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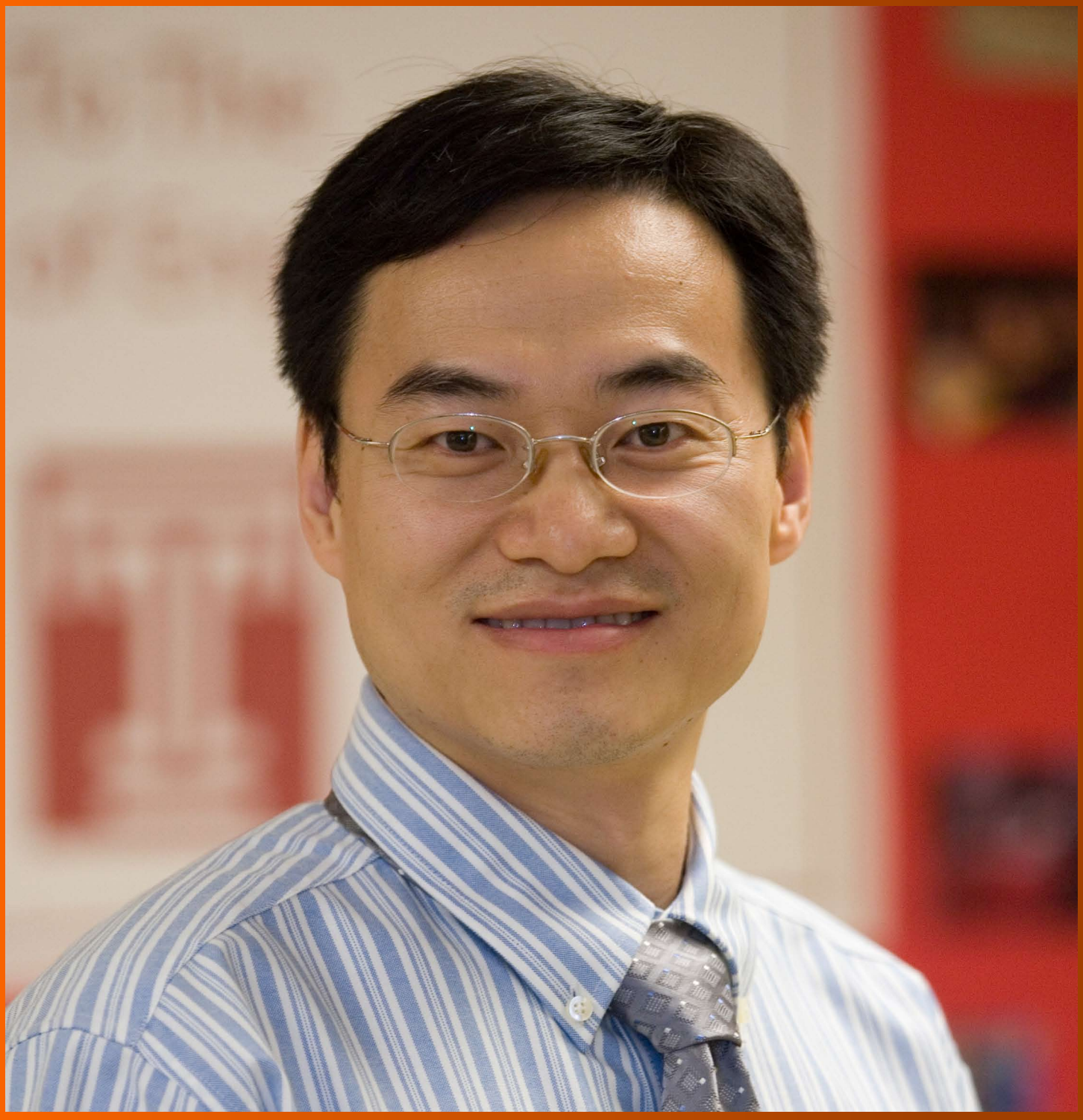

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MINIREVIEWS

# Immunotherapy in pancreatic cancer: Unleash its potential through novel combinations

Songchuan Guo, Merly Contratto, George Miller, Lawrence Leichman, Jennifer Wu

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Author contributions: Wu J provided the concept, the outline, the structure, and the major references for this manuscript, provided critical revisions for this manuscript; Guo S drafted the majority of the manuscript, incorporated several revisions based on feedback from Wu J, Leichman L and Miller G; Contratto M incorporated essential components into the manuscript and performed critical revisions of this manuscript; Miller G and Lawrence L provided critical feedback and offered major ideas to optimize the manuscript; all authors approved the final manuscript.

