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Next-generation immunotherapy for pancreatic ductal adenocarcinoma: navigating pathways of immune resistance

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Abstract

To date, the use of immune checkpoint inhibitors has proven largely ineffective in patients with advanced pancreatic ductal adenocarcinoma. A combination of low tumor antigenicity, deficits in immune activation along with an exclusive and suppressive tumor microenvironment result in resistance to host defensives. However, a deepening understanding of these immune escape and suppressive mechanisms has led to the discovery of novel molecular targets and treatment strategies that may hold the key to a long-awaited therapeutic breakthrough. In this review, we describe the tumor-intrinsic and microenvironmental barriers to modern immunotherapy, examine novel immune-based and targeted modalities, summarize relevant pre-clinical findings and human experience, and, finally, discuss novel synergistic approaches to overcome immune-resistance in pancreatic cancer. Beyond checkpoint inhibition, immune agonists and anti-tumor vaccines represent promising strategies to stimulate host response via activation and expansion of anti-tumor immune effectors. Off-the-shelf natural killer cell therapies may offer an effective method for bypassing downregulated tumor antigen presentation. In parallel with this, sophisticated targeting of crosstalk between tumor and tumor-associated immune cells may lead to enhanced immune infiltration and survival of anti-tumor lymphocytes. A future multimodal treatment strategy involving immune priming/activation, tumor microenvironment reprogramming, and immune checkpoint blockade may help transform pancreatic cancer into an immunogenic tumor.

Keywords Immunotherapy · Pancreatic cancer · Review · Tumor microenvironment · Targeted therapy · Developmental therapeutics

1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) has the highest case-fatality rate of any solid tumor and is projected to surpass colorectal cancer as the 2nd leading cause of cancer-related mortality nationally in the next 5 years [1, 2]. Even for the 15–20% of patients who are eligible for curative resection at diagnosis, their 5-year overall survival remains discouraging low at 20% with >80% of cases recurring just 2 years post-surgical intervention [3]. The current mainstay of treatment for advanced PDAC continues to be limited to largely two cytotoxic chemotherapy regimens: (1) fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX); (2) gemcitabine (Gem) and nanoparticle albumin-bound paclitaxel (NP) [4–6]. While immune checkpoint blockade (ICB), namely inhibitors of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1)T-cell checkpoints, has dramatically changed frontline therapy and survival outcomes in an impressive breadth of solid tumors, it has proven, largely, ineffective in patients with PDAC. With the exception of mismatch repair-deficient/microsatellite instability high (dMMR/MSI-H) tumors, which account for <1% of all PDAC tumors, there are currently no approved immunotherapy (IO) regimens for PDAC [7, 8]. However, IO remains an area ripe for novel targets and strategies that could lead to therapeutic breakthroughs in PDAC. In this review, we will describe tumor-intrinsic and microenvironmental barriers to effective IO in PDAC, examine novel IO and targeted modalities, summarize relevant pre-clinical findings and clinical trial experience, and discuss novel

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synergistic approaches to overcome the intrinsic immune-resistance in PDAC.

