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## Immunotherapy and prevention of pancreatic cancer

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### Abstract

Pancreatic cancer is the third leading cause of cancer mortality in the United States, recently surpassing breast cancer. A key component of pancreatic cancer's lethality is its acquired immune privilege, which is driven by an immunosuppressive microenvironment, poor T-cell infiltration, and a low mutational burden. Although immunotherapies such as checkpoint blockade or engineered T cells have yet to demonstrate efficacy, a growing body of evidence suggests that orthogonal combinations of these and other strategies could unlock immunotherapy in pancreatic cancer. In this review, we will discuss promising immunotherapies currently under investigation in pancreatic cancer and provide a roadmap for the development of prevention vaccines for this and other cancers.

### Keywords

Immunotherapy; prevention vaccines; pancreatic cancer

## CHALLENGE OF PANCREATIC CANCER

In early 2017, pancreatic cancer surpassed breast cancer to become the third leading cause of cancer-related mortality in the United States, behind only colon and lung cancer [1]. Unlike many other cancers, pancreatic cancer is increasing in both incidence and mortality and is predicted to be the second-leading cause of cancer-related death by 2030 [1]. Current therapies are severely lacking; recently approved combination chemotherapies such as FOLFIRINOX and gemcitabine/nab-paclitaxel improve median survival by only 2–4 months and are associated with significant, toxic side effects [2,3]. Encouragingly, a few long-term survivors are beginning to be observed after such treatment, yet the 5-year survival – although improving – remains a grim 8% [4]. Moreover, for a variety of complex and unfortunate reasons, including limited geographical access to trial sites, restrictive eligibility

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criteria, and patient decisions [5], 95% of pancreatic cancer patients do not enroll in trials of investigative therapies.

Immunotherapy has had remarkable efficacy in many malignancies [6–10] but has not yet translated to pancreatic ductal adenocarcinoma (PDA). Immune checkpoint blockade seems to have minimal activity, and despite promising phase I data, whole cell therapeutic vaccines have demonstrated no effect in late stage trials [6,11,12]. There are many reasons for these failures, but key contributors are the immunosuppressive tumor microenvironment (TME)—characterized by typically poor infiltration of effector T cells and prominent myeloid inflammation [13–15]—and a low mutational burden predicted to generate very few immunogenic antigens [16,17]. Promisingly, a small subset of patients present with tumors exhibiting high effector T-cell infiltration and have longer overall survival [18–20], suggesting the potential for effective treatment of PDA with immunotherapy. Investigations into an increasingly diverse array of immunotherapies and subsequent rational combinations with other therapeutic approaches likely hold the most promise for patients with PDA. Moreover, the development of prevention vaccines for PDA is now within reach and could transform the way PDA is treated by targeting malignant cells before the immunosuppressive TME is fully established, thereby obviating the need for toxic immunotherapies.

In this review, we will discuss the major immunotherapies and combinations that are being investigated in pancreatic cancer, both clinically and preclinically, with an eye toward the most promising approaches (Figure 1). We will then discuss cancer prevention vaccines and the rationale for investigating the use of these vaccines in the quest to cure pancreatic cancer.

## **SINGLE AGENT IMMUNOTHERAPIES IN PANCREATIC CANCER**

### **Immune checkpoint blockade**

Checkpoint blockade has resulted in remarkable successes in other cancers, including melanoma and lung cancer, but has shown little efficacy in PDA [6,11]. Checkpoint blockade targets immune checkpoint molecules—primarily programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)—that negatively regulate T-cell function. Inhibition of these molecules “takes the brakes off” the immune system, resulting in tumor killing. The reasons for the failure of immune checkpoint blockade in PDA are multifactorial. PDA has low baseline PD-1<sup>+</sup> T-cell infiltration into the tumor [15,21] and a paucity of neoepitopes [17,22], both of which are predictive of response to PD-1 blockade in other solid tumors [23,24]. Indeed, in a very small subset (~1%) of PDA patients with a high burden of microsatellite instability (MSI-high)—and therefore high neoepitope burden—PD-1 blockade is effective [25,26] and was recently FDA approved [27,28]. In the absence of high neoepitope burden, preclinical models have shown that therapies capable of improving T-cell infiltration into the TME sensitize PDA to checkpoint blockade [29], suggesting combinations of treatments that improve T-cell trafficking with checkpoint blockade may be successful. However, a small portion of PDA patients have both activated T cells and a detectable neoepitope burden, and yet are resistant to therapy [17]. The complete lack of efficacy of checkpoint blockade in these patients suggests there is more to T-cell responses in PDA than the PD-1/PD-L1 axis.

Multiple other immune molecules can suppress T cell responses in cancer, including TIM3, TIGIT, and LAG3, which are inhibitory receptors on T cells analogous to PD-1; VISTA, an inhibitory ligand on myeloid cells analogous to PD-L1; and CD73, an extracellular enzyme that generates the immunosuppressive and pro-metastatic molecule adenosine. All of these immunosuppressive pathways are highly expressed in PDA [17] and investigating these targets may unlock checkpoint blockade in PDA.

### Therapeutic vaccines

Therapeutic vaccines have the potential to induce robust antitumor immune responses, but they have so far failed to deliver on their early stage promise in pancreatic cancer. Vaccine approaches, including whole tumor cells, peptides, proteins, and recombinant constructs, aim to prime circulating tumor-specific T cells that can then eliminate tumors. In small phase I studies, almost all of these formulations have generated tumor-specific T-cell immunity in subsets of patients [30–32]. Tantalizingly, patients who generated vaccine-specific T-cell immunity appeared to have superior survival in many of these small, early stage trials. Unfortunately, results from later stage trials did not support these early findings. A phase III trial of a vaccine using a single peptide derived from the tumor-associated self-antigen human telomerase (hTERT) showed no survival benefit in patients with metastatic disease, even in immunologic responders [33]. Whole-cell vaccine approaches, which may broaden the immune response against both tumor-specific and shared tumor/self-antigens, have also had limited success. GVAX, a vaccine composed of irradiated, allogenic PDA cells that express granulocytic-macrophage colony stimulating factor, failed to improve survival in phase IIb/III trials in metastatic PDA [12], even among the immunologic responders. Together, these results have diminished excitement for therapeutic vaccines.