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## Abstract

Pancreatic cancer is the third leading cause of cancer mortality in both men and women in the United States, with poor response to current standard of care, short progression-free and overall survival. Immunotherapies that target cytotoxic T lymphocyte antigen-4, programmed cell death protein-1, and programmed death-ligand 1 checkpoints have shown remarkable activities in several cancers such as melanoma, renal cell carcinoma, and non-small cell lung cancer due to high numbers of somatic mutations, combined with cytotoxic T-cell responses. However, single checkpoint blockade was ineffective in pancreatic cancer, highlighting the challenges including the poor antigenicity, a dense desmoplastic stroma, and a largely immunosuppressive microenvironment. In this review, we will summarize available clinical results and ongoing efforts of combining immune checkpoint therapies with other treatment modalities such as chemotherapy, radiotherapy, and targeted therapy. These combination therapies hold promise in unleashing the potential of immunotherapy in pancreatic cancer to achieve better and more durable clinical responses by enhancing cytotoxic T-cell responses.

**Key words:** Immunotherapy; Pancreatic cancer; Anti-programmed cell death protein-1; Anti-programmed cell death protein-ligand1; Anti-cytotoxic T lymphocyte antigen-4; Single therapy; Combination therapies; Radiation therapy; GVAX; CRS-207; CD40 agonist

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**Core tip:** Pancreatic cancer is the third leading cause of cancer mortality in both men and women in the United States. Pancreatic cancer is one of nonimmunogenic

cancers that lacks of optimal treatments especially from immunotherapy prospective. Therefore, combining immune checkpoint therapies with other treatment modalities in pancreatic cancer will be the best strategy to achieve better and more durable clinical responses by enhancing cytotoxic T-cell responses.

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## INTRODUCTION

Pancreatic cancer is the third leading cause of cancer mortality in both men and women in the United States[1]. The vast majority of patients with pancreatic cancer are diagnosed with advanced disease, and there has been a lack of optimal treatment option as the cancer is highly refractory to standard chemotherapy. Recently, two chemotherapy regimens, FOLFIRINOX and gemcitabine plus albumin-bound paclitaxel (nab-paclitaxel), have emerged as the standard of care for metastatic pancreatic cancer. These two regimens showed improved overall and progression-free survival (PFS) compared to gemcitabine alone in two phase Ⅲ randomized controlled trials[2,3]. Nevertheless, only up to 30% of patients showed response to either of these two regimens. The median PFS and overall survival (OS) remain poor, under 6 and 12 mo, respectively. Thus, there is still an urgent need to develop therapies that deliver more effective and durable clinical responses.

## RELEVANCE OF IMMUNITY TO PANCREATIC CANCER

Observations in human disease and murine modeling has suggested that pancreatic cancer is almost invariably associated with a robust inflammatory infiltrate which can have divergent influences on disease progression by either combating cancer growth *via* antigen-restricted tumoricidal immune responses or by promoting tumor progression *via* induction of immune suppression (Figure 1)[4-6]. For example, cluster of differentiation 8 ($CD8^+$) and T-helper type 1 cells (Th1)-polarized cluster of differentiation 4 ($CD4^+$) T cells mediate antitumor effects in murine models of pancreatic cancer and are associated with increased survival in patients with pancreatic cancer[7-10]. Conversely, we recently reported that T- helper type 2 cells (Th2)-polarized $CD4^+$ T cells promote pancreatic cancer progression in mice and intra-tumoral $CD4^+$ Th2 cells infiltrates correlate with reduced survival in human disease[7-9,11-13]. Similarly, $Foxp3^+$ T-regulatory cells (Tregs) facilitate tumor immune escape in pancreatic cancer[14]. Myeloid cells can influence T cells differentiation and cytotoxicity in pancreatic cancer. We reported that tumor-infiltrating myeloid-derived suppressor cells (MDSCs) negate cytotoxic $CD8^+$ T cells anti-tumor responses, accelerates pancreatic cancer growth and metastasis[8,15-17]. Similar to T cells, macrophages also have cell types with different properties such as classically activated (M1) macrophages induce immunogenic responses, whereas alternatively activated (M2) macrophages have permissive influences on tumor growth by recruiting Tregs and Th2 cells[18]. However, the drivers of immunosuppressive cell differentiation in pancreatic cancer are based on comprehensive understanding of regulation of the balance between immunogenic and immune-suppressive T cell populations.