2 Contemporary IO and PDAC

2.1 CTLA-4 and PD-[L]1 Checkpoint Inhibition

Unrivaled in clinical experience and commercial ubiquity, inhibitors of CTLA-4 and PD-[L]1 T-cell checkpoints form the cornerstone of modern immunotherapy. Briefly, the binding of CTLA-4 on activated T-cells by its ligands B7-1|2 prevents CD28 co-stimulation and leads to T-cellanergy/apoptosis [9]. Generally, while CTLA-4 functions during central T-cell priming, PD-1 signaling functions during the T-cell effector phase in the peripheral tissues. The binding of PD-1 on T-cells with its ligand, PD-L1, inhibits T-cell activation and leads to T-cell exhaustion. Unlike CTLA-4 which is T-cell exclusive, PD-1 is expressed on activated T-cells, B cells, and myeloid cells [9]. Cancer cells and tumor-recruited immune cells overexpress PD-L1 as a means to blunt and escape T-cell-mediated immune response [10]. Though the expression of both CTLA4 and PD-L1 is upregulated and associated with poor outcomes in PDAC [11, 12], the targeting of these checkpoints has not improved upon outcomes with current standard of care (SOC). In early phase clinical trials, the anti-CTLA-4 antibodies, ipilimumab and tremelimumab, were ineffective as monotherapies and demonstrated no additive benefit when added to a Gem-backbone in patients with previously treated PDAC [13–15]. In KEYNOTE-028, objective response rate (ORR) among PDAC patients treated with pembrolizumab monotherapy (aPD-1 mAb) was 0% and median progression-free survival (mPFS0) was just 1.7 months [16]. Durvalumab (aPD-L1 mAb) also proved ineffective both as a monotherapy (0% ORR) and when combined with CTLA-4 blockade (3.1% ORR and 22% incidence of grade 3+ toxicity) in patients advanced PDAC [17].

2.2 IO-responsive PDAC

While conventional ICB has disappointed in PDAC, overall, there are rare, but notable exceptions. Patients with mutations in homologous recombination repair genes may lead to increased genomic instability and IO-sensitivity but evidence remains anecdotal. In small case series of patients with refractory mPDAC harboring either germline BRCA or RAD51 mutations, one patient (gBRCA1 mutated) achieved a durable complete response while another (gRAD51C mutated) had an ongoing PR when treated with combination ipilimumab and nivolumab [18]. More robust data in ICB-responsive PDAC has been observed in patients with tumors characterized as dMMR/MSI-H. KEYNOTE-158 included 22 patients with dMMR/MSI-H advanced, heavily pretreated, PDAC who had an observed 18% ORR (1 CR, 3 PR) and a median duration of response (DOR) of 13.2 months with pembrolizumab monotherapy. It should be noted that mPFS and mOS for patients with this rare genotype were still only 2.0 and 4.0 months, respectively. When comparing across dMMR/MSI-H GI primaries, the 18% ORR of PDAC underperforms compared to cholangiocarcinoma (40.9%), small intestine (42.1%), gastric (45.8%), or colorectal adenocarcinomas (53%) [8, 19]. While this remains a promising treatment signal, the noticeable disparity in therapeutic response reinforces the need for novel combinatorial strategies to achieve a breakthrough in IO and improve survival in PDAC, regardless of MMR status.

2.3 Intrinsic immune-resistance

An anti-tumor immune response requires tumor recognition, immune cell activation, tumor bed infiltration, and immune-mediated cytolysis (Fig. 1). PDAC has adapted well to evade immune surveillance and suppress immune response at each of these levels: a combination of low tumor antigenicity, deficits in immune activation along with an exclusive and suppressive tumor microenvironment all act as individual roadblocks to effective IO in PDAC (Fig. 2). Strategic targeting of these immunologic barriers may optimize the anti-tumor potential of IO-based therapies in PDAC.

3 [IO barrier] impaired tumor recognition and blunted host immune response

The process of adaptive immune recognition should be initiated when tumor antigens are processed and displayed onto major histocompatibility complexes (MHC/HLA) by nucleated cells (class I) and antigen presenting cells (class II) [20]. Once these antigenic flags are taken up by antigen presenting cells (APCs), such as dendritic cells (DCs), these immunostimulatory cells then traffic to lymph nodes and secondary immune organs to mature and present their antigen-MHC complex to previously quiescent naïve T-cells [20]. Following T cell receptor (TCR) binding with the antigen-MHC(or antigen-HLA) complex, along with a co-stimulatory signal, the T cell undergoes clonal expansion and differentiation towards effector (CD8+ cytotoxic T lymphocytes [CTL] and CD4+ helper T cells [Th]) and memory functions (central [Tcm], tissue resident [Trm]& effector [Tem] subtypes) [21]. There are three main areas where PDAC hampers this process: (1) antigenic load, (2) tumor cell MHC presentation, and (3) APC dysfunction.