Therapeutic vaccination has the potential to be more effective in the adjuvant setting, where the volume of tumor and immunosuppressive stroma is greatly reduced. Small phase I/II trials have shown that adjuvant vaccines to WT-1, mutant Kras, and MUC1 can generate a T-cell immune response and have suggested that the potency of this response correlates with patient outcomes [34–38]. However, only a fraction of patients in these trials had durable responses. Moreover, the whole-cell lysate vaccine algenpantucel-L (irradiated allogenic PDA cells expressing murine alpha-1,3-galactosyltransferase) failed to improve survival in a recent phase III trial despite similarly promising immunologic responses in early trials [39]. Emerging data suggests that the adjuvant setting may be less conducive to vaccination than previously thought. Comparisons to healthy patients have found that the overall immunologic response to vaccination is reduced in the adjuvant setting [40], and in lung cancer the post-operative TME has been shown to be strongly immunosuppressive [41].

Despite the negative top-line results of phase IIb/III vaccine trials, these trials contain key insights that should provide a path forward for therapeutic vaccines. Importantly, these trials have proven that vaccines can break tolerance and generate T-cell immunity to tumor-associated self-antigens without obvious short-term side effects. GVAX vaccination even induced formation of tertiary lymphoid structures and T-cell infiltration in many patients [42]. Why this T-cell response did not improve survival remains incompletely understood, but may be due to suboptimal antigen selection or T-cell dysfunction. The path forward for

antigen selection is encouraging, as many antigenic targets have been identified and are under investigation [43], and improvements in bioinformatics tools are rapidly enabling the prediction of other high priority antigens and neoantigens for vaccination [20]. Similarly, there is hope for rescuing T cells from dysfunction. Preclinical evidence suggests that depletion of regulatory T cells (Tregs) can reduce suppression by the TME and enable effective therapeutic vaccination [44,45]. Moreover, GVAX-induced T cells in human PDA upregulate checkpoint molecules, including PD-1 [42], suggesting checkpoint blockade can rescue vaccine-primed CD8 T cells from inhibition by the TME; trials combining therapeutic vaccines with checkpoint blockade are underway [46]. Finally, the vaccine delivery vector can be changed or enhanced with cytokines, as is currently under investigation in a Phase I trial using DNA electroporation to increase the immunogenicity of hTERT and IL-12 to improve the priming of the anti-hTERT T cell response in the adjuvant setting (NCT02960594<sup>i</sup>) [47].

### Engineered T cells

Engineered T cells, such as chimeric antigen receptor T cells (CAR-Ts), have shown remarkable efficacy in B-cell malignancies, with response rates up to 90% [48–50], but have been slow to translate to solid tumors like PDA. Recently, tisagenlecleucel and axicabtagene ciloleucel were FDA-approved for B-cell acute lymphoblastic leukemia and non-Hodgkin's lymphoma, respectively. These CAR-Ts have T-cell receptors engineered to bind specifically to CD19 on B cells, inducing potent tumor cell killing. B-cell malignancies are uniquely suited to engineered T cells because CD19 expression is restricted to B cells, limiting off-target toxicities, and depletion of B cells is non-lethal, allowing for complete systemic clearance of all CD19<sup>+</sup> cells. Unfortunately, translating CAR-T therapy to other malignancies remains challenging, as safe, specific, and homogeneously expressed targets are harder to identify [51]. Nevertheless, many self-antigens, such as CEA, PSCA, mesothelin, and HER2, are significantly overexpressed in PDA, are associated with worse prognoses [52], and may be promising targets. CAR-Ts to these antigens have proven effective in murine tumors [53–56] and phase I trials of many of these CAR-Ts are now underway in PDA [57]. Importantly, these self-antigens are also expressed on normal cells, creating a significant risk of autoimmunity, especially if the T cells persist. A HER2 CAR-T led to on-target, off-tumor toxicity and a patient death [58] and other CAR-Ts have induced colitis and anaphylaxis [59]. Promisingly, interim results of a phase I trial in PDA of a CAR-T to mesothelin demonstrated short-term immunogenicity without significant toxicity [60,61]. Nevertheless, targeting non-self-antigens or mutated self-antigens may be required to improve the safety profile of engineered T cells. A recent case report demonstrated that adoptive transfer of T cells specific to the patient's HLA type and Kras mutation led to widespread regression in a patient with metastatic colorectal cancer [62]. Targeting broadly expressed mutated or altered self-antigens, such as the abnormally glycosylated MUC1, may be the key to safely translating engineered T cells to patients with PDA [54]. Regardless of target, careful attention to safety will be paramount as engineered T cells are further developed.

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<sup>i</sup><https://clinicaltrials.gov/ct2/show/NCT02960594>

Translating engineered T cells to PDA has the added challenge of inducing T-cell persistence within the tumor site. Many CAR-T therapies under investigation in PDA are murine-derived and contain a partially murine single-chain variable fragment, rendering them susceptible to antibody-mediated elimination, which may have occurred in one phase I trial [60]. This is not an issue in B-cell malignancies because B cells themselves are the target of CART-19 therapy. For durable responses, generation of a fully human CAR or combination with B-cell depletion will likely be necessary. A trial investigating mesothelin CAR-Ts together with CART-19s is now underway in PDA (NCT02465983<sup>ii</sup>). In addition to physical persistence, CAR-T cells must also functionally persist in PDA, but preclinical evidence has shown that CAR-Ts in PDA are quickly exhausted by the TME [63,64]. The addition of CTLA-4 blockade to tumor-specific T-cell transfer induced T-cell persistence and memory in patients with melanoma [65]; similar combinations of checkpoint blockade with engineered T cells will likely be necessary in PDA. Finally, CAR-Ts must effectively traffic into the tumor before they can persist there. Multiple preclinical studies in mesothelioma have shown that regional administration of CAR-Ts is more effective than systemic administration, likely due to tumor-mediated trafficking impairment [66]. Although little has been specifically studied in PDA, T-cell infiltration into the tumor is poor at baseline. Studies in other solid malignancies have demonstrated that the addition of heparanase—which degrades the stroma—or tumor-targeting cytokine receptors to CAR-Ts can significantly improve intratumoral trafficking and antitumor response [67–69]. Similar strategies may be beneficial in PDA.