## THE EMERGENCE OF CHECKPOINT IMMUNOTHERAPY

The last few years witnessed a paradigm shift in cancer treatment strategy incorporating immunotherapy. Unprecedented clinical success has been observed for therapies targeting two major checkpoints of T cell response (Figure 2): Cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1). Both checkpoints are expressed on activated T cells, but they act in distinct pathways. CTLA-4 blocks the essential cluster differentiation 28 (CD28) costimulation by competing and depleting the ligand of CD28 (B7-1 and B7-2) on antigen presenting cells (APCs). On the other hand, PD-1 interferes with the signaling pathways mediated by the T cell receptor and serves as a more distal block of T cell response by binding to its ligands (programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2) which are present on many cell types including tumors cells[19].

Monoclonal antibodies targeting CTLA-4 or PD-1 have shown durable clinical responses and prolonged OS in patients with melanoma, a highly immunogenic cancer. While single agent PD-1/PD-L1 inhibitors demonstrate impressive clinical benefits in many cancers such as non small cell lung cancer (NSCLC), renal cell carcinoma, bladder cancer, and Hodgkin's lymphoma[20-29]. These results have led to FDA approval of Ipilimumab (anti-CTLA-4) in 2011 in melanoma[30]. PD-1 inhibitors such as pembrolizumab and nivolumab were approved later in melanoma as well[23,28,29]. PD-1 inhibitors (nivolumab and pembrolizumab), along with PD-L1 inhibitors such as atezolizumab have been approved in NSCLC, another example of immunogenic cancer[21,22,24,29]. The activity of CTLA-4 and PD-L1 inhibitors are being explored in pancreatic cancer as well[22,31].

## EVIDENCE OF MINIMAL ACTIVITY OF SINGLE AGENT CHECKPOINT IMMUNOTHERAPY IN PANCREATIC CANCER

In early clinical trials single agent therapy with anti-CTLA-4

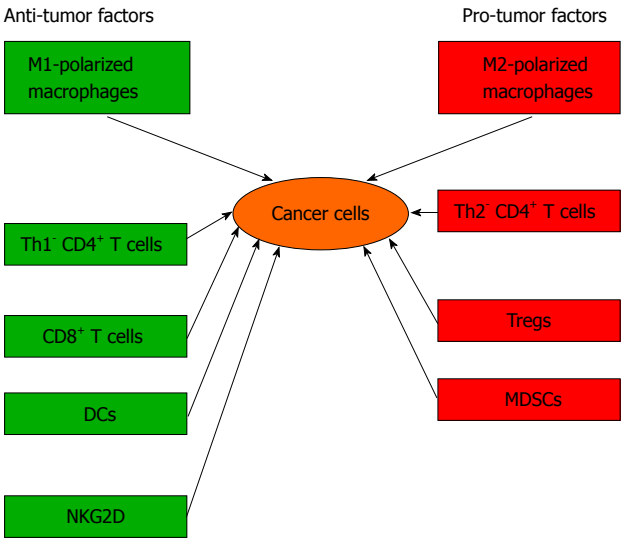


**Figure 1 Anti-tumor and pro-tumor factors.** Anti-tumor factors: M1 (classically activated macrophages), $Th1^{-}CD4^{+}$ T cells (T-helper type 1-cluster differentiation 4 T cells), $CD8^{+}$ T cells, DC (dendritic cells), NKG2D (natural killer group 2 member). Pro-tumor factors: M2 (alternatively activated macrophages), $Th2^{-}CD4^{+}$ T cells (T-helper type 2-cluster differentiation 4 T cells) Th2, Tregs (T-regulatory cells), and MDSCs (myeloid-derived suppressor cells).

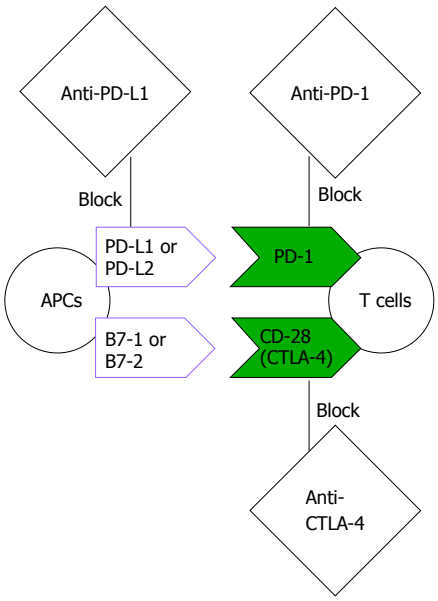


**Figure 2 Immunotherapy basics.** Anti-PD-L1 inhibit PD-L1 (programmed cell death-ligand 1) binding to PD-1 (Programmed cell death protein-1). Anti-PD-1 inhibit PD-1 on T-cell that binds to PD-L1 or PD-L2 (programmed cell death ligand-2) on APC (antigen presenting cell). Anti-CTLA-4 (anti-cytotoxic T lymphocyte antigen 4) inhibit CD28 (cluster differentiation 28) on T cell that binds to B7-1 or B7-2 (ligand of CD28) on APC.

