

Rational combinations of immunotherapy for pancreatic ductal adenocarcinoma

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Abstract: The complex interaction between the immune system, the tumor and the microenvironment in pancreatic ductal adenocarcinoma (PDA) leads to the resistance of PDA to immunotherapy. To overcome this resistance, combination immunotherapy is being proposed. However, rational combinations that target multiple aspects of the complex anti-tumor immune response are warranted. Novel clinical trials will investigate and optimize the combination immunotherapy for PDA.

Keywords: Immunotherapy; pancreatic cancer; combination immunotherapy; vaccine therapy; GVAX; checkpoint inhibitors

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Introduction

Pancreatic ductal adenocarcinoma (PDA) remains an aggressive malignancy with 1- and 5-year survival rates of 29% and 7% for all stages (1). Surgical resection remains the only potentially curative option; however, even with the recent advancement in adjuvant chemotherapy, the median survival following surgical resection with a curative intent is approximately 28 months (2,3). PDA is resistant to existing radiation and/or chemotherapy regimens. Effective treatment options associated with durable responses are in desperate need. Immunotherapy provides a promising treatment alternative by harnessing the immune system to potentially kill tumor cells. Cancer cells often express tumor-associated antigens which can naturally activate the host immune system and initiate an anti-tumor response. A normal response leads to foreign tumor cell elimination by host T cells during the process of immunoediting (4). Alternatively, the tumor cell overcomes, evades or alters the immune system and progresses to detectable disease. Immunotherapy offers a targeted strategy to counteract

tumor cell defense mechanisms and tilt the favor back to tumor cell destruction by an activated immune system.

Single agent immunotherapy has found to be safe and efficacious in a selection of solid malignancies including: melanoma, renal cell carcinoma (RCC) and non-small cell lung cancer (NSCLC) with objective responses demonstrated in 20–30% of patients (5–7). These agents have not seen similar success in the treatment of PDA (6,8). The tumor microenvironment (TME) of melanoma, RCC and NSCLC is “immunogenic” with naturally high infiltration of effector lymphocytes in immunotherapy naïve patients (9). In contrast, PDA has a dense fibroblastic stroma and highly immunosuppressive TME infiltrated with multiple regulatory cells impeding an effective immune response (10). Many of these cells promote tumor development as well as alter cell polarization [M2 macrophages, TH2 cells, regulatory T cells (Treg cells)] contributing further to immune evasion and preventing a sufficient anticancer response to eliminate altered pancreatic cells (10). Because of this multitude of

immunosuppressive signals and effective immune evasion found in the PDA TME, strategies in immunotherapy that can overcome multiple barriers for effective antitumor immunity are needed, highlighting the necessity of rational combinations of immunotherapeutic agents. Until recently, most of the immunotherapy strategies for pancreatic cancer have been single agent immunotherapeutics, lacking rational combinations. Therefore, these treatments have not been successful. Here, we first reviewed single agent immunotherapeutics and identified the potential mechanisms of resistance to these immunotherapeutics as single agent treatments. We then discussed rational combinations to target the immune response from different approaches in an attempt to improve treatment effectiveness in pancreatic adenocarcinoma.

Immune checkpoint/T-cell co-inhibitory pathways

The immune response is regulated by multiple signal pathways and cells such as tumor associated macrophages (TAM), myeloid derived suppressor cells (MDSC), and regulatory T cells (Treg). Coordinated intercellular communication via surface receptors mediates the immune response and provides homeostatic mechanisms to mitigate excessive damage by chronic inflammation, as well as prevent autoimmunity (11). Immune checkpoints and other T-cell co-inhibitory pathways are a major class of receptors that have gained growing attention as an attractive immunotherapeutic target. These receptors include programmed death-1 (PD-1) and its ligand (PD-L1), cytotoxic T-lymphocyte antigen-4 (CTLA4), T cell immunoglobulin and mucin domain-containing 3 (TIM3), indoleamine 2,3-dioxygenase (IDO) and lymphocyte activation gene 3 (LAG3). These pathways operate to inhibit development, decrease function or initiate cell death in effector cells as an evolutionary means to prevent excessive inflammation. However, tumor cells take advantage of these pathway serving as a prominent tumor immune evasion mechanism. Identification of these immunosuppressive pathways has led to the development of monoclonal antibodies to bind and block these inhibitory ligands or receptors potentiating underlying antitumor immune activity.