### Agonistic immunotherapy

Due to the time and cost per patient required to develop engineered T cells, more general therapies that can prime and expand T cells may be needed. Antigen-presenting cell (APC) agonists and T-cell agonists are two approaches under investigation. Agonistic CD40 therapy simulates T-cell help and licenses APCs, allowing them to more effectively present antigen to T cells and activate them [70]. Agonistic CD40 monotherapy, in combination with gemcitabine, activated tumoricidal macrophages and showed signs of efficacy in a phase I study [71]. However, no enhancement of long-term survival was seen in this trial, suggesting the therapy did not induce immune memory. Further combining agonistic CD40 with nab-paclitaxel and gemcitabine induced T-cell mediated tumor killing, generated immune memory [72], and sensitized tumors to immune checkpoint blockade in preclinical models [29,73]. This improved benefit of agonistic CD40 with both gemcitabine and nab-paclitaxel (versus alone or only with gemcitabine) suggests that the effect of agonistic CD40 is mediated by different cell types depending on the therapeutic context of CD40 administration. Studies investigating agonistic CD40 combined with chemotherapy and PD-1 blockade are currently ongoing (NCT02588443<sup>iii</sup>, NCT03214250<sup>iv</sup>). Other APC agonists under investigation include toll like receptor (TLR) [74,75] and STING [76] agonists, which activate dendritic cells to improve T-cell priming. TLR agonists appeared to improve immune responses to therapeutic vaccination in a phase I study [77]. Direct co-

<sup>ii</sup><https://clinicaltrials.gov/ct2/show/NCT02465983>

<sup>iii</sup><https://clinicaltrials.gov/ct2/show/NCT02588443>

<sup>iv</sup><https://clinicaltrials.gov/ct2/show/NCT03214250>

stimulation of T cells can be induced with OX40 agonists, and the combination of OX40 and checkpoint blockade has shown preclinical promise in other tumors [78–80]. Importantly, many of these agonistic pathways appear to be orthogonal, as CD40 signaling does not require STING and TLR [72] while STING and OX40 agonism had additive effects when added to checkpoint blockade in a breast cancer model [81].

### Myeloid-based immunotherapy

The dysfunctional immune response in PDA is in part modulated by immunosuppressive myeloid cells, whose function is controlled by a host of cytokines, chemokines, and signaling molecules that serve as therapeutic targets [82]. As mentioned previously, agonistic CD40 therapy can shift macrophages from an inflammatory to a tumoricidal phenotype and lead to short-term clinical responses [71]. Cytokines, chemokines, and their receptors also contribute to the establishment of the immunosuppressive TME and make attractive targets. The most clinically advanced of these is CCR2, a chemokine receptor whose binding recruits inhibitory macrophages to the TME and is associated with a worse prognosis [83]. A phase I study in PDA combining the CCR2 inhibitor PF-04136309 with FOLFIRINOX led to objective responses in almost half of patients [84], and a phase II study is underway (NCT02732938<sup>v</sup>). Other cytokine and chemokine receptors of interest in the PDA TME include CSF-1R, a regulator of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages, and CXCR2, a regulator of neutrophil and MDSC migration. The combination of CSF-1R inhibition with checkpoint blockade has shown preclinical promise in PDA [85], and the combination of CSF-1R inhibition and CD40 agonism generated potent T-cell mediated tumor killing in a preclinical melanoma model [86]. CXCR2 inhibition improved T-cell infiltration into the PDA tumor and subsequently improved tumor responses when combined with checkpoint blockade or CSF-1R inhibition [87–89]. IDO1, an immunosuppressive enzyme produced by DCs and MDSCs, is an additional contributor to T cell dysfunction in the PDA TME. IDO1 inhibition combined with hyaluronidase improved T cell entry into PDA and induced remissions in preclinical models [90]. Combinations of these molecules with checkpoint blockade are underway.

### Stroma-modulating immunotherapies

The desmoplastic stroma of PDA is a key component of the immunosuppressive TME and a barrier to effective therapies. Early stage studies are beginning to demonstrate the therapeutic potential of modulating the stroma, although some controversy remains over whether stromal targeting is always beneficial [91,92]. The most clinically advanced stromal modulator, the hyaluronidase PEGPH20, degrades stromal protein, improves intratumoral blood flow, and improved progression-free survival in a phase II trial when added to standard-of-care chemotherapy [93]; a phase III study (NCT02715804<sup>vi</sup>) is currently underway. Multiple other direct modulators of the stroma are under investigation and reviewed in detail elsewhere (see [94]), so the focus here is on a few therapies that modulate signaling between the stroma, tumor, and immune cells. Focal adhesion kinase (FAK) is a regulator of TME fibrosis and immunosuppression, and increased FAK expression is

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<sup>v</sup><https://clinicaltrials.gov/ct2/show/NCT02732938>

<sup>vi</sup><https://clinicaltrials.gov/ct2/show/NCT02715804>

associated with reduced T-cell infiltration in human PDA [95]. Preclinically, inhibition of FAK potentiates both chemotherapy and checkpoint blockade [95] and also reduces the infiltration of suppressive myeloid cells into the TME; a phase I study of FAK inhibition with PD-1 blockade is underway (NCT02758587<sup>vii</sup>). Provocatively, vitamin D also plays a role in stromal immunomodulation, as patients with vitamin D deficiency have a worse prognosis [96]. The vitamin D receptor (VDR) is expressed on leukocytes and stellate cells and VDR activation in the pancreas reduced fibrosis and inflammation in preclinical models. Moreover, vitamin D analogs improved the response of PDA to gemcitabine in these models [97]; clinical trials of vitamin D analogs are underway [46]. Finally, stromal cells that express fibroblast activation protein (FAP) induce desmoplasia, promote tumor growth and metastasis, and are associated with worse prognosis [98,99]. FAP-specific CAR-Ts improve survival in preclinical models of PDA [100], providing a rationale for this strategy in future clinical trials.

## COMBINATION THERAPY IN PANCREATIC CANCER

Developing the right combination therapies will be critical to bringing successful immunotherapy to pancreatic cancer. While we have discussed only immunotherapy in this review, key combinations are likely to include other standard-of-care treatments, such as chemotherapy and radiation. Both therapies have the potential to be immunomodulatory via the immunogenic death of tumor cells, which results in the stimulation of innate immune cells and can thereby synergize with immunotherapies. The list of possible combinations to test far outstrips the number of patients and the capacity of the current clinical trial infrastructure; combinations that address orthogonal mechanisms in the antitumor immune reaction will be of the highest priority (Figure 2). For example, combining T-cell activation through therapeutic vaccines with checkpoint blockade to prevent exhaustion and stromal modulation to improve T-cell infiltration would target three non-redundant mechanisms and potentially be highly potent. Toxicity, dosing, and sequencing remain critical challenges in developing combination approaches, especially for agonists. For example, the combination of nivolumab and ipilimumab significantly improved survival compared to either monotherapy in melanoma [101], but the combination comes with the tradeoff of greater toxicity and greater expense. Ideal therapies for combination will also include reliable immune pharmacodynamic biomarkers to rapidly assess response to therapy. For a detailed list of many current combination trials, see [46].

