Review

Recent Advancements in Pancreatic Cancer Immunotherapy

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Abstract

The overarching goal of this review is to highlight the current progress of immunotherapy in pancreatic cancer. Despite all the efforts, pancreatic cancer remains a disease that is refractory to almost all therapies and immunotherapy for pancreatic cancer remains in its infancy. In this review, we summarize promising advances and major hurdles in developing immunotherapeutic strategies for pancreatic cancer as presented in recent publications and a clinical trial database. Notably, a combination regimen of chemotherapy followed by immunotherapy appears to be superior to chemotherapy alone, wherein chemotherapeutic agents may play a dual role by reducing overall tumor burden through direct killing of cancerous cells and by indirect release of pro-inflammatory molecules and tumor associated antigens which, when presented in an immunogenic fashion, may function as an in situ "vaccine". Critically, the timing of administration of standard chemotherapy can markedly impact the induction of antitumor responses. We anticipate that among the gamut of combination immunotherapy and chemo-radiation therapies that are now being evaluated, we will eventually be able to optimize a regimen that can generate long-lasting responses and usher a new weapon in the fight against pancreatic cancer.

Key Words: pancreatic cancer; immunotherapy; tumor microenvironment

Introduction

Immunotherapy has emerged as a pillar (1) in cancer treatment through its gradual acceptance as standard of care for some liquid and solid tumor malignancies, such as: B cell leukemia (2), metastatic melanoma (3, 4) and Non-Small-Cell Lung Cancer (NSCLC) (5, 6), joining the ranks of conventional modalities such as surgery, chemo/radiation, and targeted therapies. While this era has witnessed remarkable success in immune-based therapies for B cell malignancies as well as more limited effects on solid tumor malignancies such as melanoma and NSCLC, advanced

pancreatic cancer is a disease that remains refractory to almost all the therapies (7, 8). However evidence of success in other solid tumors and a renaissance in our understanding of pancreatic tumor biology has led to translational efforts to pioneer immune-based approaches for the treatment of pancreatic cancer that has been accompanied by significant progress in the field (9).

Here, we present a review of the literature and clinical databases, highlighting promising advances and major hurdles in immunotherapy of pancreatic cancer, in the hope that it may provide insight into potential combination immune-based strategies and a rational therapeutic window within which these approaches may be most effective.

Current therapies against pancreatic cancer

Pancreatic cancer is a devastating and almost uniformly lethal malignancy, notoriously resistant to most therapies. Over 90% of pancreatic cancers present as pancreatic ductal adenocarcinoma (PDAC). In 2015, ~48,960 people in the United States will be diagnosed with this disease (10). Because of the aggressive nature of this cancer, the annual mortality rates closely match the incidence rate, and it is expected that ~40,000 will die from PDAC in the same year, with a 6% 5-year survival rate. For the 20% of patients with disease involving only the pancreas, surgical resection is the primary therapy. In the ~80% of patients with regional disease extension or metastases at presentation, chemotherapy is the primary treatment (11). Among the therapeutic options, polychemotherapy with infusional 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine plus albumin-bound paclitaxel (nab paclitaxel) are commonly employed (11). Nab-paclitaxel is a cytotoxic agent that binds to overexpressed SPARC (Secreted Protein Acidic and Rich in Cysteine) in cancer cells and stroma in the PDAC tumor microenvironment (TME), thus increasing drug delivery and accumulation in tumor cells. As compared to gemcitabine alone, nab-paclitaxel plus gemcitabine significantly improved overall survival, progression-free survival, and response rate in metastatic PDAC, but rates of peripheral neuropathy and myelosuppression were increased (12). However, because of the inherent chemoresistance of PDAC, median progression-free survival (PFS) with these intensive regimens is ≤ 6 months (12, 13). Approximately 45% of patients who receive such first-line regimens are alive and sufficiently fit to receive second-line therapy (12, 13), but only a few therapies have been approved by the Food and Drug Administration (FDA) for such patients. On October 22, 2015 the U.S. FDA approved Onivyde (irinotecan liposome injection), in combination with fluorouracil and leucovorin, to treat patients with advanced (metastatic) pancreatic cancer who have been previously treated with gemcitabine-based chemotherapy. Onivyde represented a nanotherapeutic version of chemotherapy that directly delivers the agent to the tumor microenvironment and prolongs the active drug uptake. Recent results from these pilot studies demonstrated promise for pancreatic cancer with increased median survival for 2 months (14). Despite off-label use of existing chemotherapeutic agents, survival at 2 years is < 10%. Thus, while antitumor benefit has been observed with such regimens, toxicity is substantial and therapeutic options are limited. Novel, less toxic approaches are desperately needed for this lethal cancer, particularly in patients who experience failure of existing first-line therapies. Despite these efforts, the best supportive care and treatment regimens for patients with pancreatic cancer can only prolong survival for a few months, with the goal of achieving palliation rather than cure (15).

Tumor microenvironment (TME) is a barrier to immune infiltration in pancreatic cancer

In the multistep progression of PDAC, the emergence of initiating genetic events within neoplastic cells, such as oncogenic *KRAS* mutations, is subsequently sculpted by additional pressures in the TME, including co-opting of the innate and adaptive arms of the host immune system (16). The importance of the TME in the biology of this disease, as well as a potential substrate for therapy, has become increasingly recognized (17-19). PDAC exists in a complex desmoplastic stroma that provides a structural framework for tumor growth, and conceals the tumor cells from immune surveillance. Tumor-associated stroma comprises a mix of fibroblasts (myofibroblasts

and pancreatic stellate cells) and an abundance of immunosuppressive regulatory T cells (Tregs), myeloid derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs) and mast cells (20-22) that restrain immunologically-mediated tumor cell killing (23). PDAC cells secrete chemokines that recruit this myriad of immune suppressor cells to the TME, which are then activated either by direct contact, or by cancer cell–derived triggers to selectively release additional tumor-promoting mediators (17, 20). In preclinical models, genetic or pharmacological modulation of either the number, or function, of immune suppressor cells in the TME has been shown to decrease the growth of PDAC (24-26). However, none of these approaches have yet made their way into the clinic, and therefore, single-agent immunotherapy approaches attempted to date, such as checkpoint inhibitors or vaccines, have been at best modestly successful (27-33). In contradistinction to melanoma, PDAC has long been considered a "non-immunogenic" neoplasm, in part due to the formidable barrier of the TME. Converting a non-immunogenic PDAC into an "immunogenic" neoplasm may create a treatment window for judicious application of immunotherapeutic strategies (30, 34, 35).