PD-1/PD-L1

The PD-1/PD-L1 pathway plays a prominent role in the

development of a tolerant TME. PD-L1 expressed on the surface of tumor cells, antigen presenting cells (APC) and stroma binds with PD-1 on the surface of T cells. This interaction initiates T cell exhaustion (12,13). Tumors hijack this mechanistic pathway by expressing PD-L1, binding to PD-1 and contributing to T cell anergy thereby reducing effector activity (14). Two FDA approved monoclonal antibodies, pembrolizumab (KEYTRUDA) and nivolumab (OPDIVO), have been developed to block the interaction between PD-1 and its ligand. Two anti-PD-L1 antibodies, atezolizumab and avelumab, have also received FDA approval. This blockade has shown encouraging results in multiple tumor types (5,6). However, as a single agent in pancreatic cancer anti-PD-1 antibodies are ineffective and did not prolong survival (6).

CTLA4

CTLA4 blocks the costimulatory molecule CD28 by binding to the ligand B7-1/B7-2 on antigen presenting cells. T-cell activation requires multiple stimulatory signals and the blocking of B7-1/B7-2 prevents the stimulation signal inhibiting T-cell activation. CTLA4 inhibition signal occurs predominately during the priming phase of T-cell activation (13,15). Ipilimumab (YERVOY) is a fully humanized antibody that binds to CTLA4 blocking its action and enabling T cell activation (16). As a single agent in pancreatic cancer anti-CTLA4 antibodies are ineffective and did not prolong survival (8).

IDO

IDO is a tryptophan catabolizing enzyme. Tryptophan is required for T cell activation and its absence leads to Treg differentiation and immunosuppression (17). Pancreatic cancer hijacks this mechanism of immune tolerance and increases IDO levels likely playing a role in the immunosuppressive balance of low effector T cells and high Tregs infiltrating the TME. Metastatic PDA cells select for overexpression of IDO to evade detection and immunologic elimination (18). Inhibition of IDO has been explored as therapy for pancreatic cancer, but remains limited.

LAG3

LAG3 is an inhibitory receptor progressively expressed on exhausted T cells and is thought to be involved in tumor immune evasion (11,19). Blocking the LAG3 pathway may

serve to reverse T cell exhaustion and enhance antitumor effector function. LAG3 and PD-1 are commonly co expressed on exhausted T cells (20). The therapeutic benefit of LAG3 inhibition in pancreatic cancer remains to be well described.

Inducing T cells by vaccine therapy

The TME of PDA is predominately immunosuppressive with poor host tumor lymphocyte infiltration likely playing a role in the ineffectiveness of checkpoint inhibitor therapy (10). Vaccines have been designed to generate a humoral/cellular immune response with an aim of stimulating the host immune system to recognize and eliminate tumor cells with specific effector and memory T cells. There are two major categories of tumor vaccines: whole cell vaccines and antigen specific vaccines.