## NEXT FRONTIER: PREVENTION VACCINES IN PANCREATIC CANCER

### Rationale for prevention vaccines

All of the above immunotherapies face the challenge of overcoming the highly immunosuppressive TME found in established PDA. But what if we could prevent the establishment of this TME altogether? To do this, we can borrow lessons from the success of preventative childhood vaccines, which have nearly eliminated many viral diseases around the world. In oncology, vaccines to hepatitis B and human papillomavirus can now prevent

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<sup>vii</sup><https://clinicaltrials.gov/ct2/show/NCT02758587>

hepatocellular carcinoma [102] and cervical adenocarcinoma [103], respectively. Bringing effective vaccination to non-viral malignancies is critical and was underscored in the 2016 Cancer Moonshot Blue Ribbon Panel's report. Unlike in childhood vaccines, whose success is based almost entirely on antibody responses, vaccines in cancer will most likely require T-cell responses. Tumor-specific immune responses have been shown to recognize both neoantigens generated by mutations in tumor cells [104] and self-antigens that are overexpressed by tumors [105], suggesting a relatively broad list of possible vaccine targets to which we can already generate T-cell responses [43]. Moreover, a small but meaningful portion of PDA patients have heritable disease, whose underlying common mutations could serve as vaccine targets. Recently, the first human trial of a non-viral prophylactic cancer vaccine was performed in colon cancer using a peptide-based vaccine for MUC1, a protein overexpressed and abnormally glycosylated in many cancers, including PDA. This trial demonstrated long-lasting antibody production to MUC1 without any clinical autoimmunity [40]. Vaccines to altered self-antigens such as MUC1 may be safer than those to overexpressed self-antigens and are thus enticing options for primary prevention vaccines. Overall, a growing body of evidence suggests we are on the cusp of prevention vaccines that successfully produce T-cell immunity against self- or mutant-self antigens.

### Primary prevention vaccines

More than 65% of PDA patients present with metastatic disease and are not candidates for surgery. As such, a truly preventative vaccine is critically needed. Unlike viral infections, cancer begins as a precursor lesion rather than a novel antigen and slowly grows and transforms into a malignant tumor. Eliminating the precursor lesion might be enough to prevent development of malignancy or at least “reset the clock.” Even if T-cell memory wanes, the effective downstaging of the precancerous lesion from therapy could have dramatic clinical benefit, especially given that pancreatic cancer metastasizes early in its progression [106]. Preclinically, multiple vaccines have been able to prevent progression from the precancerous PanIN to PDA and thereby prolong survival [44,107]. Of course, to use vaccines at these early stages requires identifying PDA at earlier stages than we now can or identifying patients at very high risk for PDA. Patients with hereditary forms of pancreatic cancer, such as those with inherited *BRCA1/2* mutations, make up ~5% of all PDA [108] and are excellent candidates for this approach. Beyond familial pancreatic cancer, there is hope for novel biomarkers, including circulating tumor miRNAs and DNA [109–111], to detect PDA at extremely early stages. Recently, levels of THBS2, a molecule present in PDA and its precursors, were shown to separate pancreatic cancer from pancreatitis with >98% specificity [112] when used in combination with CA19-9. Despite this promise, prevention vaccines face many hurdles. Beyond germline mutations, we do not yet know if biomarkers will identify patients early enough in PDA development for prevention vaccines to have any benefit. Moreover, we have not yet identified the optimal antigenic targets or fully characterized the safety profile of prevention vaccines. Nevertheless, development of primary prevention vaccines will be a key pillar in the fight against pancreatic cancer.



## CONCLUDING REMARKS

Immunotherapy for pancreatic cancer has shown glimmers of promise, but true clinical benefit remains elusive. With each negative late stage trial it becomes more evident that single agent immunotherapies are unlikely to be successful in PDA, and that combinations hold the most near-term promise. Given the vast number of possible combinations and the relatively small patient pool, it is important that we prioritize those combinations supported by preclinical work that target non-overlapping mechanisms (see Outstanding Questions for priority areas of investigation). The prospect of a prevention vaccine would be of highest impact. Building on recent advances in genetic risk assessment (e.g., BRCA1/2 mutations) and continued preclinical efforts to identify the right antigenic targets and prevention vaccine formulations will be critical to the success of this approach. Despite the many challenges in treating PDA, there is hope for the development of effective therapies to treat and eventually prevent this devastating disease.

### OUTSTANDING QUESTIONS BOX

- What explains the failure of single-agent checkpoint blockade to have clinical efficacy in PDA?
- Are other checkpoint pathways outside of PD-1/PD-L1 more relevant to pancreatic cancer, and which is highest priority for further investigation?
- Which combination therapies are most likely to act synergistically in PDA and are therefore highest priority?
- Can we develop biomarkers that identify patients most likely to benefit from each immune therapy or combination thereof so we can match patients to their optimal therapy?
- How do we better identify subjects at high risk for pancreatic cancer so we can intervene immunologically before the immunosuppressive microenvironment develops?