Current strategies in cancer immunotherapy

With great strides in the understanding of immunology and cancer biology over the past 20 years, cancer immunotherapy has emerged as a model for successfully translating scientific discovery from the laboratory to the clinical arena. Effective immunotherapies have mediated durable antitumor immune response and cancer regressions, leading to remarkable prolongation in the survival of patients with leukemia, melanoma, lung cancer, liver, bladder, ovarian, renal, and prostate cancers (36). On the heels of these studies, immunotherapy may be poised to revolutionize in similar fashion the treatment of pancreatic cancer. We summarize below the current immunotherapeutic strategies for human cancers in Table 1.

Current clinical trials for pancreatic cancer

Pancreatic cancer mouse models provide an entry point for the study of immunotherapy in this disease. Syngeneic orthotopic pancreatic cancer allograft mouse models assessing the potency of immune reagents have demonstrated the ability to eliminate small burdens of established tumors, a situation that recapitulates the condition of minimal residual disease commonly found after surgical removal of human tumors (37). In an example of this approach, we have demonstrated that by stabilizing the mast cell membrane, we are able to cure mice with pre-established pancreatic cancer by blocking immunosuppression and unleashing an enhanced endogenous anti-tumor immune response (20, 21).

Genetically engineered mouse models (GEMM) that yield spontaneous PDAC have led to renewed enthusiasm to exploring potential therapies with a mechanistic perspective. A commonly used, well-validated, clinically relevant model, using KrasG12D;Trp53R172H;Pdx1-Cre (KPC) mice (48), can recapitulate the heterogeneity of tumorigenesis and the TME of human PDAC. Similar to the clinical scenario among patients, these mice are largely resistant to conventional therapies allowing the full spectrum of current immunotherapy strategies to tested in this model; however, with only sporadic success. To date, there is no FDA approved immunotherapeutic regimen for the specific treatment of pancreatic cancer. On the basis of additional studies using novel immune modulatory combinations, in multiple pre-clinical PDAC models, a new wave of clinical trials was launched. In the following Tables 2-16, we surveyed the database of clinicaltrials.gov to identify the most recent immune-based clinical regimens. The key words used in the search included: immune, immunotherapy, vaccine, antibody, antigen, CTLA-4, PD-1, tumor infiltrating lymphocyte (TIL), IDO, CAR-T, mesothelin.

CD40 agonist trials

As a member of the tumor necrosis factor receptor superfamily, CD40 is expressed on the cell surface of immune cells, in particular B cells, dendritic cells, macrophages and monocytes as well as some normal and malignant cells. Binding of CD154 (the primary ligand for CD40) on T cell surface, CD40 activates T cells by ligand-receptor direct interaction. In addition, this binding indirectly activated T cells by CD154 mediating cytokine release from dendritic cells and

Table 1. Current immunotherapeutic strategies on human cancers

Category	Examples	Description	Tables
Vaccines	Whole cell vaccines, Peptide vaccines, Dendritic cell vaccines (9), Listeria-based vaccines, Recombinant virus-based vaccine	In contrast to traditional prophylactic vaccines against infection, cancer vaccines induce an immune response involving both cellular (T cell), as well as humoral immunity (37, 38). Recent vaccine trials have represented some of the most successful modalities during the past decade for pancreatic cancer patients (38).	3, 5, 6, 14, 15
Antibodies that target tumor antigens	Monoclonal antibodies, Bi-specific antibodies (e.g. bi-specific T-cell engager, BiTE, and dual-affinity re-targeting, DART) (39)	Tumor-binding immunoglobulin can kill tumor cells, either directly by fixing complement, or by inducing antibody-dependent cell-mediated cytotoxicity (ADCC), or indirectly, following opsonization and presentation by APCs to elicit T cell responses (40).	4, 13
Antibodies that target checkpoint pathways and co-inhibitory/ co-stimulatory molecules	Anti-CTLA-4, Anti-PD-1/Anti-PD-L1	Ipilimumab (Anti-CTLA-4), pembrolizumab (Anti-PD-1), and nivolumab (Anti-PD-1) (1) target inhibitory molecules involved in regulation of T cell response, leading to boosting of the anti-tumor immune response (41).	8, 9
Adoptive cell therapy	Peripheral blood-derived antigen-specific T cells (7), Tumor-infiltrating lymphocytes (TIL) (8)	The use of endogenous T cells derived from peripheral blood or tumor infiltrating lymphocyte populations has been successfully used to treat patients with several solid tumors (42).	10,
Adoptive cell therapy	Engineered T cells (43)	T cells transduced to express chimeric antigen receptors (CAR) can be genetically engineered not only to redirect specificity to desired antigen, but also confer enhanced function, persistence and safety (44-46).	11
Non-specific adjuvants	Cytokines, such as interleukins (e.g. IL-2, IL-15) or Interferon	These may be co-administered for facilitate the in vivo function of immune cells and/ or modulate the tumor cells and TME.	16
Targeting on tumor microenvironment	Anti-CD40, inhibitors to BTK or IDO	Overcoming the immunosuppressive microenvironment may sensitize combination immunotherapy.	2, 7, 12

*Format of the Tables adopted from the previous review (47). All the NCT numbers and their corresponding details are from clinicaltrials.gov.

Addition notes for all Tables:

No: Number of patients (estimated number for ongoing trials); PR: partial responses; SD: stable disease; PD: progressive disease; DFS: disease-free survival; PFS: progression-free survival; OS: overall survival; GVAX: Granulocyte-macrophage colony-stimulating factor (GM-CSF) secreting tumor vaccine or GVAX pancreatic cancer vaccine.

macrophages (49). Anti-CD40 agonist antibodies induce tumor regression by both stimulating T cell activation (T-cell-dependent) and macrophage reprogramming (T-cell-independent) (50). It is believe that the T-cell-independent mechanism is related to turnaround of the pro-tumorigenic macrophage and interference of the desmoplastic tumor stroma in PDAC. Several trials (see Table 2) using agonistic CD40 monoclonal antibody CP-870,893 (51) have demonstrated effective anti-tumor activity in PDAC patients.