or anti-PD-1/anti-PD-1 pathway (anti-PD-L1) alone were largely ineffective in pancreatic cancer[22,31,32]. In a single-arm phase Ⅱ study, Ipilimumab failed to induce tumor response in patients with advanced pancreatic cancer[32]. Similarly, single agent BMS-936559, an anti-PD-L1 monoclonal antibody, did not show any activity in 14 patients with advanced pancreatic cancer in a phase Ⅰ study[22].

## POTENTIAL BARRIERS THAT HINDER EFFICACY OF IMMUNOTHERAPY

The efficacy of immunotherapy in pancreatic cancer is handicapped by small number of cumulative mutational load that can lead to expression of non-self-antigens, or "neoantigens" which are recognized by the immune system as foreign. Cancers with higher number of mutational load are associated with more neoantigens that are easier to be recognized by the immune system, compared to cancer with lower number of mutational load[33-35]. There are 3 major barriers for the utility of immunotherapy in pancreatic cancer. First, the mutational load in pancreatic cancer is very low as compared with melanoma and lung cancers[36,37]. Second, pancreatic cancer features a largely immunosuppressive microenvironment, characterized by a dense desmoplastic reaction with prominent infiltration of tumorigenic macrophages and myeloid derived suppressor cells (MDSCs)[38]. Third, there are very few infiltrating T cells in the microenvironment of pancreatic cancer, therefore could not provide sufficient T cell responses. Pancreatic cancer creates a nonimmunogenic (or "cold") tumor microenvironment, limiting the activity of immune checkpoint therapies[31].

## EVIDENCE OF T CELL IMMUNITY

On the other hand, there is still evidence of T cell-mediated immunity in pancreatic cancer. An analysis of resected surgical samples of pancreatic cancer patients has shown that higher levels of $CD4^{+}$ and $CD8^{+}$ tumor infiltrating T cells are associated with better prognosis[10]. In addition, since immunosuppression occurs early during tumorigenesis as shown in $Pdx1^{Cre}$;$Kras^{G12D}$;$Tp53^{R172H}$ (KPC) mouse model, the tumor cells may have been shielded from immune pressure, thus preserving their sensitivity to T cell attack[38].

In addition, downstream signals are also critical in the T cell immune responses. Interferon-gamma (IFN-γ) promotes inhibition of melanoma cell growth and induces apoptosis of tumor cells by regulating T-cells responses[39-44]. Immune checkpoint inhibitors increase production of IFN-γ from T-cell[45-50]. However its effect will be suboptimal if there is a defect in the IFN-γ pathway[51]. Studies in patients with melanoma showed that a defect in the IFN-γ pathway can lead to resistance to anti-CTLA4 and anti-PD-1 therapies[51,52]. Several genomic biomarkers of IFN-γ pathways such as interferon gamma receptor 1, janus kinase 1 (JAK1), and JAK2 have been identified in melanoma patients with good response to immune checkpoint therapies[41-43,51,52]. On the other hand, genes such as suppressor of cytokine signaling 1 (SOCS1) and protein inhibitor of activated signal transducer and activator of transcription 4 (PIAS4) have