Whole cell vaccines

Whole-cell vaccines deliver a range of multiple antigens without the need for specific knowledge of the relevant target antigens. Irradiated whole tumor cells are processed and multiple tumor antigens can then be presented. An irradiated granulocyte macrophage colony stimulating factor (GM-CSF) secreting allogenic PDA vaccine (GVAX) has been developed and shown to be safe with a survival benefit associated with induction and enhancement of CD8+ T cell responses specific to mesothelin in phase I and II studies (21,22). Additionally, increased disease-free survival was appreciated in pancreatic cancer patients with an immune response generated to the tumor associated antigen mesothelin following GVAX vaccination (23). Pancreatic GVAX consists of two allogenic pancreatic tumor cell lines that have been transfected to produce human GM-CSF. Local cytokines are of utmost importance in enhancing antigen presentation and eliciting a maximal immune response (24). The GM-CSF serves this role recruiting and providing maturation signals to antigen presenting cells (APC) resulting in upregulation of costimulatory molecules and cytokine production (24,25). These recruited APCs then orchestrate the immune response by processing tumor antigens expressed by the vaccine PDA cell lines and presenting them to the host T effector cells.

Preclinical data suggest that cyclophosphamide may enhance the intended immune responses by depleting Treg cells resulting in higher avidity of effector T cells specific for tumor antigen (26). A clinical study compared the effects of administering low dose cyclophosphamide prior

to GVAX vaccine in patients with advanced PDA. Thirty patients received GVAX alone and 20 patients received intravenous cyclophosphamide 1 day before GVAX therapy. This combination was well tolerated with minimal adverse effects. Prolonged median survival and tumor-specific immune responses were appreciated in the combination cohort of patients with metastatic PDA compared to GVAX alone (23). A follow up clinical study treated 39 resectable PDA patients with GVAX administered either alone or in combination with immune modulating doses of Cy as neoadjuvant and adjuvant therapy and revealed formation of vaccine induced intratumoral tertiary lymphoid aggregates in 33 patients (27).

Algenpantucel-L is another whole cell vaccine composed of two human allogenic irradiated cancer lines genetically modified to express murine alpha-1,3-Galactosyl transferase (aGT) which leads to synthesis of a-galactosyl (aGal) residues to their cell surface (28). While present on many mammalian cells, humans are unable to recognize the common aGal pathway. Due to antigenic stimulation by normal gut flora expressing aGal, humans constitutively produce large amounts of aGal targeted antibodies. Following immunization with algenpantucel-L, hyperacute rejection is induced via complement mediated lysis and antibody-dependent cell mediated toxicity towards aGal epitopes leading to an enhanced antitumor immune response (29). A phase 2 trial enrolled 70 patients with PDA who had undergone R0 or R1 resection to receive algenpantucel-L in addition to standard adjuvant chemoradiotherapy. Algenpantucel-L was well tolerated with 1 year survival of 86% (28). However, recent press release from NewLink Genetics reported the phase 3 algenpantucel-L trial failed to achieve its primary endpoint of improved overall survival (30.4 months in control *vs.* 27.3 months in treatment group) (30).

CRS-207 and GVAX

Preclinical data have suggested that sequential combination of GVAX and CRS-207 in a prime/boosting approach induced a synergistic enhancement of T cell induction and anti-tumor effect. The first vaccine is given to initiate or “prime” the immune system and this immune response is then “boosted” following re-administration of antigen. A phase II trial randomized patients with previously treated metastatic PDA to receive GVAX followed by CRS-207 *vs.* GVAX alone (31). Overall survival was higher in the CRS-207 + GVAX group (6.1 *vs.* 3.9 months) and for patients

that received at least 3 doses of GVAX, overall survival was 9.7 months when also boosted by CRS-207 compared to 4.6 months when boosted by GVAX. Enhanced mesothelin specific T cell responses were associated with longer survival in both groups (31). Unfortunately, on maturation of a phase 2b trial of CRS-207 and GVAX, a significant difference in overall survival was not appreciated between the groups treated with either CRS-207/GVAX or CRS-207 alone and the group treated with chemotherapy (32).