GVAX and CRS-207

GVAX is a vaccine comprised of tumor cells transfected with GM-CSF, which recruits and activates dendritic cells (DCs) *in vivo*. As highly efficient T-cell activator, DCs in the TME is required for stimulating a robust adaptive anti-tumor immune response due to its

Table 2. Anti-CD40 clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT00711191 2013 (29)	Chemotherapy-naïve surgically incurable pancreatic cancer (Dose escalation open label)	I	anti-CD40 agonist monoclonal antibody Gemcitabine	22	19% had PR, 50% had SD, and 18% had PD. Median PFS was 5.6 months, and the median OS was 7.4 months. Gemcitabine alone achieves a historical tumor response rate of 5.4%, with median PFS of 2.3 months and median OS of 5.7 months. Therefore, combination treatment showed efficacy.
NCT02588443 2015	Newly diagnosed resectable pancreatic carcinoma (Neo-adjuvant)	I	anti-CD40 agonist monoclonal antibody Nab-Paclitaxel Gemcitabine	10	Active, not recruiting
NCT02225002 2014	Solid tumors (Open-label, dose-escalation)	I	anti-CD40 agonist monoclonal antibody	N	Completed

ability to present tumor-associated antigens to T cells and maintain the antigen-specific T cell potency (38). CRS-207 (52) is a live-attenuated recombinant Listeria monocytogenes bacterium engineered to express human mesothelin that was overexpressed in pancreatic cancerous ducts but not in pancreatitis and normal tissues. CRS-207 is capable of both delivering mesothelin antigen into both class I and II antigen-processing pathways to induce tumor-specific T cell response and triggering cytokine release to boost natural killer (NK) cell activation. As a whole-cell vaccine platform, GVAX and CRS-207 form a potent sequential 2-vaccine program. On the basis of safety, feasibility, and immune activation (53) with GVAX plus CRS-207, other regimens, such as chemo/radiotherapy, checkpoint control antibodies were introduced to the trials to maximize the efficacy. GVAX in conjunction with immunomodulatory cyclophosphamide (54) has been applied to many preclinical tumor models and several human cancers as the low dose cyclophosphamide serves as a vaccine enhancer in disrupting immune tolerance through depleting regulatory T cell in situ and promoting dendritic cell maturation. Indeed, heterologous prime/boost with GVAX and CRS-207 in pancreatic patients conditioned with cyclophosphamide extended survival with minimal toxicity (28). Recent trials involving this combinational vaccine approach are listed in Table 3. Chemotherapy, such as Folfirinox, or radiation therapy, such as high-energy X rays, work in different ways to kill tumor cells and are being tested in these trials with GVAX/CRS-207/Cyclophosphamide combination therapy. In addition, checkpoint control antibodies, such as anti-PD-1 and anti-CTLA-4, are the most current immunotherapeutic regimens for boosting pre-existent anticancer immunity initiated by GVAX/CRS-207/Cyclophosphamide combination therapy.

G17DT

Transgenic, hypergastrinemic InsGas mice (56) were developed to express human CCK2 receptor for investigating the role of gastrin/CCK in pancreatic exocrine cells. Because gastrin and its receptors are co-expressed on human pancreatic adenocarcinoma, this mouse model validated the mitogenic potency of gastrin peptides. When it was discovered that intramuscular injection of gastric antigens can generate an immune response, clinical trials were

Table 3. GVAX clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT00305760 2015 (55)	Metastatic or locally advanced pancreatic cancer	II	GVAX Cyclophosphamide (Cy) Cetuximab	60	The median DFS is 17.3 months with median survival of 24.8 months. The postimmunotherapy induction of mesothelin-specific $CD8^+$ T cells in HLA-$A1^+$ and HLA-$A2^+$ patients correlates with DFS.
NCT02451982 2015	Surgically resectable pancreatic cancer (Neoadjuvant/adjuvant)	I/II	GVAX PD-1 Antibody CY	50	Not yet recruiting
NCT00727441 2015	Patients undergoing chemotherapy and radiation therapy for stage I or stage II pancreatic cancer that can be removed by surgery		GVAX CY	87	Active, not recruiting
NCT00084383 2013	Resected stage I or stage II adenocarcinoma (cancer) of the pancreas	II	GVAX Adjuvant Chemoradiotherapy	60	Completed
NCT01417000 2015	Pancreatic cancer (Safety and efficacy)	II	GVAX CRS-207	93	Active, not recruiting
NCT02243371 2015 (28)	Previously treated metastatic adenocarcinoma of the pancreas	II	GVAX CRS-207 PD-1 Blockade Antibody (Nivolumab)	94	Recruiting
NCT02004262 2015	Pancreatic cancer (Safety and efficacy)	II	GVAX CRS-207	240	Active, not recruiting
NCT01595321 2015	Resected adenocarcinoma of the pancreas		GVAX Low Dose Cy Fractionated Stereotactic Body Radiation Therapy (SBRT) FOLFIRINOX	19	Active, not recruiting
NCT01896869 2015	Metastatic pancreatic cancer (Multicenter study)	II	GVAX CTLA-4 antibody FOLFIRINOX	92	Recruiting

initiated to exploit the use of this target for eliciting an antitumor response. G17DT, an antigastrin immunogen, can produce neutralizing antibodies against the tumor growth factors amidated and glycine-extended form of gastrin-17 (57). Rapid and sustained antibody production after immunization with G17DT can generate a robust anti-tumor response, thus, G17DT may represent a new therapeutic option for responders with pancreatic cancer (Table 4).

Table 4. Gastrin immunogen clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT02118077 2014 (57)	Advanced pancreatic cancer (Prospective, randomized, double-blind, placebo-controlled, group sequential trial)	III	G17DT Gemcitabine 5-fluorouracil	154	Patients developing anti-G17DT responses (73.8%) survived longer than non-responders or those on placebo (176 vs. 63 vs. 83 days)
NCT00044031 2014	Previously untreated subjects with locally advanced (nonresectable stage II and III), recurrent disease following primary resection, or metastatic (stage IV) adenocarcinoma of the pancreas (Protocol No. PC4) (Prospective, randomized, controlled, double-blind, multi-national, multi-center)	III	G17DT Gemcitabine	394	Completed
NCT02098239 2014	Advanced pancreatic cancer (Open, multiple dose, single centre)	II	G17DT	41	Completed
NCT02098291 2014	Advanced Pancreatic Carcinoma (Open, single-center, safety and tolerability)	II	G17DT	34	Completed

CEA/MUC-1

CEA (carcinoembryonic antigen, an oncofetal antigen) and MUC-1 (mucin, a highly glycosylated protein) are expressed at high levels on most human pancreatic cancers. T cells can recognized HLA-restricted epitopes derived from CEA and non-HLA-restricted epitopes encoded by MUC-1 (58, 59). A vaccine, engineered with poxviruses targeting both CEA and MUC-1, can generate polyclonal T cells, which produce antigen-specific anti-tumor effects and appear to prevent tumor escape during antigen loss. This vaccination protocol has proven to be safe and well tolerated (60) with some significant response, as indicated in Table 5.