3.1 [IO barrier] low tumor neoantigen burden

Although the proteins encoded by cancer genes are intracellular, short peptides (epitopes) derived through proteolytic

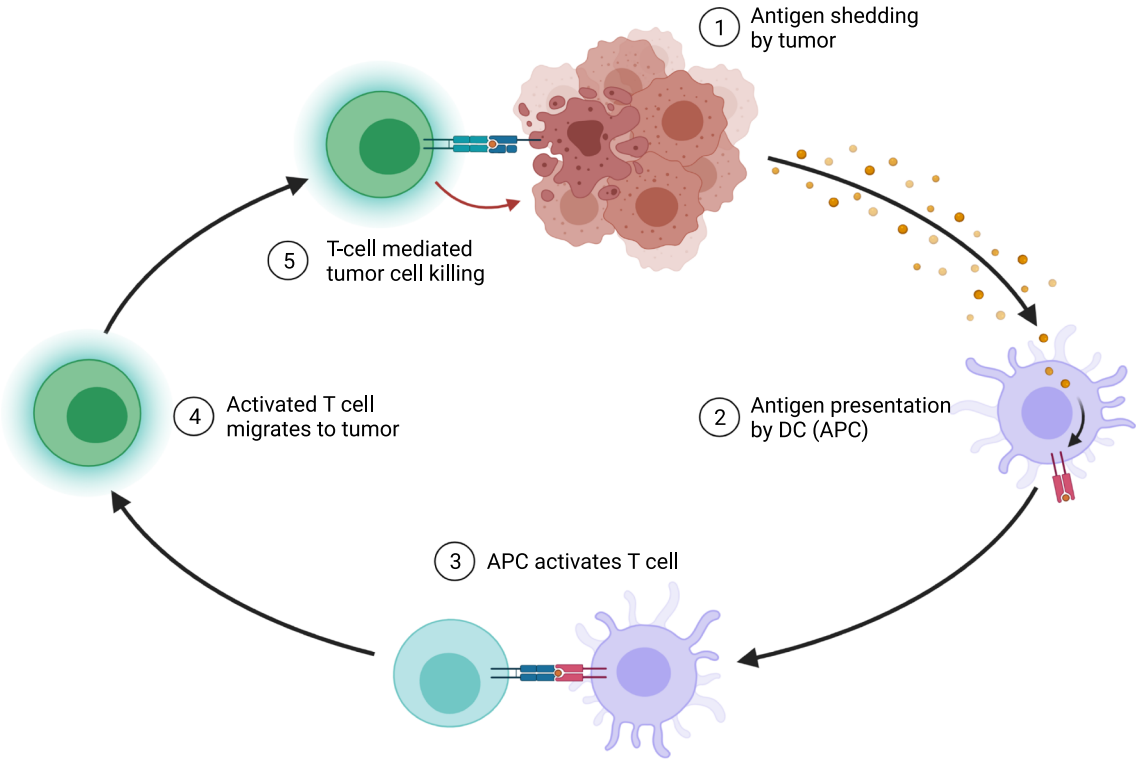

Fig. 1 Adaptive Immune Response in Cancer Immunotherapy relies on the ability of host immune cells to recognize cancer as cells that need to be eliminated. For this to happen, a tumor cell needs to alert surveilling antigen presenting cells (APCs), such as dendritic cells (DC), that they are abnormal by expressing antigens on their cell surface. When APCs recognize this abnormal signal, they take up the antigen, traffic to lymph nodes to mature and, in turn, activate cytotoxic and helper T cells with T cell receptors (TCR) specific to that tumor antigen. Once these T cells are activated, they should further differentiate, expand, and migrate to the tumor bed and kill that tumor cell. Adapted from "Antigen Presentation in Cancer", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates

processing within the tumor cell are presented on the cell surface by MHC (HLA) molecules for recognition as self/foreign antigen by surveilling immune cells. There are three broad categories of tumor antigens:

1) Tumor-associated antigens (TAA)—normal host proteins that demonstrate distinct expression profiles between host and tumor cells. Though the best characterized, TAAs induce limited endogenous T cell responses due to central tolerance and/or lower TCR-MHC binding affinity due to similarity to self-peptides [22].
2) Cancer-germline or cancer/testis antigens (CTA)—CTAs can be expressed in testes, fetal ovaries, or trophoblasts, but are otherwise absent in healthy somatic cells [22]. Although CTA targets are also shared between tumors, they are known to be expressed in only a limited number of tumor types, potentially reducing the applicability of CTA-targeted immunotherapy [23].
3) Tumor-specific antigens (TSA)—these cancer-restricted antigens are generated from tumor-specific mutations (neoantigens) and oncogenic viral proteins (e.g., HPV, EBV). Since neoantigens arise from non-synonymous somatic mutations during oncogenesis, they are uniquely expressed on tumors, and T cells involved in their recognition are less likely to be eliminated by central tolerance [23]. For the purposes of this review, antigens in the context of "antigen burden" or "tumor antigenicity" will be in reference specifically to tumor neoantigens (TSAs).

Tumor mutational burden (TMB), a predictor of ICB response [24], strongly correlates neoantigen load [25]. As compared to PDAC, ICB-responsive tumors, such melanoma, non-small cell lung cancer (NSCLC), and dMMR tumors, generally have significantly higher TMB indices and neoantigen loads (1000s–10,000s) [26]. In comparison, PDAC expresses an average of 30–50 neoantigens per tumor [27]. Among those small numbers, only a select few immunogenic neoantigens can trigger T cell activation and expansion. Consistent with this, data shows that tumors with both abundant $CD8^+$ T cell infiltrates and a high volume of neoantigens—but neither alone—are associated with the longest survival in patients with PDA [28].

3.1.1 [IO strategy] increase the tumor antigen/neoepitope pool with radiation and DNA damage repair inhibition

Radiation Combining localized radiation therapy (RT, SBRT) with ICB may provide a boost to what is known as the