Rationale for combination immunotherapies

The immune response to cancer occurs in a series of steps, each serving as a potential target to enhance immunotherapy. Cancer antigen is released from tumor cells and must be presented to antigen presenting cells. T cells are then primed and activated to recognize this antigen and subsequently must be trafficked to the tumors themselves. T cells then need to infiltrate the tumor, navigate surrounding stroma, recognize and kill the tumor cells. All of these steps are regulated by a backdrop of complex interactions between inhibitory cells and pathways naturally developed to prevent unchecked inflammation. This offers a multitude of potential targets for immunotherapy. The discoveries of checkpoint inhibitors and tumor vaccines recognizing tumor associated antigens have been promising initial steps, however, single agent therapy is insufficient for PDA due to low constitutive checkpoint expression and a naturally immunosuppressive TME.

Combination therapy has thus become a growing area of investigation for PDA, however, not all combinations are effective and significant barriers still exist. The combinations most likely to be effective and enhance immune effector function are rational combinations: utilizing agents that target separate steps of this anti-cancer immune response. Combinations of agents that target the same area of immune function are not the best place to investigate synergistic combinations. For example, the benefits of a combining two agents that similarly target T cell exhaustion in PDA are limited due to the initial barriers of T cell trafficking into the PDA TME. While some success has been found in combining checkpoint inhibitors in immunogenic cancers such as melanoma (7,33,34), little success was achieved in other types of malignancies, reducing enthusiasm for testing it in immune-excluded tumors such as PDA.

Chemotherapy is the current first-line treatment approach for most advanced cancers and thus an optimal

and appropriate incorporation with immunotherapy is of utmost importance. Multiple standard chemotherapeutic regimens utilized for PDA deplete T cells and increase circulating TAM. Thus, combinations of chemotherapy with immunotherapeutics that depend on activated T cells, such as anti-PD-1 antibodies, are not optimal. Additionally, preclinical data are important in guiding appropriate synergistic combinations to maximize anti-tumor immune function. However, in many cases, preclinical data do not exist, or the preclinical model does not well represent human PDA. Moreover, although immunotherapy is typically well tolerated, combination therapy may potentiate side effects. For instance, anti-CTLA4 therapy which itself is associated with nearly 30% incidence of grade III/IV autoimmune toxicities, in combination with other checkpoint inhibitors, is shown to further exacerbate the high grade autoimmune toxicities (35). These are important factors to consider to guide the development of combination immunotherapeutics. Rational combinations of immunotherapy that offer an approach to target the complex network of suppressive pathways and signals at appropriate, distinct angles are warranted.

Combination of vaccine and checkpoint inhibitor therapy

Vaccine therapy offers an approach to prime and activate the immune system and increase T cell infiltration in the immune-quiet TME of PDA. This serves as an ideal combination with checkpoint inhibitor therapy.

In a phase I study anti-CTLA4 antibody alone or in combination with GVAX was evaluated in 30 patients with previously treated advanced PDA. Objective responses were observed in 20% of patients receiving the combination of anti-CTLA4 therapy and GVAX, whereas none of the patients responded to single agent anti-CTLA4 therapy (36). In patients with overall survival of greater than 4.3 months, there was an increase in the number of mesothelin specific T cells in peripheral blood (36). While providing interesting initial results, the sample size is small and needs to be validated in bigger studies.

A preclinical murine model of metastatic PDA shows modest benefit from anti-PD-1/PD-L1 antibody treatments (37). However, a synergy was appreciated with significantly improved survival in pancreatic tumor bearing mice when treated with both anti-PD-1 antibody and GVAX as compared to GVAX or anti-PD-1 therapy alone (37). Consistently, immunohistochemistry (IHC) analysis identified immunotherapy induced lymphoid aggregates

in the resected PDA tumors of GVAX treated patients in the previously discussed clinical trial (NCT00727441). PD-1 expression was induced in these lymphoid aggregates, thereby priming the pancreatic cancer for potential anti-PD1 treatment (27). The induction of lymphoid aggregates and increased effector T cells leads to enhanced IFN γ production and subsequent upregulation of the PD-1/PD-L1 immunosuppressive pathways during the induction of adaptive immune response (38). While only a small fraction of PDA tumor cells expressed low levels of PD-L1, GVAX treatment modulated expression of PD-L1 on tumor cells as well as inducing infiltration of innate immune cells expressing high levels of PD-L1 (27,39). Thus, vaccine therapy may prime the environment for immune cell infiltration and upregulation of the PD-1/PD-L1 pathway now serving as a more appropriate therapeutic target.

