review articles

Immunologic Strategies in Pancreatic Cancer: Making *Cold* Tumors *Hot*

Nicholas A. Ullman, MD, MSCI[1]; Paul R. Burchard, MD[1]; Richard F. Dunne, MD, MSCI[1]; and David C. Linehan, MD[1]

abstract

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

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CONTEXT

Key Objective

What are the current strategies being investigated to overcome the profoundly immunosuppressive pancreatic adenocarcinoma (PDAC) tumor microenvironment (TME)?

Knowledge Generated

PDAC uses several intrinsic and extrinsic mechanisms to develop an immunosuppressive TME, thus rending previous immunotherapy strategies ineffective. Combination immunotherapy strategies targeting these mechanisms are currently being investigated.

Relevance

Overcoming the immunosuppressive TME will allow for immunotherapy to become a valuable treatment option in PDAC. Well-designed clinical trials with robust correlative science are necessary to further understand potential mechanisms of immune evasion and inform future studies.

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 cancer[20] and is associated with several downstream effects including production of granulocyte-macrophage colony-stimulating factor (GM-CSF), leading to recruitment of immunosuppressive myeloid cells[21]; promotion, formation, and maintenance of the fibroinflammatory stroma[22]; upregulation of programmed death ligand-1 (PD-L1) expression through mRNA stabilization[23]; increased CD73 expression leading to elevated immunosuppressive extracellular adenosine[24]; 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 growth[28] 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]