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## References

1. Rahib L, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res.* 2014; 74:2913–2921. [PubMed: 24840647]
2. Von Hoff DD, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013; 369:1691–1703. [PubMed: 24131140]
3. Conroy T, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011; 364:1817–1825. [PubMed: 21561347]

4. Siegel RL, et al. Cancer statistics, 2017. *CA Cancer J Clin.* 2017; 67:7–30. [PubMed: 28055103]
5. Unger JM, et al. The role of clinical trial participation in cancer research: barriers, evidence, and strategies. *Am Soc Clin Oncol Educ B.* 2016; 36:185–198.
6. Brahmer JR, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med.* 2012; 366:2455–2465. [PubMed: 22658128]
7. Sharma P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. *Lancet Oncol.* 2016; 17:1590–1598. [PubMed: 27733243]
8. Motzer RJ, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med.* 2015; 373:1803–1813. [PubMed: 26406148]
9. Robert C, et al. Nivolumab in previously untreated melanoma without *BRAF* mutation. *N Engl J Med.* 2015; 372:320–330. [PubMed: 25399552]
10. Borghaei H, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med.* 2015; 373:1627–1639. [PubMed: 26412456]
11. Royal RE, et al. Phase 2 trial of single agent ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother.* 2010; 33:828–833. [PubMed: 20842054]
12. Le DT, et al. Results from a phase 2b, randomized, multicenter study of GVAX pancreas and CRS-207 compared to chemotherapy in adults with previously-treated metastatic pancreatic adenocarcinoma (ECLIPSE study). *J Clin Oncol.* 2017; 35:345–345.
13. Vonderheide RH, Bayne LJ. Inflammatory networks and immune surveillance of pancreatic carcinoma. *Curr Opin Immunol.* 2013; 25:200–205. [PubMed: 23422836]
14. Johnson BA, et al. Strategies for increasing pancreatic tumor immunogenicity. *Clin Cancer Res.* 2017; 23:1656–1669. [PubMed: 28373364]
15. Stromnes IM, et al. T-cell localization, activation, and clonal expansion in human pancreatic ductal adenocarcinoma. *Cancer Immunol Res.* 2017; 5:978–991. [PubMed: 29066497]
16. Dreyer SB, et al. Pancreatic cancer genomes: implications for clinical management and therapeutic development. *Clin Cancer Res.* 2017; 23:1638–1646. [PubMed: 28373362]
17. Balli D, et al. Immune cytolytic activity stratifies molecular subsets of human pancreatic cancer. *Clin Cancer Res.* 2017; 23:3129–3138. [PubMed: 28007776]
18. Ino Y, et al. Immune cell infiltration as an indicator of the immune microenvironment of pancreatic cancer. *Br J Cancer.* 2013; 108:914–923. [PubMed: 23385730]
19. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature.* 2017; 541:321–330. [PubMed: 28102259]
20. Balachandran VP, et al. Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer. *Nature.* 2017; 551:512–516. [PubMed: 29132146]
21. Clark CE, et al. Dynamics of the immune reaction to pancreatic cancer from inception to invasion. *Cancer Res.* 2007; 67:9518–9527. [PubMed: 17909062]
22. Alexandrov LB, et al. Signatures of mutational processes in human cancer. *Nature.* 2013; 500:415–421. [PubMed: 23945592]
23. Tumeh PC, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature.* 2014; 515:568–71. [PubMed: 25428505]
24. Rizvi NA, et al. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science.* 2015; 348:124–128. [PubMed: 25765070]
25. Lupinacci RM, et al. Prevalence of microsatellite instability in intraductal papillary mucinous neoplasms of the pancreas. *Gastroenterology.* 2017; doi: 10.1053/j.gastro.2017.11.009
26. Humphris JL, et al. Hypermutation in pancreatic cancer. *Gastroenterology.* 2017; 152:68–74. e2. [PubMed: 27856273]
27. Le DT, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med.* 2015; 372:2509–2520. [PubMed: 26028255]
28. Le DT, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science.* 2017; 357:409–413. [PubMed: 28596308]

29. Winograd R, et al. Induction of T-cell immunity overcomes complete resistance to PD-1 and CTLA-4 blockade and improves survival in pancreatic carcinoma. *Cancer Immunol Res.* 2015; 3:399–411. [PubMed: 25678581]
30. Le DT, et al. Safety and survival with GVAX pancreas prime and listeria monocytogenes-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. *J Clin Oncol.* 2015; 33:1325–33. [PubMed: 25584002]
31. Bernhardt SL, et al. Telomerase peptide vaccination of patients with non-resectable pancreatic cancer: a dose escalating phase I/II study. *Br J Cancer.* 2006; 95:1474–1482. [PubMed: 17060934]
32. Mayanagi S, et al. Phase I pilot study of Wilms tumor gene 1 peptide-pulsed dendritic cell vaccination combined with gemcitabine in pancreatic cancer. *Cancer Sci.* 2015; 106:397–406. [PubMed: 25614082]
33. Middleton G, et al. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer (TeloVac): an open-label, randomised, phase 3 trial. *Lancet Oncol.* 2014; 15:829–840. [PubMed: 24954781]
34. Wedén S, et al. Long-term follow-up of patients with resected pancreatic cancer following vaccination against mutant K-ras. *Int J Cancer.* 2011; 128:1120–1128. [PubMed: 20473937]
35. Abou-Alfa GK, et al. Targeting mutated K-ras in pancreatic adenocarcinoma using an adjuvant vaccine. *Am J Clin Oncol.* 2011; 34:321–325. [PubMed: 20686403]
36. Toubaji A, et al. Pilot study of mutant ras peptide-based vaccine as an adjuvant treatment in pancreatic and colorectal cancers. *Cancer Immunol Immunother.* 2008; 57:1413–1420. [PubMed: 18297281]
37. Miyazawa M, et al. Phase II clinical trial using novel peptide cocktail vaccine as a postoperative adjuvant treatment for surgically resected pancreatic cancer patients. *Int J Cancer.* 2017; 140:973–982. [PubMed: 27861852]
38. Lepisto AJ, et al. A phase I/II study of a MUC1 peptide pulsed autologous dendritic cell vaccine as adjuvant therapy in patients with resected pancreatic and biliary tumors. *Cancer Ther.* 2008; 6:955–964. [PubMed: 19129927]
39. Hardacre JM, et al. Addition of algenpantucel-L immunotherapy to standard adjuvant therapy for pancreatic cancer: a phase 2 study. *J Gastrointest Surg.* 2013; 17:94–101. [PubMed: 23229886]
40. Kimura T, et al. MUC1 vaccine for individuals with advanced adenoma of the colon: a cancer immunoprevention feasibility study. *Cancer Prev Res.* 2013; 6:18–26.
41. Predina J, et al. Changes in the local tumor microenvironment in recurrent cancers may explain the failure of vaccines after surgery. *Proc Natl Acad Sci.* 2013; 110:E415–E424. [PubMed: 23271806]
42. Lutz ER, et al. Immunotherapy converts nonimmunogenic pancreatic tumors into immunogenic foci of immune regulation. *Cancer Immunol Res.* 2014; 2:616–631. [PubMed: 24942756]
43. Chu NJ, et al. Nonviral oncogenic antigens and the inflammatory signals driving early cancer development as targets for cancer immunoprevention. *Clin Cancer Res.* 2015; 21:1549–1557. [PubMed: 25623216]
44. Keenan BP, et al. A listeria vaccine and depletion of T-regulatory cells activate immunity against early stage pancreatic intraepithelial neoplasms and prolong survival of mice. *Gastroenterology.* 2014; 146:1784–1794. [PubMed: 24607504]
45. Jang J-E, et al. Crosstalk between regulatory T cells and tumor-associated dendritic cells negates anti-tumor immunity in pancreatic cancer. *Cell Rep.* 2017; 20:558–571. [PubMed: 28723561]
46. Thind K, et al. Immunotherapy in pancreatic cancer treatment: a new frontier. *Therap Adv Gastroenterol.* 2017; 10:168–194.
47. Shields, AF., et al. A multi-center study of hTERT immunotherapy in adults with solid tumors at high risk of relapse post-standard therapy [abstract]. *J Immunother Cancer*; 32nd annual meeting and pre-conference programs of the Society for Immunotherapy of Cancer; 2017 Nov 8–12; National Harbor, MD. 2017. p. 86Abstract nr P141
48. Maude SL, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med.* 2014; 371:1507–1517. [PubMed: 25317870]
49. Neelapu SS, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017; 377:2531–2544. [PubMed: 29226797]