A randomized trial of GVAX with or without anti-PD-1 therapy for neoadjuvant and adjuvant treatment of patients with surgically resectable PDA has begun recruitment of patients (NCT02451982) and will further investigate the potential synergistic benefits of these two therapies in concert.

Combination of vaccine, anti-PD-1 antibody, and radiation

Ionizing radiation therapy is a primary treatment option for advanced PDA. The “abscopal effect” has been described as a phenomenon of tumor regression distant from the irradiated volume and is theorized to be mediated by the stimulated immune system (40). Further study has identified many immunogenic effects of radiation therapy: increased release of tumor antigen, upregulation of MHC 1 for presentation, activation and migration of dendritic cells, and upregulation of checkpoint expression (40,41). Combination of radiation with chemotherapy has been beneficial in many tumor types underlining the need to study similar potential benefits in combination with immunotherapeutics.

A phase III trial is investigating the combination of algenpantucel-L vaccine with chemotherapy FOLFIRINOX (a standard of care chemotherapy combination for pancreatic cancer: 5-fluorouracil, folinic acid, irinotecan and oxaliplatin) or gemcitabine + nab/paclitaxel and conventional radiation therapy (CRT) in patients with locally advanced or borderline resectable PDA (NCT01836432). This study attempts to study the ability of immunotherapy and chemoradiation to work in cooperation. It is however unclear if the benefits of tumor debulking and increased

antigen release with chemoradiation will outweigh the negatives of radiation induced immune cell death.

A phase II trial of Cy/GVAX with pembrolizumab and stereotactic body radiation (SBRT) is underway for patients with locally advanced PDA to similarly investigate synergistic immune effects as well as the potential to convert tumors to resectability (NCT02648282). This study will allow analysis of the effectiveness of vaccine/checkpoint combination in the setting of radiation induced cell death and increased antigen release. SBRT has been suggested to lead to less radiation induced lymphopenia than CRT, and thus may serve as a more rational combination choice with immunotherapy (42).

Combination of adoptive T cell therapy and anti-PD-1 antibody

An alternative approach to increasing intratumoral T cell infiltration is infusion of a patient’s own harvested tumor infiltrating lymphocytes (TIL) (43). In metastatic melanoma CD8+ enriched TIL infusion following a lymphodepleting preparative regimen led to an objective response in 58% of patients including three complete responders (44). While PD-1 has a clear role in T cell suppression, the Rosenberg group additionally identified the clonally expanded tumor-reactive lymphocytes in the TIL of melanoma patients also preferentially expressed PD-1 (45). A phase II clinical trial investigating the combination of adoptive T cell therapy and checkpoint inhibition is ongoing in patients with metastatic PDA. These individuals will undergo biopsy to obtain tumor for generation of autologous TIL. Patients will then receive a non-myeloablative lymphocyte depleting regimen of chemotherapy along with pembrolizumab. Subsequently patients will receive infusion of TIL with aldesleukin (IL2) and pembrolizumab (NCT01174121). This may offer a similar combination rationale as vaccine and checkpoint inhibitor therapy.

