v 7% in CTLA only |
|                       | NCT00569387 | II    | Resected PDAC | Standard-of-care adjuvant therapy | NA  | Algenpantucel-L   | Increased 1-year DFS 62% and OS 86% compared with 45%/65% historical controls |
|                       | NCT01072981 | III   | Resected PDAC | Standard-of-care adjuvant therapy | NA  | Algenpantucel-L   | No difference v standard-of-care therapy |
|                       | NCT01836432 | III   | Borderline resectable or locally advanced PDAC | FOLFIRINOX, nab-paclitaxel/gemcitabine, capecitabine | NA  | Algenpantucel-L   | No difference in OS (HR, 1.02; 95% CI, 0.66 to 1.58; \( P = .98 \)) and PFS (HR, 1.33; 95% CI, 0.72 to 2.18; \( P = .59 \)) |
|                       | NCT02405585 | II    | Borderline resectable or locally advanced PDAC | Standard-of-care neoadjuvant therapy followed by SBRT | NA  | Algenpantucel-L   | Terminated study |
|                       | NCT01410968 | I     | Unresectable PDAC | NA | NA  | Poly-ICLC and peptide-pulsed dendritic cells | mOS 7.7 months. 3 of 4 patients with SD had antigen-specific T cells |

(continued on following page)
| Therapeutic Mechanism | ID         | Phase | Patient Population          | Chemotherapy, RT | ICB          | Treatment (target)     | Significant Results                          |
|-----------------------|------------|-------|-----------------------------|------------------|--------------|-----------------------|-----------------------------------------------|
| Adoptive cell transfer| NCT03192462| I     | Metastatic PDAC             | Standard-of-care chemotherapy | NA           | Multi-TAA-specific T cells | 8 of 13 patients with disease control Three with PR One with CR |
|                       | NCT02465983| I     | Previously treated advanced or metastatic PDAC | Cyclophosphamide | NA           | Autologous T cells     | Terminated for lack of efficacy               |
|                       | NCT01583686| I     | Previously treated metastatic tumors including PDAC | NA | NA           | Mesothelin CAR T cells | Terminated for slow accrual                   |
|                       | NCT02159716| I     | Previously treated metastatic tumors including PDAC | NA | NA           | Mesothelin CAR T cells | Completed enrollment—awaiting results         |
|                       | NCT00570713| II    | Untreated advanced or metastatic PDAC | Gemcitabine      | NA           | MORAb-009 (mesothelin) | No difference v placebo group (6.5 v 6.9 months, P = NS) |

Abbreviations: CAR-T cell, chimeric antigen receptor T cell; CR, complete response; CTLA-4, cytotoxic T-cell lymphocyte-4; DC, dendritic cell; DCR, disease control rate; DFS, disease-free survival; FAK, focal adhesion kinase; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFIRINOX, 5-fluorouracil, irinotecan, and oxaliplatin; FU, fluorouracil; HR, hazard ratio; ICB, immune checkpoint blockade; poly-ICLC, Poly-L-lysine and carboxymethyl cellulose; JAK-STAT, Janus kinase–signal transducers and activators of transcription; mFOLFIRINOX, modified FOLFIRINOX; mOS, median overall survival; NA, not available; NS, not significant; ORR, overall response rate; OS, overall survival; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival; PR, partial response; RT, radiotherapy; SBRT, stereotactic body radiotherapy; SD, stable disease.
As mentioned above, mutated KRAS is found in more than 92% of PDAC, presenting itself as an ideal vaccination target. Early studies paired mutant KRAS vaccine with the GM-CSF peptide in the adjuvant setting, and although it was found to be safe, an immune response was seen in only 11% of patients as measured by delayed type hypersensitivity.100 This was in contrast to the results of a phase I/II trial evaluating a mutant KRAS peptide vaccine in an adjuvant setting that demonstrated an immune response in 85% of patients. In this study, 10-year survival was found to be 20% of immune responders versus 0% in matched controls.101 Adjuvant trials using mutant KRAS–specific DC vaccination alone or with dual ICB are currently ongoing (ClinicalTrials.gov identifiers: NCT03592888 and NCT04117087).

PDAC vaccines have demonstrated ability to enhance an antitumor T-cell response; however, the number of nonresponders is not insignificant, suggesting that vaccination therapy is insufficient as monotherapy and that additional mechanisms of immune evasion are present.