50. Schuster SJ, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med.* 2017; 377:2545–2554. [PubMed: 29226764]
51. Yong CSM, et al. CAR T-cell therapy of solid tumors. *Immunol Cell Biol.* 2017; 95:356–363. [PubMed: 28003642]
52. Winter JM, et al. A novel survival-based tissue microarray of pancreatic cancer validates MUC1 and mesothelin as biomarkers. *PLoS One.* 2012; 7:e40157. [PubMed: 22792233]
53. Chmielewski M, et al. T cells that target carcinoembryonic antigen eradicate orthotopic pancreatic carcinomas without inducing autoimmune colitis in mice. *Gastroenterology.* 2012; 143:1095–1107. e2. [PubMed: 22750462]
54. Posey AD, et al. Engineered CAR T cells targeting the cancer-associated Tn-glycoform of the membrane mucin MUC1 control adenocarcinoma. *Immunity.* 2016; 44:1444–1454. [PubMed: 27332733]
55. Abate-Daga D, et al. A novel chimeric antigen receptor against prostate stem cell antigen mediates tumor destruction in a humanized mouse model of pancreatic cancer. *Hum Gene Ther.* 2014; 25:1003–1012. [PubMed: 24694017]
56. Maliar A, et al. Redirected T cells that target pancreatic adenocarcinoma antigens eliminate tumors and metastases in mice. *Gastroenterology.* 2012; 143:1375–1384. e5. [PubMed: 22819865]
57. DeSelm CJ, et al. CAR T-cell therapy for pancreatic cancer. *J Surg Oncol.* 2017; 116:63–74. [PubMed: 28346697]
58. Morgan RA, et al. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. *Mol Ther.* 2010; 18:843–51. [PubMed: 20179677]
59. Bonifant CL, et al. Toxicity and management in CAR T-cell therapy. *Mol Ther oncolytics.* 2016; 3:16011. [PubMed: 27626062]
60. Beatty GL, et al. Mesothelin-specific chimeric antigen receptor mRNA-engineered T cells induce anti-tumor activity in solid malignancies. *Cancer Immunol Res.* 2014; 2:112–120. [PubMed: 24579088]
61. Beatty GL, et al. Activity of mesothelin-specific chimeric antigen receptor T cells against pancreatic carcinoma metastases in a phase 1 trial. *Gastroenterology.* 2018; doi: 10.1053/j.gastro.2018.03.029
62. Tran E, et al. T-cell transfer therapy targeting mutant KRAS in cancer. *N Engl J Med.* 2016; 375:2255–2262. [PubMed: 27959684]
63. Moon EK, et al. Multifactorial T-cell hypofunction that is reversible can limit the efficacy of chimeric antigen receptor-transduced human T cells in solid tumors. *Clin Cancer Res.* 2014; 20:4262–73. [PubMed: 24919573]
64. Stromnes IM, et al. T cells engineered against a native antigen can surmount immunologic and physical barriers to treat pancreatic ductal adenocarcinoma. *Cancer Cell.* 2015; 28:638–652. [PubMed: 26525103]
65. Chapuis AG, et al. T-cell therapy using interleukin-21–primed cytotoxic T-cell lymphocytes combined with cytotoxic T-cell lymphocyte antigen-4 blockade results in long-term cell persistence and durable tumor regression. *J Clin Oncol.* 2016; 34:3787–3795. [PubMed: 27269940]
66. Parente-Pereira AC, et al. Trafficking of CAR-engineered human T cells following regional or systemic adoptive transfer in SCID beige mice. *J Clin Immunol.* 2011; 31:710–718. [PubMed: 21505816]
67. Moon EK, et al. Expression of a functional CCR2 receptor enhances tumor localization and tumor eradication by retargeted human T cells expressing a mesothelin-specific chimeric antibody receptor. *Clin Cancer Res.* 2011; 17:4719–4730. [PubMed: 21610146]
68. Craddock JA, et al. Enhanced tumor trafficking of GD2 chimeric antigen receptor T cells by expression of the chemokine receptor CCR2b. *J Immunother.* 2010; 33:780–788. [PubMed: 20842059]
69. Caruana I, et al. Heparanase promotes tumor infiltration and antitumor activity of CAR-redirected T lymphocytes. *Nat Med.* 2015; 21:524–529. [PubMed: 25849134]