Combination of anti-PD-1 antibody and anti-CTLA4 antibody

As single agent in pancreatic cancer, anti-CTLA4 and anti-PD-1 antibodies are ineffective (6,36). CTLA4 and PD-1 are involved in different signaling pathways within T cell activation and anergy. PD-L1 is upregulated following IFN γ exposure and prolonged activation. Binding of PD-L1 to PD-1 induces T cell exhaustion. Alternatively, CTLA4 blocks the costimulatory molecule on antigen presenting

cells preventing T cell activation during priming. These signals may cooperate to maintain T cell exhaustion; and thus treatments blocking both CTLA4 and PD-1 have shown synergistic effects and broaden effector T cell function. Resistance to single checkpoint therapy is common, and may be due to upregulation of alternative exhaustion pathways. Multiple studies have compared the combination of anti-CTLA4 antibodies with anti-PD-1 antibodies in advanced melanoma resulting in higher objective response rates than those receiving single immune checkpoint inhibitors (7,33,34). Combination of anti-CTLA4 antibody and radiation promotes regression of irradiated tumors; but tumors eventually escape by PD-L1 expression and T cell exhaustion. Therefore, a combination of radiation, anti-CTLA4 and anti-PD-1 therapy has been tested in metastatic melanoma (46). A similar combination is currently under investigation in a phase I trial of patients with advanced PDA (NCT02311361).

Combination of anti-PD-1 antibody and stromal targeting

Targeting the stroma of PDA may shift the balance in TME from an immunosuppressive one to one that supports an active effector T cell immune response and sensitize PDA to anti-PD1 therapy. Focal adhesion kinase (FAK) is a cytoplasmic protein tyrosine kinase that is expressed at high levels in many solid tumors and is inversely associated with survival (47,48). FAK serves as a key regulator of signals from the extracellular matrix leading to migration of tumor cells and associated stromal cells, particularly the macrophages and pancreatic stellate cells (48). A preclinical mouse model of PDA demonstrated that FAK inhibition treatment led to reduced tumor fibrosis and decreased inhibitory TAM, MDSC and Treg (47). These changes in the TME allowed a previously unresponsive mouse model of PDA to become responsive to T cell immunotherapy and PD-1 antagonists (49). A Phase I/IIa clinical study is underway in patients with advanced PDA combining defactinib (FAK inhibitor) with pembrolizumab (NCT02758587).

Another therapeutic target within the PDA stroma is hyaluronic acid (HA), which is an extracellular glycosaminoglycan component of human tissues that binds to proteoglycans and other hyadherins and forms a complex network in the extracellular matrix. Accumulation of HA is predictive of more aggressive disease and treatment resistance. The HA matrix prevents maximal drug accumulation, protects malignant cells from immune

surveillance, and is thought to contribute to the pro-tumorigenic impact of the TME (50,51). A PEGylated recombinant human hyaluronidase (PEGPH20) was developed to degrade hyaluronic acid and has been studied in combination with chemotherapy in metastatic PDA. It has been shown that patients whose tumor expressed a high level of HA had a higher objective response rate and a longer disease free survival when receiving the combination of gemcitabine/Nab-paclitaxel and PEGPH20 compared to those receiving chemotherapy alone (51-53). Additional preclinical studies have shown that PEGPH20 greatly enhanced NK cell infiltration, antibody delivery, and antibody dependent cell mediated cytotoxicity in mouse models of various solid tumors (54). Moreover, a preclinical study reported that the combination of PEGPH20 with shIDO-ST (a *Salmonella*-based therapy targeting IDO) led to an increased immune infiltration into previously impermeable desmoplastic PDA (55). These results have suggested that PEGPH20 can assist in overcoming stromal barriers to antitumor immune cell infiltration and thereby enhance the anti-tumor activity of cancer immunotherapy. Clinical trials testing PEGPH20 in combination with anti-PD-1/PD-L1 antibodies are underway (NCT02563548).

Combination of chemotherapy and immunotherapy

Traditional chemotherapy also has the ability to affect the immune response and thus potentially augment immunotherapeutic effectiveness when used in combination. Cyclophosphamide in immune modulating doses can decrease the number and function of Tregs (26) and has shown to improve the response when combined with GVAX (23). Gemcitabine has been found to increase *de novo* T cell activation in treated PDA patients (56). FOLFIRINOX has also been shown to modulate monocytes in patients following treatment. Chemotherapy is a current standard of care for PDA and thus ideally would be combined with immunotherapy, especially in this investigational phase.