Adoptive Cell Transfer (chimeric antigen receptor T cell)

Rapid advances in the field of adoptive cell transfer have resulted in unprecedented clinical outcomes for patients with hematologic malignancies; however, these promising results have not translated to PDAC. Adoptive cell transfer refers to harvesting and ex vivo expansion of the patient’s own tumor antigen–specific T cells. Enhanced T cells are then reinfused to produce a robust adaptive immune response. Of the adoptive cell transfer therapies, chimeric antigen receptor T-cell (CAR-T) therapy is the most clinically developed.

An early trial of CAR T cells in unresectable or recurrent PDAC used MUC-1 peptide-pulsed DCs and activated T lymphocytes.103 Of 20 treated patients, one patient with multiple lung metastases experienced complete response (CR) and five had SD. Unfortunately, several subsequent studies have attempted to use CAR-T technology in PDAC, with the majority lacking efficacy (Table 2).

In the adjuvant setting, MUC-1–primed CAR-T in combination with gemcitabine demonstrated a DFS of 15.8 months and an OS of 24.7 months. Long-term DFS in this study was independently associated with the average number of CTLs administered ($P = .0133$).104 A recent phase I study of patients with metastatic PDAC treated with a combination of standard-of-care chemotherapy and CAR-T demonstrated a DCR in 8 of 13 patients, an increase compared with historical controls. Of these eight metastatic patients, three had PR and one had CR.105

Although adoptive cell transfer is a new and promising field of immunotherapy, it possesses many limitations. Antigen selection poses a significant hurdle for CAR-T as most studies to date target tumor-associated antigens, rather than TSAs. Tumor-associated antigens might have variable or heterogeneous expression on tumor cells and may pose a greater risk of off-target toxicity. Serious adverse events have occurred in patients treated with human epidermal growth factor receptor 2–primed106 and carcinoembryonic antigen-primed107 CAR-T therapy. In addition to tumor antigen selection, tumor-infiltrating lymphocytes and CAR T cells have been shown to become progressively dysfunctional over time and upregulate various inhibitory receptors including PD-1 and lymphocyte-activation gene 3,108 making them ineffective to overcome the potentially immunosuppressive TME. As with other immunotherapies, adoptive cell transfer alone seems to be inadequate for PDAC treatment, but may play a role in future combination immunotherapy.

Tumor-Targeted Immunotherapy Strategies

Recently, immunotherapies have been paired with nonimmunologic PDAC-targeted therapies. An ongoing trial combining AB680 (CD73 inhibitor) and zimberelimab (anti–PD-1) with first-line gemcitabine/nab-paclitaxel has demonstrated a tolerable safety profile, with 3 of 9 patients showing PR (one CR) and 5 of 9 with SD.109 The SWOG S2001 is an ongoing randomized phase II study (ClinicalTrials.gov identifier: NCT04548752), which seeks to add pembrolizumab to standard-of-care maintenance olaparib for patients with BRCA+ PDAC. It is still to be seen if adding immunotherapies to targeted PDAC regimens will be effective for these select patient populations.

Future Trial Design

Future trial design is imperative to efficiently gather and accurately assess data to best inform on the complex immune profile of PDAC. Inflammatory-specific end points, such as iRECIST imaging criteria, and correlative studies with explicit aims to evaluate the TME will prove to be invaluable to understand the effects of immune modulation. Paired baseline and on-treatment tumor biopsies have the ability to provide insight into patient-specific responses. These studies should include assessment of the investigational drug’s ability to adequately hit its intended target, change the TME, and identify compensatory evasion mechanisms in nonresponders. Proper correlative science will allow for all patients, both responders and nonresponders, to contribute information to the evolving landscape of tumor immunology. With continuing advancement in immune profiling, identification of effective immunotherapies could be on the horizon.

In conclusion, the rising incidence and persistent dismal 5-year OS of PDAC highlight the need for new effective systemic therapies. Immunotherapy has shown significant benefit in solid organ tumors, but has so far been disappointing in the treatment of PDAC. There have been several promising preclinical studies, but translation into the clinic has proved to be challenging. This is likely a result of PDAC’s complex TME that protects the tumor against a cytotoxic immune response. The intricate and nonredundant pathways of immune evasion will likely require a combination approach to improve efficacy. Fortunately, many ongoing clinical trials are evaluating combination...
immunotherapies, which at the minimum, will be able to shed light on mechanisms of immune evasion to educate future trials. It is our belief that through the multidisciplinary approach with engagement of clinicians, scientists, and most importantly patients, immunotherapy will play a key role in the treatment of PDAC in the future.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Immunologic Strategies in Pancreatic Cancer: Making Cold Tumors Hot

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