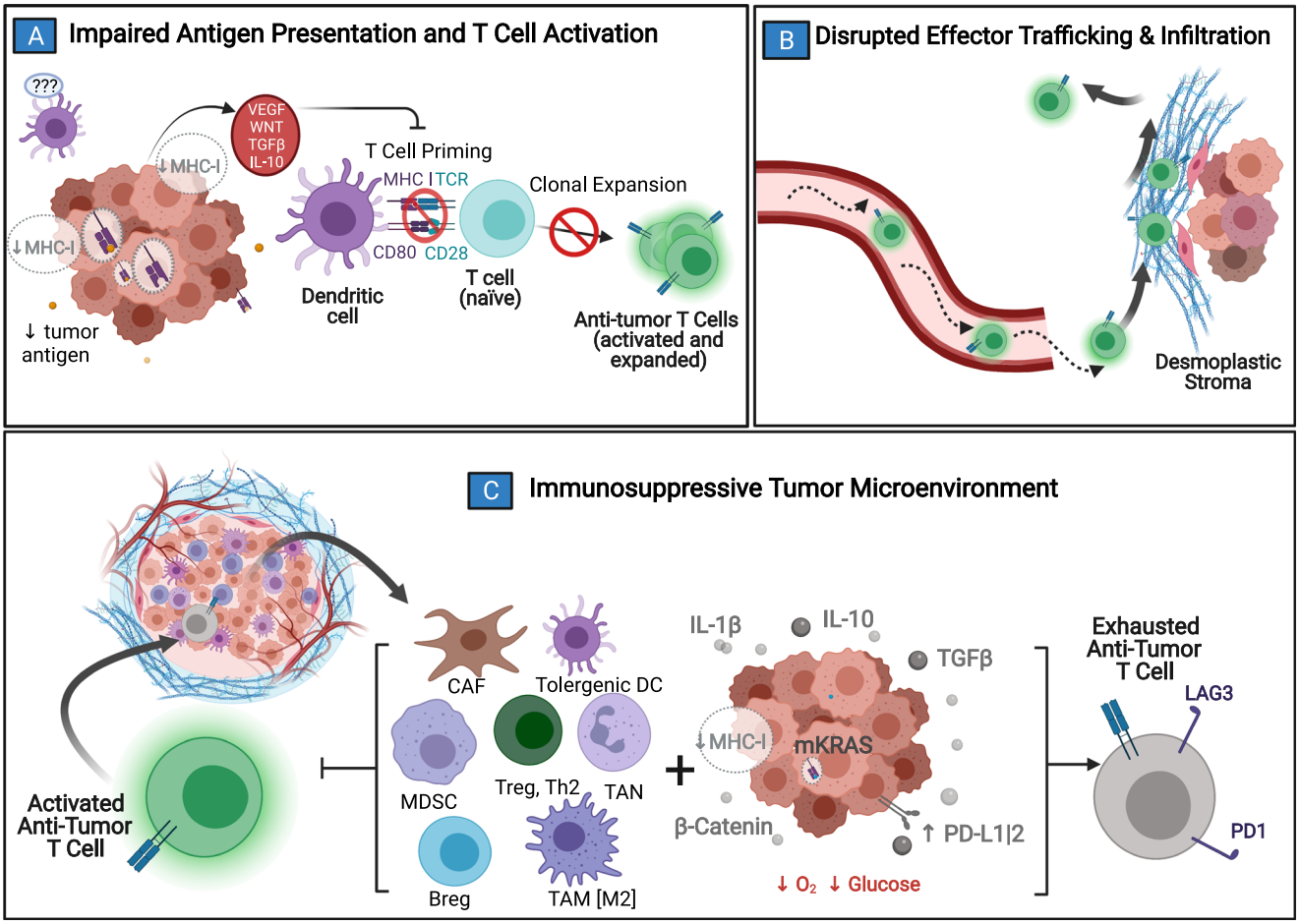

Fig. 2 Mechanisms of Immune Resistance in Pancreatic Cancer Pancreatic cancer (PDAC) has several protections against the generation and execution of an anti-tumor hostimmune response. A) PDAC's low antigen burden, sequestration of MHC/HLA-I molecules, and local tolerogenic TME signaling all contribute to poor immune surveillance and stunt normal dendritic cell maturation. Without normal antigen processing and presentation, anti-tumor effectors are not activated. B) If activation and clonal expansion of effector T cells still does manage to occur, trafficking to the tumor bed is complicated by disrupted chemokines gradients, abnormal vasculature, and the desmoplastic tumor stroma that acts as both a physical & chemical barrier to entry. C) Anti-tumor immune cells that are able to penetrate the TME are quickly exhausted by local metabolic conditions combined with immunosuppressive molecular crosstalk (e.g. upregulated interleukin 1 beta [IL-1b], transforming growth factor beta [TGFb], interleukin 10 [IL-10], and beta-catenin [b-catenin]) between tumor and tumor-coopted immune cell populations (cancer-associated fibroblasts [CAF]; tumor associated macrophages [TAM]; tumor associated neutrophils [TAN]; tolerogenic dendritic cells [DC]; myeloid derived suppressor cells [MDSC]; type II T helper cells [Th2]; T regulatory cells [Treg]; B regulatory cells [Breg]). Adapted from "Challenges for CAR T-Cell Immunotherapy in Solid Tumors" and "Tumor Extracellular Matrix Reduces Therapeutic Efficiency in Solid Tumors", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates

"Abscopal Effect"—an observation of focal intervention inducing a systemic antitumor response in sites outside the treatment area [29]. This is presumably due to RT-induced tumor cell injury leading production of additional tumor antigens which are then engulfed by APCs [30, 31]. In addition, RT can diversify the TCR repertoire of intratumoral and peripheral T-cells and can synergize with ICB through non-redundant immune activation mechanisms [32–34]. Preliminary results from a phase II study examining use of dual CTLA-4 and PD-1 blockade with RT(NCT03104439) have shown promising results as a strategy to stimulate immune response in patients with pretreated metastatic PDAC. Among 22 patients enrolled, all pMMR tumors, disease control rate (DCR) was 27% and ORR was 14% including 1 CR. Notably, all objective responses occurred outside of the radiation field [35]. There are several other ongoing clinical trials looking at RT in combination with several classes of IO and TME modifying therapies (e.g., NCT03599362, NCT02648282, NCT04327986).