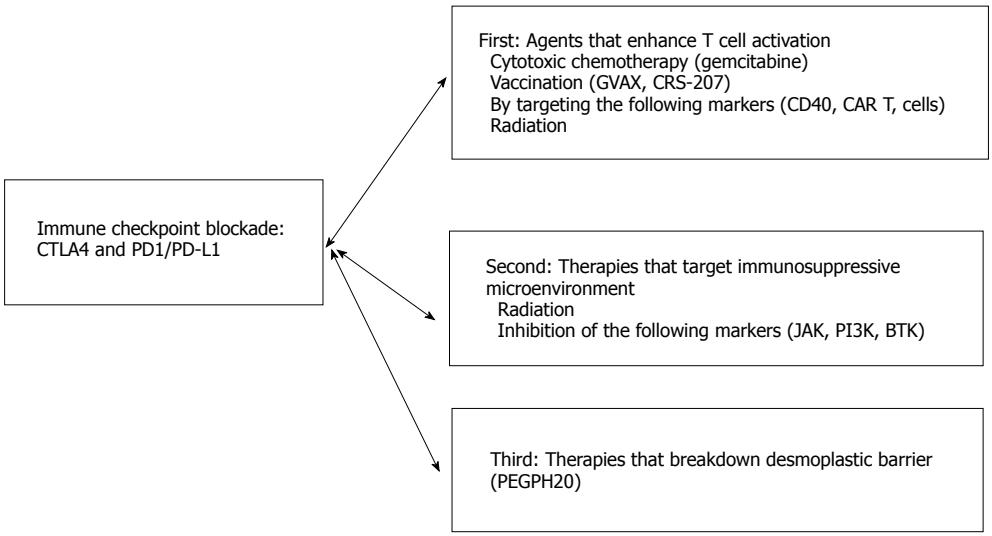


**Figure 3 Searching for the optimal combination to maximize the potential of immune checkpoint blockade for the treatment of pancreatic cancer.** CTLA-4: Cytotoxic T lymphocyte antigen-4; PD-1: Programmed cell death protein-1; PD-L1: Programmed death ligand-1; CD40: Cluster differentiation 40; CAR T cells: Chimeric antigen receptor T cells; PI3K: Phosphoinositide-3-kinase; BTK: Bruton tyrosine kinase; JAK: Janus kinase; PEGPH20: Pegylated hyaluronidase.

demonstrated the opposite effects by inhibiting IFN-γ signaling pathway[51,53,54].

## STRATEGIES OF TURNING ON THE ACTIVITY OF IMMUNOTHERAPY

Thus, the incorporation of additional therapies that can turn a "cold" tumor microenvironment into a "hot" one presents an important strategy to elicit clinical activity of immune checkpoint therapies. These additional therapies mainly fall into three categories (Figure 3): First, therapies that enhance tumor antigen presentation to help T cell priming/activation; second, therapies that modulate tumor microenvironment to relieve immunosuppression. Third, therapies which breakdown the desmoplastic barrier surrounding pancreatic cancer to bring infiltrating T cells. Below we will summarize the combination therapies that have already been assessed clinically and provide future directions of new combinations that may hold promise.

## FIRST (ENHANCE T CELL ACTIVATION)

### *Immune checkpoint therapy + chemotherapy*

Gemcitabine is one of the backbone chemotherapy agents for the treatment of pancreatic cancer. It has been suggested that gemcitabine is not immunosuppressive in pancreatic cancer patients and may be able to enhance naïve T cells activation[55]. Combination of gemcitabine and immune checkpoint blockade has been evaluated for their potential synergistic activity.

**Gemcitabine plus CTLA-4 blockade:** A phase Ⅰ clinical study evaluated the combination of gemcitabine and an anti-CTLA-4 antibody (tremelimumab) in treatment naive patients with metastatic pancreatic cancer. This combination showed a tolerable side effect. Among 28 out of 34 evaluable patients, 2 achieved partial response (PR) and 7 showed stable disease (SD) for > 10 wk[4]. In another ongoing phase Ib study of unresectable pancreatic cancer, preliminary results showed that, among 11 evaluable patients (out of 13 enrolled), ipilimumab and gemcitabine resulted in 2 PR and 5 SD[56,57].

**Gemcitabine plus PD-1/PD-L1 blockade:** An immunohistochemistry analysis has shown that positive PD-L1 expression in resected pancreatic cancer was correlated with worse OS[58]. In a mouse model of pancreatic cancer, combining gemcitabine with either anti-PD-1 or anti-PD-L1 antibody enhanced tumor infiltration of $CD8^+$ T cells and resulted in complete responses in treated mice[58]. A clinical pilot study of combination of gemcitabine and anti-PD-1 antibody has closed to enrollment (NCT01313416).

### *Immune checkpoint therapy + cancer vaccines*

The most extensively studied pancreatic cancer vaccine is GVAX. GVAX is a whole cell vaccine composed of irradiated, allogeneic pancreatic tumor cells genetically engineered to secret granulocyte macrophage-colony stimulating factor (GM-CSF), a cytokine that stimulates dendritic cell activation and T cell priming. When used as part of adjuvant therapy in the post-resection setting, GVAX was able to induce pancreatic cancer specific $CD8^+$ T cell expansion as shown in a phase Ⅱ study[59]. Also, when used as neoadjuvant and adjuvant therapy, GVAX and low dose cyclophosphamide (an alkylating agent with an ability to deplete Tregs) resulted in formation of intratumoral tertiary lymphoid aggregates and T cell infiltration, suggesting the ability of GVAX in the conversion of pancreatic cancer from a "non-immunogenic" into an "immunogenic" state[60].