Algenpantucel-L

A cell-based allogeneic pancreatic cancer vaccine, algenpantucel-L, targets alpha-1,3 galactosyl epitopes to induce better antitumor immune priming on the concept of the hyperacute rejection response. This vaccine was engineered to express alpha-Gal (murine alpha-1,3-galactosyltransferase gene) in two human pancreatic ductal adenocarcinoma cell lines (HAPa-1 and HAPa-2). Since alpha-Gal is inactive in normal human cells, Algenpantucel-L xenotransplantation will produce high titer of anti-alpha-Gal antibodies that trigger hyperacute rejection presenting as complement-mediated tumor cell lysis and antibody-dependent cell-mediated cytotoxicity (61). Through the subsequent opsonization and phagocytosis of the whole tumor cells, APCs will process and present the entire library of TAAs to cytotoxic effector T cells to fight the patient's own cancer. Algenpantucel-L has demonstrated survival benefit for pancreatic cancer patients in a Phase II trial for patients with surgically resected disease. The results shown in Table 6 reflect improved survival in patients when compared with a historical control (62) in phase II studies which remain to be proven in randomized Phase III trials (currently accruing).

Table 5. CEA/MUC-1 clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
2007 (60)	Advanced pancreatic cancer (Open-label)	I	CEA MUC-1	10	A significant increase in OS was noted in responders compared with non-responders (15.1 vs. 3.9 months).
NCT00669734 2015	Unresectable pancreas cancer: Intratumoral Recombinant Fowlpox PANVAC (PANVAC-F) plus subcutaneous recombinant vaccinia PANVAC (PANVAC-V), PANVAC-F and rH-GM-CSF	I	Falimarev (CEA & MUC-1) Inalimarev (CEA & MUC-1) Sargramostim (rH-GM-CSF)	14	This study is ongoing, but not recruiting participants.

Bruton's Tyrosine Kinase inhibitor

The first clinically approved use of ibrutinib, a novel BTK inhibitor developed by Pharmacyclics, has led to decreased mouse tumor growth and improved responsiveness to gemcitabine in orthotopic pancreatic cancer mouse models (64). In another preclinical study, Ibrutinib improved the survival of both genetically engineered PDAC models, as well as mice bearing patient-derived PDAC xenografts (65). Ibrutinib therapy also reduced the stromal desmoplasia in preclinical models, and improved delivery of chemotherapeutics to the tumor milieu.

Table 6. Algenpantucel-L clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT01836432 2015	Borderline resectable or locally advanced unresectable pancreatic cancer	III	HyperAcute®-Pancreas (algenpantucel-L)	280	Recruiting
NCT02405585 2015	Borderline resectable pancreatic cancer	II	HyperAcute®-Pancreas (algenpantucel-L)	48	Recruiting
NCT01072981 2015 (63)	Surgically resected pancreatic cancer	III	HyperAcute®-Pancreas (algenpantucel-L)	722	Active, not recruiting
NCT00569387 2015 (63)	Surgically resected pancreatic cancer	II	HyperAcute®-Pancreas (algenpantucel-L)	73	12-month DFS was 62 %, and the 12-month OS was 86 %
NCT00614601 2015	Surgically resected pancreatic cancer (Low dose)	II	HyperAcute®-Pancreas (algenpantucel-L)	9	Terminated
NCT00255827 2015	Surgically resected pancreatic cancer	I/II	HyperAcute®-Pancreas (algenpantucel-L)	7	Completed

Table 7. ACP-196 clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT02362048 2015	Advanced or metastatic pancreatic cancer (KEYNOTE144)	II	ACP-196 pembrolizumab	76	Recruiting
NCT02570711 2015	Previously untreated metastatic pancreatic cancer	II	ACP-196 Nab-paclitaxel gemcitabine	120	Recruiting

Inhibiting BTK has the desired effect of inhibiting mast cell degranulation and cytokine secretion, a result that our group and others have shown, mediating tumor suppression in PDAC (20-22). However, Ibrutinib suffers from multiple off-target effects that limit its application in solid tumors where enhancing effector T-cell function is a crucial intent (2). Ibrutinib's potency on ITK (IL2-inducible T-cell kinase) and TXK (Tyrosine-protein Kinase) may explain why it interferes with cell-mediated anti-tumor activities and immune-mediated killing in the TME.

Acerta Pharma has developed ACP-196, an orally bioavailable, 2nd generation inhibitor of Bruton's tyrosine kinase (BTK). BTK is a non-receptor enzyme in the Tec kinase family that is expressed by cells of hematopoietic origin, including B cells, myeloid cells, and mast cells, where it regulates multiple cellular processes, including proliferation, differentiation, apoptosis, and cell migration (66-68). In addition, BTK-dependent activation of mast cells, myeloid cells and other immunocytes in the peritumoral inflammatory stroma has been shown to sustain the complex microenvironment needed for solid tumor maintenance (69-71). Overall, BTK inhibition interferes with the cross-talk between neoplastic cells and the TME, such as immune regulatory cells recruitment and infiltration into tumor, suggesting disruption of intrinsic and extrinsic survival signals (70, 72). Importantly, unlike Ibrutinib, ACP-196 did not inhibit ITK or TXK, which are both involved in Teff function (73-75). Two ongoing trials at MD Anderson Cancer Center (Table 7) will evaluate whether the combination therapy of BTK inhibition and checkpoint blockade leads to greater benefit compared with monotherapy.

Immune checkpoint control antibodies

The activation and inhibition of the immune system are controlled through signals from a panel of ligands and receptors of co-stimulatory and co-inhibitory molecules, which have been recognized as immune checkpoint control pathways. Anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies have been applied in cancer immunotherapy for interfering with the inhibitory signaling in T cells (76). By rescuing anti-tumor immune responses, these antibodies can mediate durable cancer regressions and long-term survival (77).