DNA damage repair modulators Defective DNA repair response (DDR) pathway mutations—such as *BRCA1*, *BRCA2*, *ATM*, and *PALB2*—occur frequently in both inherited and sporadic PDAC [36]. Germline DDR mutations are found in 5–10% of PDAC patients. Additionally, a quarter of PDAC tumors carry somatic mutations in either BRCA1, BRCA2,

and other "BRCA-like" DNA repair genes (e.g., *ATM, ATR, BARD1, BRIP1, CHK1, CHK2, PALB2, RAD51*, and *FANC*) [37]. These mutations may predict increased sensitivity to platinum-based chemotherapy and could be therapeutically targetable [34]. Poly ADP-ribose polymerase inhibitors (PARPi) were welcomed into the arsenal of approved pancreatic cancer treatments after maintenance olaparib demonstrated a significant PFS and OS benefit of in advanced PDAC patients harboring germline BRCA mutations who had disease control with first-line metastatic therapy [38]. Inhibiting DDR with PARPi may lead tumor cells to develop a more immunogenic repertoire of antigens and cause release interferons to serve as signals for immune response that can be further augmented with ICB [39]. Preclinical data have shown that treatment with PARP inhibition is associated with upregulated PD-L1 expression in the TME [40]. Consistent with this observation, synergy between PARPi and ICB has been demonstrated in mouse models of BRCA1-deficient ovarian and breast cancers [41, 42]. Current ongoing studies of BRCA-mutated PDAC patients include neratinib (PARPi) in combination with dostarlimab (anti-PD1) (NCT04493060), dostarlimab plus RT (NCT04409002), nivolumab, or ipilimumab (anti-CTLA-4) (NCT03404960). Outside of PARPi, ATM and ATR inhibitors are in the early stages of clinical development in patients with solid tumors, but preclinical data has suggested potential therapeutic synergy between these inhibitors, chemotherapy, ICB, and RT. [43–46]

3.1.2 [IO strategy] administering anti-cancer vaccines and immune adjuvants to optimize immune priming

To overcome the issue of low immune recognition of PDACs, several anti-cancer vaccine platforms have been developed to generate a novel or boost existing immune responses [47]. Several vaccination strategies have demonstrated antigen-specific immunological responses in patients with PDAC [48–50].

GVAX The most extensively studied vaccine in PDAC is the allogenic, whole-cell vaccine, GVAX. GVAX is composed of two human PDAC cell lines modified to express granulocyte-macrophage colony stimulating factor (GM-CSF) to activate T-cells against a variety of tumor antigens. This whole cell, allogeneic vaccine is less specific, but offers the advantages of being standardized, and faster to give off-the-shelf to patients. This is as opposed to autologous, personalized vaccines that use the patient's own tumor as an antigen source [51]. In clinical trials, GVAX combined with chemoRT in the adjuvant setting for resected PDAC revealed an expansion of mesothelin-specific CD8+ T cells. Mesothelin, a TAA, has relatively high specificity for PDAC and has been implicated as mediator of tumor progression/metastasis [52, 53]. This led to the development of a live-attenuated, mesothelin-expressing, *Listeria monocytogenes vaccine (CRS-207) added as a method to prime-boost response to GVAX. Despite promising phase I results in a metastatic PDAC population* [54*], this combination, ultimately, failed to improve OS compared physician's choice chemotherapy in the 2*nd- *and 3*rd-*line metastatic settings* [55*]. Notably, on correlative tissue analysis, vaccination-induced* increases in tumor infiltrating (TILs) CD8+ Teff cells were met with an upregulation of PDL1 and other immunosuppressive markers suggesting potential synergy with ICB [56]. In line with this hypothesis, a phase Ib study in pretreated mPDAC patients showed that combining GVAX and ipilimumab (anti-CTLA4) was associated with improved overall survival compared to treatment with ipilimumab alone (5.7 vs. 3.6 mo) [57]. However, in a recent phase II trial, the addition of nivolumab to a backbone of a combined GVAX+ CRS-207 vaccine regimen provided no additional benefit to OS compared to vaccination alone in mPDAC patients [58]. This has prompted investigation into combining anti-tumor vaccination with immunomodulators beyond conventional aCTLA-4/aPD-1 targets. Combinatorial GVAX + nivolumab + an anti-CD137 immune agonist, administered to 10 resectable PDAC patients prior surgery, resulted in three moderate pathologic responses on resected tumor surgical specimens. Additional doses of this regimen were given prior to and continued (every 4 weeks) after completion of standard adjuvant chemotherapy. At a median 12-month follow-up, 9 of 10 enrolled patients remained disease-free. Correlative studies notably showed treatment-related expansion of activated, cytolytic Granzyme B+ CD8 TILs [59].