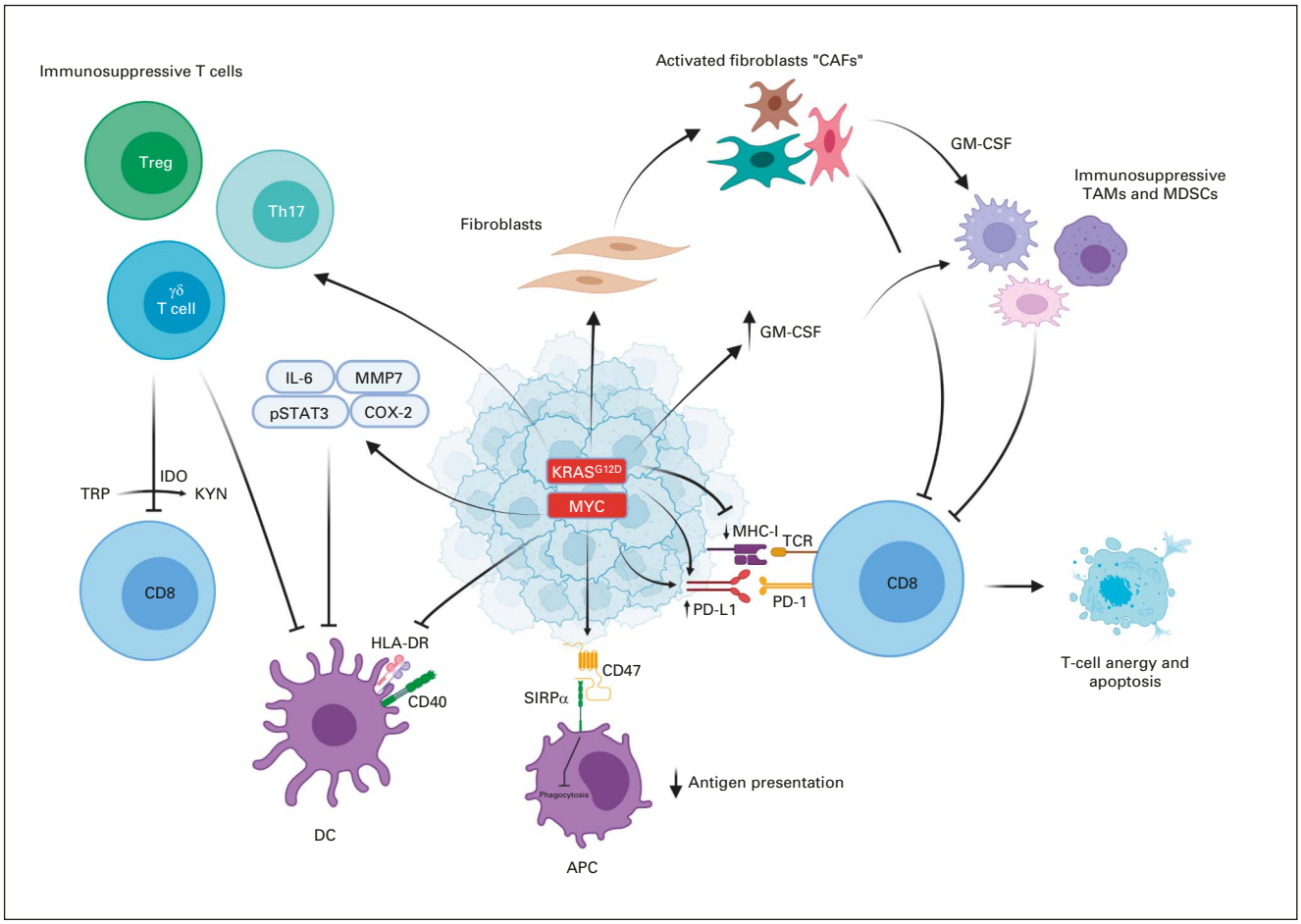

FIG 1. PDAC-intrinsic immunoevasive properties. APC, antigen-presenting cell; CAF, cancer-associated fibroblasts; DC, dendritic cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLA-DR, human leukocyte antigen-DR isotype; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; KYN, kynurenine; MDSCs, myeloid-derived suppressor cells; MHC-1, major histocompatibility complex-1; PD-1, programmed death-1; PDAC, pancreatic adenocarcinoma; PD-L1, programmed death ligand-1; SIRPα, signal regulatory protein alpha; TAM, tumor-associated macrophages; TCR, T-cell receptor; Treg, regulatory T-cell; TRP, tryptophan.

The marked desmoplasia results in elevated interstitial fluid pressure limiting perfusion and diffusion of small molecule therapies secondary to intratumoral small vessel collapse.[36] The associated hypoperfusion produces an overall hypoxic environment resulting in a Treg-mediated CD8+ T-cell inhibition.[37] 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.[36,38]

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.[39] Preclinical models of FAK inhibition limited tumor progression, doubled survival, decreased immunosuppressive cells, and synergized with ICB therapy.[40] 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.[41] 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.[40]

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, and macrophage colony-stimulating factor. These pathways have been shown to encourage peripheral blood mononuclear cell differentiation toward immunosuppressive myeloid-derived suppressor cells (MDSCs),[42] whereas CAF-derived GM-CSF directly leads to tumor cell proliferation, invasion, and transendothelial migration.[43] In turn, myeloid cell–derived IL-1β can reprogram normal fibroblasts into proinflammatory CAFs that further mediate tumor-enhancing inflammation by recruiting and polarizing macrophages toward a cancer-promoting M2