CTLA-4

CTLA-4 (cytotoxic T lymphocyte antigen 4) (77-79), a costimulatory molecule similar to CD28, is expressed on activated T cells and also bind to the ligands CD80 (B7-1) and CD86 (B7-2) on antigen-presenting cells. CD28 molecule is constitutively expressed on T cell surface and stimulating T cell activation through binding to the ligands, whereas CTLA-4 can transmit an inhibitory signal due to compete for CD28 binding to CD80/86. Anti-CTLA-4 antibody, via blocking the high affinity binding of CTLA-4 to CD80/86, allows CD28 to interact with CD80/86. In patients with melanoma (80), anti-CTLA-4 can magnify anti-tumor response induced by the neoepitopes from tumor mutations. By releasing the "brake" on T cell activation (81), CTLA-4 blockade expands immunological memory and boosts long-lasting immunogenicity. Ipilimumab anti-CTLA-4 IgG1 antibody gained FDA-approval for second-line treatment of patients with metastatic melanoma. Trials incorporating combination regimens in Table 8 are being tested in patients with pancreatic cancer. Tremelimumab (82) anti-CTLA-4 IgG2 antibody

Table 8. CTLA-4 antibody clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT01473940 2014	Stage III-IV or recurrent pancreatic cancer that cannot be removed by surgery	I	CTLA-4 antibody (Ipilimumab) Gemcitabine	28	Recruiting
NCT00112580 2009 (83)	Stage IV pancreatic cancer that cannot be removed by surgery	II	CTLA-4 antibody (Ipilimumab)	82	Single agent Ipilimumab at 3.0 mg/kg/dose is ineffective for the treatment of advanced pancreas cancer.
NCT00836407 2013	Locally advanced, unresectable or metastatic pancreatic cancer	I	CTLA-4 antibody (Ipilimumab) Pancreatic Cancer Vaccine	30	Completed
NCT01896869 2015	See Table 3				
NCT02311361 2014	Unresectable pancreatic cancer	I	CTLA-4 antibody (Tremelimumab) PD-L1 antibody (MEDI4736) Radiation Therapy	60	Recruiting GEMM model (41)
NCT02558894 2016	Metastatic Pancreatic Ductal Carcinoma	II	CTLA-4 antibody (Tremelimumab) PD-L1 antibody (MEDI4736)	130	Recruiting
NCT02639026 2015	Pancreatic Cancers	I	CTLA-4 antibody (Tremelimumab) PD-L1 antibody (MEDI4736) Radiation Therapy	30	Recruiting
NCT02527434 2016	Advanced Solid Tumors (including pancreatic ductal adenocarcinoma)	II	CTLA-4 antibody (Tremelimumab) PD-L1 antibody (MEDI4736)	76	Recruiting

achieved survival benefit for 9 patients with pancreatic cancer when combined with gemcitabine in a phase I trial, and its subsequent combination regimens were under the trials in Table 8.

PD-1/PD-L1

PD-1 (84) is an inhibitory receptor that down-regulates T-cell activation when bound to a PD-L1 or PD-L2 ligand on tumor cells. Notably, for patients with melanoma with positive expression of the PD-1 ligand, anti–PD-1 immunotherapy has been associated with a better response (85). Nivolumab (86), a fully humanized immunoglobulin G4 (IgG4) mAb targeting human PD-1 with high affinity, has been approved by FDA for treatment on melanoma and lung cancer. There was no difference in the overall median survival rate for nivolumab or nivolumab and ipilimumab combined, but among patients with PD-1 ligand–negative tumors, progression-free survival was longer with the combination therapy of nivolumab and ipilimumab than with nivolumab alone (3). In light of these promising results in melanoma, PD-1/PD-L1

blockades are being evaluated in several clinical trials (see Table 9) involving combination/chemotherapy regimens for the treatment of patients with pancreatic cancer.

Table 9. PD-1/PD-L1 clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT01313416 2015	Resected pancreatic cancer	II	PD-1 antibody (CT-011, Pidilizumab) Gemcitabine	29	Suspended
NCT02451982 2015	See Table 3				
NCT02309177 2015	Pancreatic Cancer (Safety)	I	PD-1 antibody (Nivolumab) Nab-Paclitaxel Plus or Minus Gemcitabine	138	Recruiting
NCT02243371 2015	See Table 3				
NCT02546531 2015	Advanced cancer	I	PD-1 antibody (Pembrolizumab) Defactinib Gemcitabine	50	Not yet recruiting
NCT02452424 2015	Advanced melanoma and other solid tumors	I/II	PLX3397: a selective colony-stimulating factor 1 receptor (CSF1R) kinase inhibitor PD-1 antibody (Pembrolizumab)	400	Recruiting
NCT02303990 2015	Advanced and metastatic cancers (RADVAX: stratified phase I)	I	PD-1 antibody (Pembrolizumab) Hypofractionated Radiotherapy	70	Recruiting
NCT02305186 2015	Resectable or borderline resectable pancreatic cancer (Safety and immunological effect)	I/II	PD-1 antibody (Pembrolizumab)	56	Recruiting
NCT02331251 2015	Advanced cancer (PembroPlus)	I/II	PD-1 antibody (Pembrolizumab) Chemotherapy	90	Recruiting
NCT02432963 2015	Vaccine Therapy and Pembrolizumab in Treating Patients With Solid Tumors That Have Failed Prior Therapy	I	Modified Vaccinia Virus Ankara Vaccine Expressing p53 PD-1 antibody (Pembrolizumab)	12	Not yet recruiting
NCT02009449 2015	Advanced solid tumors	I	pegylated recombinant human IL-10 (PEG-rHuIL-10, AM0010) PD-1 antibody (Pembrolizumab)	135	Recruiting
NCT02268825 2015	Advanced GI cancers	I/IIA	PD-1 antibody (MK-3475) Chemotherapy	128	Recruiting
NCT02528357 2016	Advanced solid tumors	I	OX40 antibody PD-1 antibody	264	Recruiting
NCT02221960 2016	Advanced solid tumors	I	OX40 antibody PD-1 antibody	224	Recruiting

Table 10. Tumor infiltrating lymphocyte (TIL) clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT01174121	Metastatic cancer	II	Young TIL with IL-2	260	Recruiting
NCT00003780 2013	Cancer of the pancreas	II	TIL therapy Chemotherapy	150	Active, not recruiting (The information of recruitment status has not been verified recently.)
NCT00019084 2013	Advanced cancer	II	Mutant p53 or Ras peptide vaccine sargramostim Therapeutic autologous lymphocytes TIL with IL-2	null	Completed

Adoptive T cell therapy

Adoptive T-cell therapy (42) involves the ex vivo enrichment and expansion of tumor-reactive T cells for infusion. As an immune-based approach, adoptive therapy has become an increasingly attractive modality for the treatment of patients with cancer due to its potential for high specificity, non-cross resistance with conventional therapies, and the promise of long-term immunoprotection. Adoptive cellular therapy encompasses the use of tumor reactive T cells derived from an endogenous source (tumor infiltrating lymphocytes, TIL or peripheral blood) or a genetically modified lymphocyte population engineered to recognize tumor antigen through expression of the cognate chimeric antibody or T-cell receptor (CAR/TCR).