70. Vonderheide RH, Glennie MJ. Agonistic CD40 antibodies and cancer therapy. *Clin Cancer Res.* 2013; 19:1035–43. [PubMed: 23460534]
71. Beatty GL, et al. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. *Science.* 2011; 331:1612–1616. [PubMed: 21436454]
72. Byrne KT, Vonderheide RH. CD40 stimulation obviates innate sensors and drives T cell immunity in cancer. *Cell Rep.* 2016; 15:2719–2732. [PubMed: 27292635]
73. Luheshi NM, et al. Transformation of the tumour microenvironment by a CD40 agonist antibody correlates with improved responses to PD-L1 blockade in a mouse orthotopic pancreatic tumour model. *Oncotarget.* 2016; 7:18508–18520. [PubMed: 26918344]
74. Jacobs C, et al. An ISCOM vaccine combined with a TLR9 agonist breaks immune evasion mediated by regulatory T cells in an orthotopic model of pancreatic carcinoma. *Int J Cancer.* 2011; 128:897–907. [PubMed: 20473889]
75. Silva A, et al. The combination of ISCOMATRIX adjuvant and TLR agonists induces regression of established solid tumors in vivo. *J Immunol.* 2015; 194:2199–2207. [PubMed: 25646304]
76. Corrales L, et al. Direct activation of STING in the tumor microenvironment leads to potent and systemic tumor regression and immunity. *Cell Rep.* 2015; 11:1018–30. [PubMed: 25959818]
77. Mehrotra S, et al. Vaccination with poly(IC:LC) and peptide-pulsed autologous dendritic cells in patients with pancreatic cancer. *J Hematol Oncol.* 2017; 10:82. [PubMed: 28388966]
78. Shrimali RK, et al. Concurrent PD-1 blockade negates the effects of OX40 agonist antibody in combination immunotherapy through inducing T-cell apoptosis. *Cancer Immunol Res.* 2017; 5:755–766. [PubMed: 28848055]
79. Messenheimer DJ, et al. Timing of pD-1 blockade is critical to effective combination immunotherapy with anti-OX40. *Clin Cancer Res.* 2017; 23:6165–6177. [PubMed: 28855348]
80. Redmond WL, et al. Combined targeting of costimulatory (OX40) and coinhibitory (CTLA-4) pathways elicits potent effector T cells capable of driving robust antitumor immunity. *Cancer Immunol Res.* 2014; 2:142–153. [PubMed: 24778278]
81. Foote JB, et al. A STING agonist given with OX40 receptor and PD-L1 modulators primes immunity and reduces tumor growth in tolerized mice. *Cancer Immunol Res.* 2017; 5:468–479. [PubMed: 28483787]
82. Zhang Y, et al. Myeloid cells are required for PD-1/PD-L1 checkpoint activation and the establishment of an immunosuppressive environment in pancreatic cancer. *Gut.* 2017; 66:124–136. [PubMed: 27402485]
83. Sanford DE, et al. Inflammatory monocyte mobilization decreases patient survival in pancreatic cancer: a role for targeting the CCL2/CCR2 axis. *Clin Cancer Res.* 2013; 19:3404–3415. [PubMed: 23653148]
84. Nywening TM, et al. Phase 1b study targeting tumour associated macrophages with CCR2 inhibition plus FOLFIRINOX in locally advanced and borderline resectable pancreatic cancer. *Lancet Oncol.* 2016; 17:651–662. [PubMed: 27055731]
85. Zhu Y, et al. CSF1/CSF1R blockade reprograms tumor-infiltrating macrophages and improves response to T-cell checkpoint immunotherapy in pancreatic cancer models. *Cancer Res.* 2014; 74:5057–5069. [PubMed: 25082815]
86. Wiehagen KR, et al. Combination of CD40 agonism and CSF-1R blockade reconditions tumor-associated macrophages and drives potent antitumor immunity. *Cancer Immunol Res.* 2017; 5:1109–1121. [PubMed: 29097420]
87. Steele CW, et al. CXCR2 inhibition profoundly suppresses metastases and augments immunotherapy in pancreatic ductal adenocarcinoma. *Cancer Cell.* 2016; 29:832–845. [PubMed: 27265504]
88. Kumar V, et al. Cancer-associated fibroblasts neutralize the anti-tumor effect of CSF1 receptor blockade by inducing PMN-MDSC infiltration of tumors. *Cancer Cell.* 2017; 32:654–668. e5. [PubMed: 29136508]
89. Chao T, et al. CXCR2-dependent accumulation of tumor-associated neutrophils regulates T-cell immunity in pancreatic ductal adenocarcinoma. *Cancer Immunol Res.* 2016; 4:968–982. [PubMed: 27737879]

90. Manuel ER, et al. Salmonella-based therapy targeting indoleamine 2,3-dioxygenase coupled with enzymatic depletion of tumor hyaluronan induces complete regression of aggressive pancreatic tumors. *Cancer Immunol Res.* 2015; 3:1096–1107. [PubMed: 26134178]
91. Rhim AD, et al. Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma. *Cancer Cell.* 2014; 25:735–747. [PubMed: 24856585]
92. Özdemir BC, et al. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. *Cancer Cell.* 2014; 25:719–734. [PubMed: 24856586]
93. Hingorani SR, et al. Randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine (PAG) vs AG in patients (pts) with untreated, metastatic pancreatic ductal adenocarcinoma (mPDA). *J Clin Oncol.* 2017; 35(suppl) abstr 4008.
94. Melstrom LG, et al. The pancreatic cancer microenvironment: a true double agent. *J Surg Oncol.* 2017; 116:7–15. [PubMed: 28605029]
95. Jiang H, et al. Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. *Nat Med.* 2016; 22:851–860. [PubMed: 27376576]
96. Yuan C, et al. Prediagnostic plasma 25-hydroxyvitamin D and pancreatic cancer survival. *J Clin Oncol.* 2016; 34:2899–2905. [PubMed: 27325858]
97. Sherman MH, et al. Vitamin D receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy. *Cell.* 2014; 159:80–93. [PubMed: 25259922]
98. Lo A, et al. Fibroblast activation protein augments progression and metastasis of pancreatic ductal adenocarcinoma. *JCI Insight.* 2017; 2:e92232.
99. Feig C, et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. *Proc Natl Acad Sci.* 2013; 110:20212–20217. [PubMed: 24277834]
100. Lo A, et al. Tumor-promoting desmoplasia is disrupted by depleting FAP-expressing stromal cells. *Cancer Res.* 2015; 75:2800–2810. [PubMed: 25979873]
101. Wolchok JD, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med.* 2017; 377:1345–1356. [PubMed: 28889792]
102. Chang M-H, et al. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. *J Natl Cancer Inst.* 2009; 101:1348–55. [PubMed: 19759364]
103. Lehtinen M, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol.* 2012; 13:89–99. [PubMed: 22075171]
104. Reuschenbach M, et al. Serum antibodies against frameshift peptides in microsatellite unstable colorectal cancer patients with Lynch syndrome. *Fam Cancer.* 2010; 9:173–179. [PubMed: 19957108]
105. Reuschenbach M, et al. A systematic review of humoral immune responses against tumor antigens. *Cancer Immunol Immunother.* 2009; 58:1535–1544. [PubMed: 19562338]
106. Rhim AD, et al. Detection of circulating pancreas epithelial cells in patients with pancreatic cystic lesions. *Gastroenterology.* 2014; 146:647–651. [PubMed: 24333829]
107. Cappello P, et al. Vaccination with ENO1 DNA prolongs survival of genetically engineered mice with pancreatic cancer. *Gastroenterology.* 2013; 144:1098–1106. [PubMed: 23333712]
108. Shi C, et al. Familial pancreatic cancer. *Arch Pathol Lab Med.* 2009; 133:365–74. [PubMed: 19260742]
109. Cheng G. Circulating miRNAs: roles in cancer diagnosis, prognosis and therapy. *Adv Drug Deliv Rev.* 2015; 81:75–93. [PubMed: 25220354]
110. Szafranska-Schwarzbach AE, et al. Development of a miRNA-based diagnostic assay for pancreatic ductal adenocarcinoma. *Expert Rev Mol Diagn.* 2011; 11:249–57. [PubMed: 21463235]
111. Phallen J, et al. Direct detection of early-stage cancers using circulating tumor DNA. *Sci Transl Med.* 2017; 9:aan2415. [PubMed: 28814544]
112. Kim J, et al. Detection of early pancreatic ductal adenocarcinoma with thrombospondin-2 and CA19-9 blood markers. *Sci Transl Med.* 2017; 9:eah5583. [PubMed: 28701476]