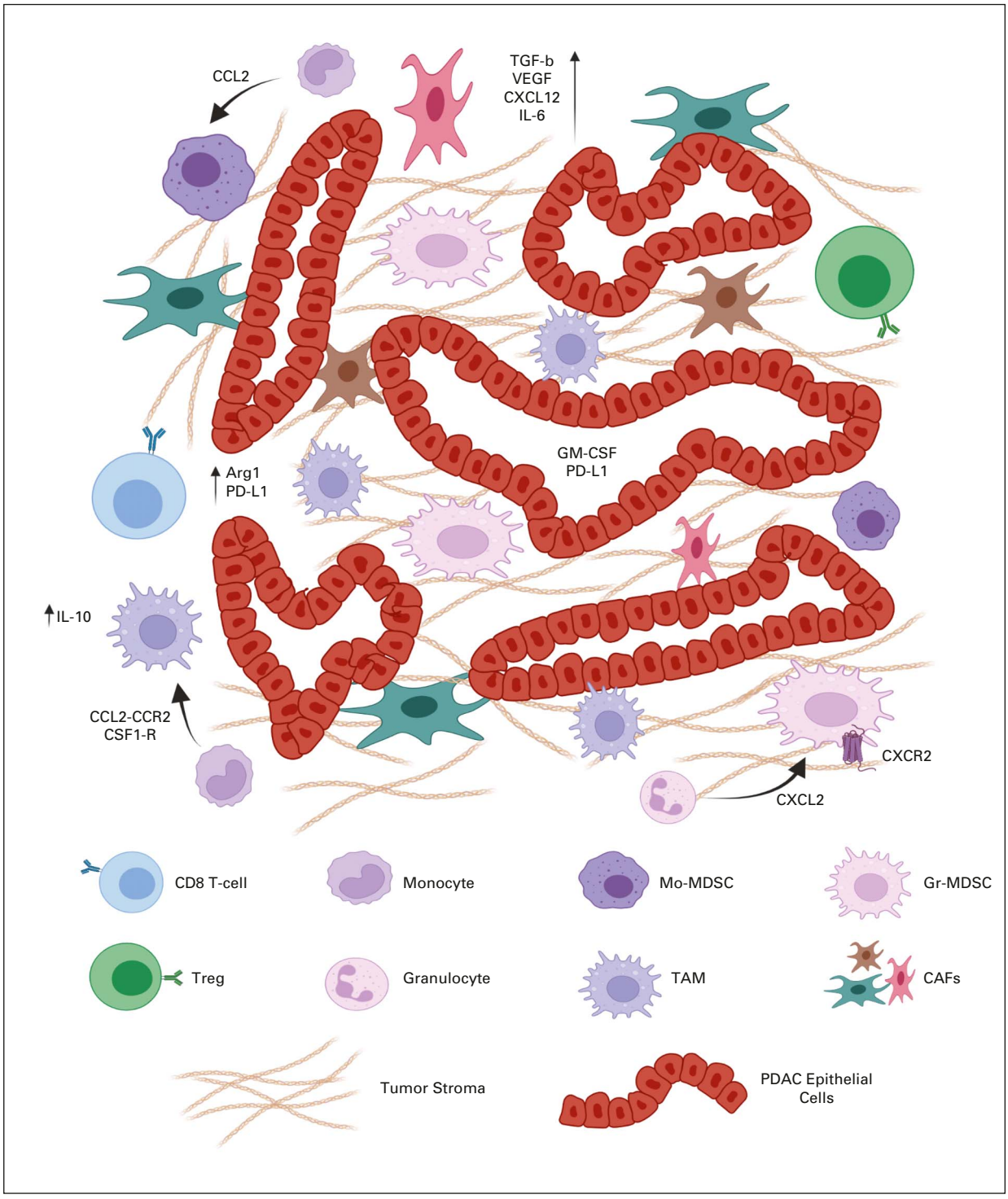

FIG 2. The highly immunosuppressive tumor microenvironment of pancreatic ductal adenocarcinoma. Pancreatic tumor cells, myeloid cells (Mo-MDSCs, TAMs, and Gr-MDSCs), and fibroblasts within the tumor microenvironment interact through various ligands, cytokines, and chemokines that disrupt antitumor immunity.[48] 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.[44] 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.[51] Inhibiting IL-10 resulted in increased IL-12 secretion from DCs and led to improved CTL infiltration and response to chemotherapy.[53] TAMs can also directly induce T-cell apoptosis through their expression of PD-L1[54] and Dectin-1/galectin-9 axis[55] 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.[32] cDCs are also subject to increasing apoptosis secondary to increased levels of IL-6.[60] 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.[61]

B cells. Recent studies have linked B cells to PDAC as resected human PDAC exhibited increased CD20 and Ig expression relative to normal pancreata,[62] whereas depletion of B cells with anti-CD20 monoclonal antibodies inhibited progression of pancreatic intraepithelial neoplasia preclinically.[63]

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.[32] 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 antitumor 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 pegvorhyaluronidase (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 clinical 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 capecitabine 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 I: 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-naïve 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 combinatory 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.[83] 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 pancreatic 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 IIb 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]

TABLE 1. Ongoing Clinical Trials

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	NCT03184870	Ib/2	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 metastic 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)

TABLE 1. Ongoing Clinical Trials (continued)

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 immunotherapies	NCT04104672	I	Previously untreated advanced or metastatic PDAC	Nab-paclitaxel/gemcitabine	Zimberelimab (anti–PD-1)	AB680 (CD73 inhibitor)	Recruiting
	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; PEGPH20, pegvorhyaluronidase; PSCA, prostate stem cell antigen; SD, stable disease.

TABLE 2. Closed Clinical Trials

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 metastic 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/FOLFIRI	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

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TABLE 2. Closed Clinical Trials (continued)

Therapeutic Mechanism	ID	Phase	Patient Population	Chemotherapy, RT	ICB	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)	mOS of 8.4 months. ORR of 19%
	NCT02588443	I	Untreated resectable PDAC	Nab-paclitaxel/gemcitabine	NA	R07009789, selicrelumab (CD40)	OS 23.4 months. Increased T-cell infiltration. Decreased fibrosis and M2 macrophages. More mature DCs
	NCT03214250	I/II	Untreated metastatic PDAC	Nab-paclitaxel/gemcitabine	Nivolumab	APX005M, sotigalimab (CD40)	ORR 58% DCR 83.3%
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 1.78; $P = .59$)
	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

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TABLE 2. Closed Clinical Trials (continued)

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 in 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[102]; 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–primed[106] and carcinoembryonic antigen-primed[107] 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 potently 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 non-immunologic 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.

AFFILIATION

[1]University of Rochester Medical Center, Rochester, NY

CORRESPONDING AUTHOR

Nicholas A. Ullman, MD, MSCI, University of Rochester Medical Center, 601 Elmwood Ave, BOX SURG, Rochester, NY, 14620; e-mail: Nicholas_ullman@urmc.rochester.edu.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Nicholas A. Ullman, Paul R. Burchard, David C. Linehan
Financial support: David C. Linehan
Administrative support: David C. Linehan
Collection and assembly of data: All authors
Data analysis and interpretation: Nicholas A. Ullman, Richard F. Dunne
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Immunologic Strategies in Pancreatic Cancer: Making *Cold* Tumors *Hot*

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Richard F. Dunne
Consulting or Advisory Role: Exelixis, Helsinn Therapeutics

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