**GVAX plus CTLA-4 blockade:** In a small phase Ib

study, GVAX in combination with anti-CTLA-4 antibody ipilimumab was evaluated in 30 patients with advanced, refractory pancreatic cancer that were previously treated with gemcitabine-based chemotherapy. Compared to ipilimumab alone, the combination therapy resulted in improved survival (27% *vs* 7% at 1 year). Also, a longer survival was associated with an increase in peak mesothelin-specific T cells and a larger T cell repertoire (the percentage of mesothelin peptides for which enhanced T-cell responses were measured), indicating a positive role of T cell response[61].

**GVAX plus PD-1/PD-L1 blockade**: Detailed analysis of lymphoid aggregates formed after GVAX therapy revealed elevated expression of PD-L1 on monocytes/macrophages[60,62], suggesting the potential benefit of targeting PD-1/PD-L1 checkpoint. This concept was supported by experiments in a pancreatic cancer mouse model, where the combination of GVAX and an anti-PD-1 antibody resulted in better survival than anti-PD-1 antibody alone, and this activity was correlated with increased $CD8^+$ T cells and elevated IFN-$\gamma$ production in the tumor microenvironment[62]. Currently, a randomized clinical study (NCT02451982) is ongoing to evaluating GVAX with or without anti-PD-1 antibody (nivolumab) as neoadjuvant and adjuvant treatment in patients with resectable pancreatic cancer.

**GVAX and CRS-207 plus PD-1/PD-L1 blockade:** CRS-207 is a bacterial vaccine composed of live-attenuated, double deleted Listeria monocytogenes expressing human mesothelin, an antigen commonly overexpressed in pancreatic cancer cells. CRS-207 can induce robust innate as well as mesothelin-specific adaptive immune response, therefore allowing for a "boost" to the immune response initiated by GVAX. In a randomized, phase Ⅱ study, GVAX prime followed by CRS-207 boost resulted in prolonged OS compared to GVAX alone in patients with metastatic, refractory pancreatic cancer. This study also showed that mesothelin-specific $CD8^+$ T cell response was correlated with better survival[63,64]. On the basis of these findings, a randomized phase Ⅱ study (NCT02243371) was to evaluate whether adding anti-PD-1 therapy (nivolumab) will further enhance the activity of this prime-boost strategy[65]. This study has closed to enrollment.

In a phase IIb study (NCT02004262) in refractory and metastatic pancreatic cancer, 303 patients were randomized between GVAX and CRS-207 (arm A), only CRS-207 (arm B), and single agent chemotherapy (arm C)[66]. No OS advantage was seen in arm A when compared to arm C[66]. A large number of patient drop out prior to treatment was observed in both arm A and C (40% versus 60%, respectively), indicating the challenge of therapeutic benefit in refractory pancreatic cancer. It also hints that these patients in the refractory setting may be too sick to benefit from immunotherapy due to rapid deterioration of disease.

### *Immune checkpoint therapy + agents enhancing T cell immunity*

**CD40 agonist:** CD40 is a member of the tumor necrosis factor receptor family. Ligation of CD40 can occur on dendritic or B cells, or at CD40 ligand (CD154) on activated T cells, such effect can enhance T cell immunity[67]. In a 22 patients series with unresectable pancreatic cancer, a CD40 agonist (CP-870, 893) and gemcitabine led to an encouraging clinical response[7,11]. Rather unexpectedly, it showed that tumor infiltration by macrophages played a larger role for depletion of tumor stroma and killing of tumor cells[7]. In a more recent study in the KPC mouse model, however, the use of CD40 agonist monoclonal antibody (mAb) with gemcitabine and nab-paclitaxel induced macrophage-independent T cell immunity. This study also found that CD40 agonist in addition to chemotherapy was able to sensitize the tumors to anti-CTLA-4 and/or anti-PD-1 therapies, leading to tumor regression and improved survival[31]. A recent study using an orthotopic pancreatic cancer mouse model also demonstrated tumor regression and enhanced immune response with the combination of CD40 agonist antibody with gemcitabine/Nab-paclitaxel[68]. It is yet to be seen whether these pre-clinical results can translate into clinical benefits.