Combination of chemotherapy and CCR2 inhibitor

The CCL2-CCR2 chemokine axis has been shown to recruit tumor-associated macrophages (TAM), diminish antitumor immune responses by lowering CD8+ cell infiltrate, and lead to worse survival (57,58). Furthermore, chemotherapy treatment with FOLFIRINOX has been shown to be associated with an increase in CCR2 positive monocytes in

patient's blood. A recent open label phase 1b trial included 39 patients who received six cycles of FOLFIRINOX alongside PF-04136309, an oral small molecule CCR2 inhibitor. The combination did not result in additional toxicity, but a 48.5% partial response rate, which is significantly higher than patients that received FOLFIRINOX therapy alone. Furthermore, only 3% of patients had disease progression (57). This study showed that the combination therapy of FOLFIRINOX and the CCR2 inhibitor led to a 36.5% decrease in circulating CCR2 positive monocytes (57). Further investigation is necessary to identify the clinical value of this decrease in monocytes in these patients.

Combination of chemotherapy and CD40 agonist

The receptor CD40 is a major contributor to the development of T cell mediated antitumor immune responses. CD40 signaling activates APCs which then provide supportive signals and permit cytotoxic T cell priming and activation (59). Blockade of this receptor inhibits cytotoxic T cell lytic (CTL) responses, while a selective CD40 agonist enhances tumor antigen presentation by APCs and antitumor T cell activity (59,60). A preclinical study identified that in combination with gemcitabine, an anti-CD40 agonist antibody reprogrammed TAMs, thus providing an additional targeted anticancer mechanism (60). A phase I trial investigating an anti-CD40 agonist antibody in combination with gemcitabine in patients with advanced PDA showed the CD40 agonist antibody is well tolerated with associated anti-tumor activity (NCT00711191) (61). Additional clinical trials are necessary to better assess potential benefits of this treatment.

Combination of chemotherapy and IDO inhibitor

As previously discussed, IDO is an enzyme hijacked by pancreatic cancer to reduce tryptophan necessary for T cell activation and lead to Treg differentiation and immunosuppression (17,18). Inhibition of IDO has been explored as a therapy for pancreatic cancer with a particular interest in combination with gemcitabine (56). A phase 1 trial revealed the safety in the combination of IDO inhibitor with gemcitabine alone or in combination with Nab-paclitaxel for metastatic pancreatic cancer as well as the promising objective response rates. A subsequent phase 2 trial investigating IDO inhibitor in combination with gemcitabine and Nab-paclitaxel reported a 37%

objective response rate, with one patient having a complete response (62). Therefore, IDO inhibitor may be offering an additional anti-tumor effect on top of chemotherapy; however, whether it will offer a survival benefit must still be assessed (63).

Conclusions and future directions

The prognosis for pancreatic cancer remains dismal. The advent of immunotherapy is exciting and presents a promising modality for the treatment of pancreatic cancer. The complex interaction between the immune system, the tumor and the microenvironment leads to a complex network of potentially therapeutic targets. Rational combinations are those that target multiple aspects of the complex anti-tumor immune response. Many of these are currently under investigation including increased antigen specific T cell infiltration with whole cell or neoantigen based vaccines combined with checkpoint inhibitors, T cell priming agents combined with checkpoint inhibitors, stromal targeting agents with checkpoint inhibitors, and cytotoxic chemotherapy in combination with macrophage chemotaxis agents. Rational immunotherapeutic combinations may prove to be the optimal way to synergistically overcome the immunosuppressive TME and shift the balance to an anti-tumor TME. Ongoing novel clinical trials will further develop and optimize the future of pancreatic cancer therapy but much remains to be learned.

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Footnote

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