Tumor Infiltrating Lymphocyte (TIL)

To date, only TIL therapies have been reported for the treatment of pancreatic cancer, as shown in Table 10, although efforts are underway in our lab and others to explore the use of MS/MS and RNAseq analysis of patient tumor immunopeptidome to develop T cell therapy targeting autologous tumor neo-epitopes for pancreatic cancer.

CAR-T cells

Adoptive therapy with T cells transduced to express chimeric antigen receptors (CAR) consisting of fusion proteins joining antibody variable regions to T-cell signaling chains. The antibody moiety confers antigen specificity and activates the T cell signaling generally in tandem with the cytoplasmic signaling domains of CD28, 4-1BB and other costimulatory molecules (44-46). CAR-T cell represents an important modality with the promise of off-the-shelf strategies for the treatment of pancreatic cancer. The following clinical trials in Table 11 are being evaluated for use in several solid tumor malignancies including pancreatic cancer (46).

IDO inhibitor

Indoleamine 2,3-dioxygenase (IDO), which is overexpressed in metastatic PDAC (87), contributes to the immune suppressive tumor microenvironment by starving T lymphocytes of tryptophan (87). Active IDO enzyme can catalyze L-tryptophan (L-Trp) into kynurenine (Kyn) pathway metabolites. In PDAC, L-Trp was completely consumed by tumor cell-derived IDO, resulting in the significant reduction of L-Trp concentration in TME. In response to L-Trp deficiency, tumor infiltrating CD8+ T cells will be subjected to cell cycle arrest and anergy through mTOR (mammalian target of rapamycin) and PKC signaling pathways. IDO inhibitors may restore L-Trp level and overcome the immune suppressive TME in vivo (88). Clinical grade IDO inhibitors are currently undergoing evaluation in

Table 11. CAR-T cells clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT02349724 2015	CEA positive cancer	I	Anti-CEA-CAR T	75	Recruiting
NCT01583686 2015	Metastatic cancer	I/II	Anti-mesothelin CAR Aldesleukin (IL-2)	136	Recruiting
NCT01897415 2015	Pancreatic cancer	I	Autologous T cells transfected with chimeric anti-mesothelin immunoreceptor SS1	10	Completed
NCT02587689 2015	MUC1 positive advanced refractory solid tumor	I/II	anti-MUC1 CAR T Cells	20	Recruiting
NCT02580747 2015	Relapsed and/or chemotherapy refractory advanced malignancies	I	anti-meso-CAR vector transduced T cells	20	Recruiting
NCT02465983 2015	Metastatic pancreatic cancer	I	CART-meso-19 T cells	12	Recruiting
NCT02541370 2015	Relapsed and/or chemotherapy refractory advanced malignancies	I	anti-CD133-CAR vector-transduced T cells	20	Recruiting
NCT02416466 2015	CAR-T Hepatic Artery Infusions and Sir-Spheres for Liver Metastases	I	anti-CEA CAR-T cells	6	Recruiting
NCT02159716 2014	Mesothelin expressing cancers	I	CART-meso	24	Recruiting

solid tumors, including pancreatic cancers listed in Table 12.

Mesothelin

Mesothelin is a tumor antigen upregulated on most human pancreatic cancer. Although the normal function of membrane-bound mesothelin is still unknown, the soluble mesothelin (89) can be detected in the peripheral blood of patients with pancreatic cancer, intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm, but not in healthy individuals. Mesothelin specific antibody and T-cell response in those patients indicated antimesothelin immunity and offered potential therapy against pancreatic cancer. In addition to mesothelin vaccine trials using GVAX and CRS-207 in combination (28), antibodies (90) against mesothelin provide an alternative for pancreatic cancer immunotherapy, as shown in Table 13.

Dendritic cell

As a professional antigen-presenting cell, dendritic cells (DCs) play an essential role in the anti-tumor immune response with their capacity to capture, process, and present antigens to T cells (91). DCs are extremely efficient for vaccination by priming naïve CD8+ T cells into cytotoxic T cells as well as cytokine release (92). In addition to the vaccine related studies listed in the above Tables, we list a broad spectrum of DC vaccine trials in Table 14. In addition to shaping the specificity of response against tumor antigens through DC vaccination, these trials also focus on modifying the function and activation of dendritic cells. In the immune-privileged microenvironment of pancreatic

Table 12. IDO inhibitor clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT02077881 2015	Metastatic pancreatic cancer	I/II	IDO Inhibitor (Indoximod) Gemcitabine and Nab-Paclitaxel	98	Recruiting
NCT00739609 2012	Relapsed or refractory solid tumors	I	IDO Inhibitor (1-methyl-D-tryptophan)	17	Terminated
NCT02318277 2015	Selected advanced solid tumors	I/II	PD-L1 antibody (MEDI4736) IDO Inhibitor (INCB024360)	157	Recruiting

cancer, insufficiency of dendritic cells is the main roadblock for T cell activation, a typical malfunction observed in many other cancer types (93). Dendritic cell expansion and maturation may overcome the resistance to checkpoint immunotherapy and reprogram the TME to an immunogenic microenvironment (93).

Ras

The oncogenic Ras mutation is an essential and initiating event in pancreatic tumorigenesis (48). Preclinical studies (94) demonstrated that Kras mutation is required for PDAC maintenance. Targeting oncogenic/mutant Ras may provide a novel therapeutic avenue for pancreatic cancer, and the ongoing trials that are associated with Ras targeting are summarized in Table 15. Notably, the long-term follow-up (over 10 years) of twenty-three patients who were vaccinated after surgical removal of pancreatic adenocarcinoma (22 pancreaticoduodenectomies, one distal resection), in two Phase I/II clinical trials (95, 96), showed great promise on correlation of sustained immunological T-cell reactivity and prognosis. The mechanism of the vaccine was attributed to the long synthetic mutant ras peptides designed primarily to trigger T-helper responses. Seventeen of 20 evaluable patients (85%) responded immunologically to the vaccine. Median survival for all patients was 27.5 months and 28 months for immune responders. The 5-year survival