**CAR T cells:** Autologous T cells genetically engineered to express a chimeric antigen receptor (CAR) have been developed to trigger cancer-specific T cell immunity and have shown impressive activity in acute lymphoblastic leukemia[69]. For the treatment of pancreatic cancer, the CARs are engineered to recognize mesothelin, a specific membrane protein antigen overexpressed on pancreatic cancer cells. Mesothelin-specific CAR T cells are currently under phase Ⅰ clinical evaluation, with preliminary results suggesting acceptable safety profiles and potential clinical activity against advanced pancreatic cancer. This study demonstrated that 2 out of 6 patients achieved SD and one patient with liver metastasis at baseline showed no fluorodeoxyglucose (FDG) uptake within 1 mo of treatment[12,70,71]. Therefore, CAR T cells represent another treatment modality to combine with immune checkpoint therapies.

### *Immune checkpoint therapy + radiotherapy*

The effects of radiotherapy (RT) on the immunology of pancreatic cancer have not been intensively studied. However, work in other cancers has suggested that RT should be considered an immune adjuvant as evidenced by radiotherapy (RT) induced enhancement of both innate and adaptive immunity. For example, the immunogenicity of dendritic cells (DCs) is reportedly improved by RT-induced necrotic tumor cell release of high mobility group box 1 protein (HMGB1) which ligates toll-like receptor 4 (TLR4) and toll-like receptor 9 (TLR9) on DCs. Such events promote DCs' cellular maturation and enhance their antigen processing capabilities[72]. Another consequence of RT-induced necrotic cell death is the translocation of calreticulin from the endoplasmic reticulum to the

plasma membrane which facilitates assembly of major histocompatibility-1 (MHC I)-peptide complexes. Calreticulin also enhances DCs cross presentation of antigens to cytotoxic T lymphocytes. In addition to upregulating the antigen-presentation machinery in DCs, RT can reportedly enhance immunogenicity by inducing the release of tumor antigens, upregulating the expression of T-cell co-activating ligands, and sensitizing tumor cells to antigen-independent cell death *via* the Fas receptor[72]. RT is further thought to augment diverse aspects of T cell immunity *via* adenosine triphosphate release from apoptotic cells which induces secretion of Interleukin-1-beta (IL-1β). A consequence of this cascade is T helper1 (Th1) polarization of antigen-restricted $CD4^+$ T cell responses and activation of cytotoxic T cells. Additionally, activation of cytotoxic T cells can be further activated by irradiation, *via* natural killer group 2 member D (NKG2D) receptor on cytotoxic T cells. NKG2D receptor can be induced in a stress event such as DNA damage which can be achieved by RT[72]. Therefore, ionizing radiation can result in "immunogenic cell death', in which the dying tumor cells trigger "danger signals" (a signal of releasing HMGB1 and binding to TLR4 and TLR9 on DCs to process the antigen) to boost T cell activation[72,73].

## SECOND (TARGETING IMMUNO-SUPPRESSIVE MICROENVIRONMENT)

As described earlier, an important barrier to the success of immunotherapy in pancreatic cancer is an immunosuppressive tumor microenvironment, enriched with immunosuppressive cells such as tumor associated macrophages (TAMs) and MDSCs. In animal models of pancreatic cancer, blockade of immunosuppressive MDSCs could promote antitumor T-cell responses and block protumor macrophage responses[6,74-76]. Therefore, drugs that block these immunosuppressive cells in the tumor microenvironment represent attractive strategies to sensitize pancreatic cancer to immune checkpoint therapies.

### *Immune checkpoint therapy + radiotherapy*

RT's theoretical potential ability to convert the tumor microenvironment from a "cold" to a "hot" state suggests the opportunity of RT combination with immune checkpoint therapy. In the KPC pancreatic mouse model, any combination of immune checkpoint inhibitor with RT substantially increased OS, when compared to anti-CTLA-4 antibody or anti-PD-L1 antibody alone without RT. In particular, the triple therapy (RT + CTLA-4 antibody + PD-1 antibody) resulted in the highest response rate and longest OS among any of the immunotherapy group as single therapy or in combinations[77].

However, our recent preclinical studies on RT in pancreatic cancer suggest caution as we found that RT induced the programming and recruitment of immunosuppressive M2-like macrophages which lead to the expansion of tumor promoting Th2-polarized CD4+ T cells and Tregs. We also found that combining RT with either macrophage neutralization or M-CSF blockade resulted in synergistic efficacy in mice model, suggesting another treatment strategy for pancreatic cancer utilizing RT combining with colony stimulating factor-1 receptor inhibitor[76,78].