**HIGHLIGHTS**

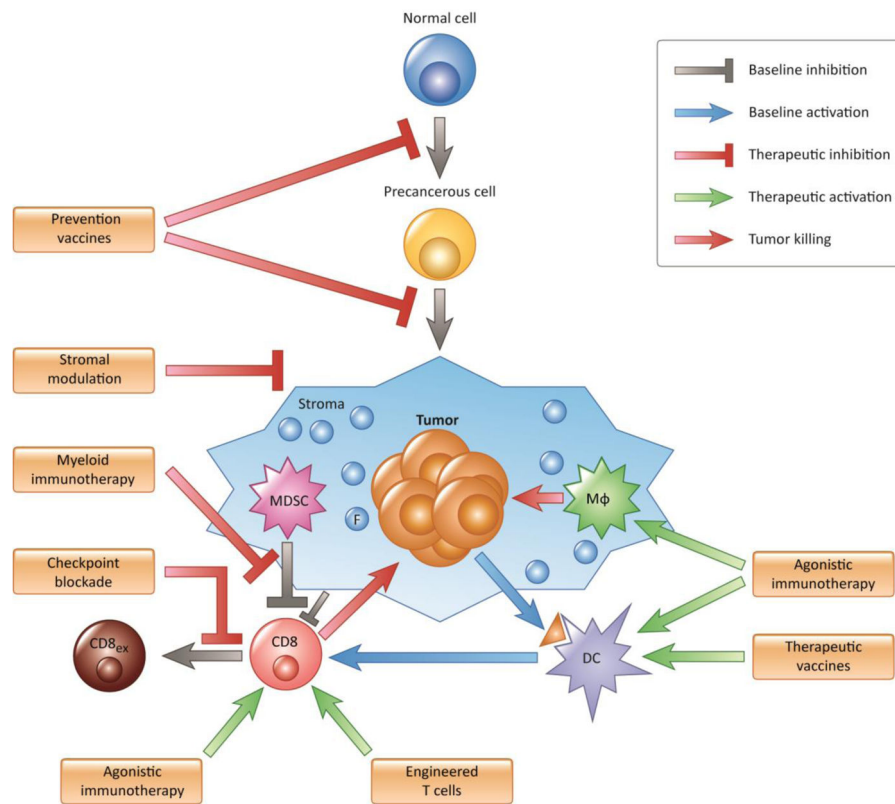
- Pancreatic cancer remains a lethal tumor that is difficult to treat and, unfortunately, immune therapies that have garnered FDA approval in other tumors have shown little efficacy to date in this tumor. These therapies include checkpoint antibodies and engineered T-cell infusions.
- A formidable problem in developing effective immunotherapy for PDA is the striking immunosuppressive and “immune privileged” tumor microenvironment. Few patients exhibit robust T-cell infiltration in the tumor microenvironment, although when this does occur patient survival is prolonged.
- Major clinical efforts, justified by preclinical models, are now aimed at combination immune therapies that address multiple immune vulnerabilities in PDA in non-redundant fashions.
- Generating stronger adaptive immunity with vaccines and immune agonists may be necessary before antibodies against CTLA-4, PD-1, or PD-L1 will have effectiveness.

Therapy	Phase I	Phase II	Phase III	Approved?	Comments
<b>Immune Checkpoint Blockade</b> PD-1/PD-L1 CTLA-4				dMMR patients only	No responses outside dMMR patients; combinations under investigation
<b>Therapeutic Vaccines</b> GVAX Algenpantucel-L hTERT peptide hTERT DNA				No	Large RCTs negative; may benefit from checkpoint blockade
<b>Engineered T cells</b> CAR-T				No	Signs of immunogenicity; need to optimize antigens
<b>Agonistic Immunotherapy</b> CD40				No	Promising preclinical data; Phase Ib/II underway
<b>Myeloid Immunotherapy</b> CCR2 CSF-1R CXCR2				No	Promising combinations, especially with checkpoint blockade
<b>Stromal Modulation</b> Hyaluronidase FAK VDR				No	Most clinically advanced; new targets emerging
<b>Prevention Vaccines</b>				No	Proof of concept in colon cancer; PDA on the horizon

**Figure 1. Clinical status of immunotherapies in pancreatic cancer**

Each line represents a single class of immunotherapy. The right end of each line indicates the latest stage of clinical trials that class of compounds has reached. Solid green arrows indicate ongoing trials. Red lines indicate negative trials. Dotted green arrow indicates successful trials in other malignancies.





**Figure 2. Mechanisms of immunotherapies in PDA**

Graphical representation of the immune response in pancreatic cancer indicating where each type of immunotherapy acts. See inset legend for significance of arrows. F = fibroblast, MDSC = myeloid derived suppressor cell, Mφ = macrophage, DC = dendritic cell, CD8 = CD8 T cell, CD8<sub>ex</sub> = exhausted CD8 T cell.