Table 13. Mesothelin related clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT00325494 2014	Pancreatic cancer	I	a chimeric monoclonal antibody that targets mesothelin (MORAb-009)	24	Completed
NCT01413451 2013	High mesothelin cancers	0	Amatuximab (MORab-009)	7	Terminated
NCT02341625 2015	Selected advanced solid tumors	I/IIa	anti-mesothelin antibody-drug conjugate BMS-986148	204	Recruiting
NCT02485119 2015	Japanese subjects with advanced malignancies (Dose escalation, intravenous infusion)	I	anti-mesothelin antibody-drug conjugate BAY94-9343	15	Recruiting

Table 14. Dendritic cell related clinical trials* against pancreatic cancer

NCT Number Year	Trial subjects	Phase	Immune intervention/ target	No	Status/Results/Impact (Median survival)
NCT00868114 2015	Unresectable pancreatic cancer (Direct tumor injection)	II	KLH-pulsed autologous dendritic cell vaccine	35	Active, not recruiting
NCT00795977 2011	Pancreatic cancer (Preoperative intratumor injection)	I/II	dendritic cells, OK-432	20	Active, not recruiting
NCT01677962 2015	Pancreatic adenocarcinoma	I	Poly-ICLC dendritic cell	12	Active, not recruiting
NCT01410968 2015	Metastatic, locally advanced, unresectable, or recurrent pancreatic adenocarcinoma (Feasibility and safety)	I	vacc. w/ Poly-ICLC & peptide-pulsed dendritic cells	12	Active, not recruiting
NCT00547144 2008	Unresectable pancreatic cancer (Intratumoral DC)	I/II	Gemcitabine Dendritic Cell XRT	2	Completed
NCT02548169 2015	Pancreatic cancer	I	DC Vaccine Chemotherapy	20	Recruiting
NCT00843830 2010	Metastatic pancreatic carcinoma (Intra-metastasis administration)	I	Autologous KLH-pulsed Dendritic cell vaccination Tumoral radiation therapy	4	Terminated
NCT01897636 2013	Unresectable pancreatic cancer (Efficacy and safety)		EUS-guided fine-needle injection of DCs vaccinations	30	Not yet recruiting
NCT00600002 2013	Resectable pancreatic adenocarcinoma	I	GM-CSF	30	Active, not recruiting
NCT00726037 2012	Metastatic pancreatic cancer (Efficacy of regulatory T-cell suppression)	II	Ontak (an engineered protein combining Interleukin-2 and Diphtheria toxin)	7	Terminated
NCT00128622 2009	Metastatic cancer	I	denileukin diftitox recombinant fowlpox-CEA(6D)/TRICOM vaccine therapeutic autologous dendritic cells	24	Completed
NCT00004604 2002	Metastatic cancer	I	CEA RNA-pulsed DC cancer vaccine	24	Completed
NCT00027534 2007	Advanced or metastatic cancer	I	TRICOM-CEA(6D)	14	Completed
NCT00003434 2002	Stage I, Stage II, or Stage III surgically resected pancreatic cancer	I	carcinoembryonic antigen peptide 1 hepatitis B antigen peptide	8	Terminated
NCT01882946 2015	Solid tumors (Safety and efficacy)	I/II	DCVax-Direct	60	Active, not recruiting
NCT00648102 2009	Incurable, locally advanced or metastatic breast, colorectal, pancreatic, bladder or ovarian Cancer	I	CDX-1307	36	Completed
NCT01781520 2015	Unresectable locally advanced pancreatic cancer	I/II	S-1 plus DC-CIK	30	Recruiting

was significantly improved to 22% and 29%, respectively. Strikingly, 10-year survival was 20% (four patients out of 20 evaluable) versus zero (0/87) in a cohort of non-vaccinated patient treated in the same

Table 15. Ras related clinical trials* against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT00019006 2005	Colon, pancreatic, or lung cancer	I	Detox-B adjuvant ras peptide cancer vaccine	null	Completed
NCT00837135 2009	Pancreatic cancer	I	GI-4000 Vaccine (a vaccine composed of yeast that is made to carry the same proteins called "mutated Ras proteins") GI-4000 Vaccine + Activated T Cells	32	Withdrawn
NCT00006387 2013	Advanced pancreatic or colorectal cancer	I	QS21 ras peptide cancer vaccine	7	Completed
NCT00019331 2007	Metastatic solid tumors	II	aldesleukin ras peptide cancer vaccine sargramostim DetoxPC	null	Completed
NCT00300950 2015	Non-metastatic, post-resection pancreas cancer (Safety and efficacy)	II	GI-4000 Gemcitabine	176	Completed
NCT00005594 2010	Advanced cancer of the pancreas	II	ISIS 2503 (an Antisense Inhibitor of H-Ras)	4	Completed

period. Three patients presented a memory response up to 9 years after vaccination. The encouraging milestone of long-term immune response together with 10-year survival following surgical resection indicates that vaccination against oncogenic/mutant K-ras may boost the effect of surgery and represent an adjuvant alternative for future treatment (97).

Combination of chemotherapy and immunotherapy

Chemotherapy with gemcitabine has been the standard first-line treatment for patients with unresectable locally advanced or metastatic pancreatic cancer for 18 years (99). Since 2013, chemotherapy with nab-paclitaxel plus gemcitabine has significantly improved overall survival, progression-free survival, and response rate in patients with metastatic pancreatic adenocarcinoma as compared with gemcitabine alone (12). Unfortunately, the improved median survival is only 8.5 months. The strength of combination with chemotherapy and immunotherapy is being tested in animal models.

It has been recognized that an optimized approach combining anti-cancer vaccination with chemotherapy and/or radiation therapy is urgently needed. The use of vaccines is also a compelling approach for maintenance therapy of patients who are grossly disease-free, or whose disease is at least stabilized, upon chemotherapy and/or radiation therapy. Prime-boost vaccination strategies, in particular those that use Listeria vaccines for boosting, are a promising approach for maintenance therapy (100).

In preclinical studies, combination therapy of chemotherapy followed by immunotherapy is superior to chemotherapy alone. In these in vivo tests, chemotherapeutic agents played a dual role. On one hand, they reduced overall tumor burden by direct killing of cancer cells; on the other hand, they indirectly lead to the release of pro-inflammatory molecules and tumor associated antigens (101), which may be functioning as a “vaccine” by presumably releasing tumor antigens in an immunogenic fashion. This may potentially explain the improved efficacy of

Table 16. Other clinical trials* with immunotherapeutic regimens against pancreatic cancer

NCT Number Year References	Trial subjects	Phase	Immune intervention / target	No	Status / Results / Impact (Median survival)
NCT00540579 2013 (98)	Untreated advanced carcinoma of the pancreas	I/II	Pomalidomide: an immunomodulating drug (IMiD). Gemcitabine	23	PRs were 15%. SDs after two cycles were 70%. CA 19-9 decreased by >50% in 43% of patients.
NCT00389610 2015	Pancreatic cancer that has been removed by surgery	II	allogenic GM-CSF tumor cell vaccine	56	Active, not recruiting
NCT00720785 2015	Pancreatic Neoplasms	I	NK cells +CliniMACs CD3 and CD56 systems	61	Recruiting
NCT01801852 2015	Pancreatic Cancer	I	NKT cells	300	Recruiting

CD40 agonists when given after, but not before, chemotherapy (102). This synergistic efficacy is also observed with combined chemotherapy using anti-CD47 antibody (103). Notably, there might be a limited window of time when chemotherapy drugs can be effective, yet without blunting anti-tumor immunity (103).