So far there have been no published clinical results on RT plus checkpoint blockade for the treatment of pancreatic cancer. Currently, an open-label, three-cohort, multi-institutional phase Ib study is ongoing at New York University (NCT02868632) to assess stereotactic body radiation therapy (SBRT) in combination with either MEDI4736 (an anti-PD-L1 antibody) alone, tremelimumab (an anti-CTLA4 antibody) alone, or the combination of MEDI4736 and tremelimumab in patients with unresectable/locally advanced previously untreated pancreatic cancer. A study with similar design that tests the combination of radiation with checkpoint blockade in second line setting is also ongoing (NCT02311361).

### *Immune checkpoint therapy + therapies targeting immunosuppressive microenvironment*

**JAK inhibitors:** The Janus kinase (JAK) and its downstream factor signal transducer and activator of transcription (STAT) are important mediators of signaling pathways initiated from cytokine and growth factor receptors. Excessive JAK/STAT signaling can lead to production and release of inflammatory cytokines, promote recruitment, expansion of MDSCs and Tregs which induce an immunosuppressive tumor microenvironment[79]. Also, JAK/STAT pathway has been shown to induce the expression of PD-L1 on cells in the tumor microenvironment[14,80]. In preclinical studies, JAK inhibitors led to decreased numbers of Tregs, TAMs and MDSCs, with enhanced number of activity of $CD4^+$ and $CD8^+$ T cells[18]. The study of JAK inhibitor Ruxolitinib and capecitabine for the treatment of advanced pancreatic cancer has closed to enrollment (JANUS study; NCT02117479)[81].

**PI3K inhibitors:** Phosphoinositide-3-kinase (PI3K) is a family of lipid kinases that catalyze the production of second messenger phosphatidylinositol-3,4,5-triphosphate (PIP3), which leads to activation of downstream kinases. PI3K was known to play an important role in signaling pathways in B cells, which were found to contribute to an immunosuppressive microenvironment that dampens T cell immunity[82]. Inactivation of PI3K was associated with a decrease in Tregs and MDSCs and an increase in $CD8^+$ cytotoxic T cell activity, indicating a role of PI3K in regulating tumor microenvironment[5]. PI3K inhibitors could shift immunosuppressive microenvironment in pancreatic cancer into a more immunogenic one. Therefore PI3K inhibitors could help potentiate the activity of immune checkpoint inhibitors.

**BTK inhibitors:** BTK is a cytoplasmic, Tec family tyrosine kinase important in B-lymphocyte development, differentiation, and signaling. In pancreatic cancer, the BTK

inhibitor (ibrutinib) was shown to inhibit mast cells, and as a result, to reduce fibrosis in the tumor microenvironment both in a KPC mouse model and patient-derived xenograft[83]. Ibrutinib was also known to inhibit interleukin-2-inducible T-cell kinase (ITK), an important enzyme for the survival of Th2 cells; thus ibrutinib may be able to shift the balance away from the Th2 cells protumor response and toward the Th1 cells antitumor immune responses. A phase I/II clinical study assessing ibrutinib in combination with anti-PD-L1 antibody MEDI4736 in relapsed or refractory solid tumors, including pancreatic cancer has closed to enrollment (NCT02403271)[84].

## THIRD APPROACH (BREAKDOWN DESMOPLASTIC BARRIER)

### *Strategy that targets the desmoplastic stroma*

**PEGPH20:** In pancreatic cancer, high levels of hyaluronan in the extracellular matrix contribute to a high interstitial pressure in the tumor stroma, leading to vascular compression and hypoperfusion. Pegylated hyaluronidase PEGPH20 is an enzyme that can degrade hyaluronan, and has been shown in a KPC mouse model to deplete hyaluronan in the tumor stroma and enhance the activity of gemcitabine[85]. In a phase Ⅰ (28 patients) and a phase Ⅱ (135 patients) studies, patients with previously untreated advanced pancreatic cancer, PEGPH20 along with chemotherapy (gemcitabine, or gemcitabine/nab-paclitaxel) resulted in good tumor response and PFS, but only in patients with high levels of hyaluronan[15,86]. Therefore, in pancreatic cancers with high levels of hyaluoran, PEGPH20 therapy may allow more effective T cell infiltration and enhance the activity of immune checkpoint therapies.

## CONCLUSION

Both challenges and opportunities exist for the development of effective immunotherapy for pancreatic cancer. Given that single agent therapies against CLTA-4 or PD-1 or PD-L1 immune checkpoint were largely ineffective in pancreatic cancer, ongoing investigations and future directions lie in the field of combination therapies, where additional treatment modalities may unleash durable anti-tumor immune responses by enhancing tumor-specific T cell activation and antagonizing the immunosuppressive microenvironment in pancreatic cancer.

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