In contrast, chemotherapy administered after immunotherapy had detrimental effects on development of beneficial antitumor memory immune responses. Chemotherapy administered after anti-CD47 treatment did not result in faster tumor regression than anti-CD47 alone. Chemotherapy can suppress the immune system and kill recently activated immune cells including memory cells. The ultimate consequence of this sequence is to destroy the therapeutic effects of immunotherapy (103). In addition, recent clinical studies have experimented using the sequential administration of anti-cancer vaccines and chemotherapy/radiation; however, the immunosuppressive effects of these standard cytotoxic regimens may compromise the efficacy of immunotherapy. Thus, the timing of administration of standard chemotherapy markedly impacted the induction of antitumor responses by immune-based therapy.

Combination of radiation therapy (radiotherapy) and immunotherapy

The most recent advancement of radiation technology, including intensity modulated radiation therapy, stereotactic radiosurgery, proton therapy, antibody-radionuclide conjugates, has been applied to cancer therapy for 20 years (104). Radiotherapy is based on the ionizing energy causing DNA damage to induce direct tumor cell death, such as apoptosis, mitotic catastrophe, or necrosis, along with the cascade events in tumor microenvironment (TME) (105). The best efficacy of radiotherapy will not only rely on the direct tumor cell death, but also the contribution of intrinsic anti-tumor immune response. The damage-associated molecular patterns in TME trigger immune sensors such as toll-like receptors (TLR) (104) which serve as the link between radiation and immune properties. The damaged tumor cells up-regulated tumor-associated antigens (TAA), recruited dendritic cell migration and maturation, and induced T effector cells to TME for removing the residual tumor cells. One of the cascade events in TME is abscopal effect, a poorly understood phenomenon that radiation can induce tumor regression outside the exposure area of radiation. Recent progress in immunology allowed researcher to demonstrate that abscopal effect is immune mediated and T cell dependent (106) peripheral clonal expansion, warranting further immune intervention in this setting of cancer therapy. Indeed, combination of immunotherapy with radiation therapy has improved cancer treatment through synergy (107). Trials (104) with TLR agonists

and radiation therapy have been tested in patients with lymphoma, breast cancer, prostate cancer, etc. The superiority (108, 109) of radiation and anti-CTLA-4 and anti-PD-1 therapy is confirmed in preclinical melanoma models, although the mechanism of TCR repertoire diversity and tumor heterogeneity remains unknown. In the near future, it might be possible that radiation can turn pancreatic cancer from an immune privileged tumor microenvironment to an immune active state. Radioimmunotherapy (110) for pancreatic cancer may emerge as a novel regimen (111) complementing to the multimodality tumor directed therapy.

Perspectives and Conclusion

The principal goal of this review is to highlight current progress of immunotherapy in pancreatic cancer. The seminal advantages that immunotherapy bring to the treatment of pancreatic cancers are: (1) The ability to broaden and encompass greater numbers of patients eligible for treatment and to achieve a personalized approach to medicine by using the autologous cancer antigens as a means of generating a populations antigen-specific effector cells. (2) A means to trigger T cell memory and retain long-term remission. (3) A means to modulate the immune microenvironment for example through targeted therapies to mitigate desmoplasia, a physical barrier where pancreatic cancer stem cells may be sequestered. (4) The development of novel Immune adjuvants defined through mouse models, that may reverse the noxious immune suppressive tumor microenvironment, a functional barrier of pancreatic cancer. (5) Immune reagents that potentiate the penetrance of chemotherapeutic reagents and improve drug delivery. It is hoped that multiple possible avenues to developing a deeper understanding of immune resistance, T cell persistence, mechanisms of immune checkpoint inhibition and vaccination strategies, will allow us to chart a strategy that exploits the potential of the immune system to eradicate the refractory disease and maintain a durable clinical response in patients with pancreatic cancer.

Abbreviations:

5-FU, fluorouracil
ADCC, antibody-dependent cell-mediated cytotoxicity
BiTE, bi-specific T-cell engager
BTK, Bruton's tyrosine kinase
CAR, chimeric antigen receptors
CEA, carcinoembryonic antigen
CTLA-4, cytotoxic T lymphocyte antigen 4
Cy, cyclophosphamide
DART, dual-affinity re-targeting
DCs, dendritic cells
DFS, disease-free survival
FDA, Food and Drug Administration
GEMM, genetically engineered mouse models
GM-CSF, granulocyte-macrophage colony-stimulating factor
GVAX, granulocyte-macrophage colony-stimulating factor (GM-CSF) secreting tumor vaccine or GVAX pancreatic cancer vaccine.
IDO, indoleamine 2,3-dioxygenase
IMiD, immunomodulating drug
IPMN, intraductal papillary mucinous neoplasm
ITK, IL2-inducible T-cell kinase
KPC, KrasG12D;Trp53R172H;Pdx1-Cre
Kyn, kynurenine
L-Trp, L-tryptophan
MDSC, myeloid derived suppressor cells
mTOR, mammalian target of rapamycin
MUC-1, mucin
NSCLC, Non-Small-Cell Lung Cancer
OS, overall survival
PD-1, programmed cell death protein 1
PD-L1, programmed death-ligand 1
PD, progressive disease
PDAC, pancreatic ductal adenocarcinoma
PFS, progression-free survival
PR, partial responses
SBRT, Stereotactic Body Radiation Therapy
SD, stable disease
SPARC, secreted protein acidic and rich in cysteine
TAA, tumor-associated antigens
TCR, T-cell receptor
Teff, effector T cells
TIL, tumor-infiltrating lymphocyte
TLR, toll-like receptors
TMAs, tumor-associated macrophages
TME, tumor microenvironment
Tregs, regulatory T cells
TXK, tyrosine-protein kinase

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