Additional TAA-targeted vaccines As with GVAX and CRS-207, other TAA-targeting vaccines using various platforms, including dendritic cells [60], viruses [61], and peptides [62], have yielded mixed results thus far. A notable phase II study of GV1001, a human telomerase reverse transcriptase AQ9catalytic subunit (hTERT) peptide vaccine, along with GM-CSF adjuvant, demonstrated objective immune responses in 63% of participants. Those same patients also experienced significantly longer OS when compared to the patients who did not have an immune response to GV1001 [50]. However, this may have been more a function of the tumor/host-immune substrate rather than due to the intrinsic-efficacy of the vaccine. In a follow-up phase III trial, the addition of GV1001 (with GM-CSF) to adjuvant gemcitabine and capecitabine failed increase OS compared to the chemotherapy alone [63]. BSK01, an intra-dermal, autologous DC vaccine (*ex vivo* primed and matured DCs pulsed with TAAs—SP17, AKAP4, PTTG1, Ropporin-1, Span-Xb) demonstrated immunogenicity and clinical response in a patient with refractory, metastatic pancreatic cancer, but has not yet moved onto a phase II trial [64]. Another vaccine, BN-CV301, a genetically modified poxvirus expressing TAAs carcinoembryonic antigen (CEA) and mucin-1(MUC-1) along with three

costimulatory molecules (B7.1, ICAM-1, and LFA-3) is currently in trial with durvalumab (anti-PDL1) and maintenance capecitabine in the advanced PDAC patients who are responsive to first-line chemotherapy (NCT03376659). Overall, TAA-based vaccination strategies remain limited in generating robust host immune responses due to variable immunogenicity and presence/expression of selected TAAs across PDAC patients and within heterogeneous tumors. The expression of TAAs by normal cells risks further damping of response due to negative selection of TAA-specific T-cells and/oroff-target autoimmune toxicity [51].

TSA-targeted vaccines Targeting TSAs, as opposed to TAAs, may offer a solution to the above limitations since it targets antigen unique solely to the tumor. However, these biologic/immunologic benefit currently comes with a high technologic and economic cost: neoantigens often being unique to each individual patient and thus typically require personalized vaccines [65]. Generating a neoantigen vaccine first must begin with neoantigen identification. Generally, this starts with tumor and host genomic and whole exome sequencing to identify unique neoepitopes produced by the tumor. Next, these antigens are assessed for immunogenicity via factors such as variant allele frequency, MHC-binding avidity predictions [66], and similarity to self. Those neoantigens identified as most likely to trigger a robust immune response are synthesized into long chain peptides and combined with an adjuvant to induce innate immune response (e.g., GM-CSF, polyinosinic-polycytidylic acid [poly-ICLC], and a synthetic RNA TLR3 agonist). This technological workflow has already been successfully carried out in human trials.

Pilot studies in melanoma, glioblastoma, and other solid tumors have shown that the generation/administration of personalized neoantigen peptide vaccines is not only feasible but also induces neoantigen-specific $CD4^+$ and $CD8^+$T-cells in peripheral blood in response to vaccines targets [67–72]. Ott and colleagues generated and administered personalized neoantigen peptide vaccines (n=13–21, 21-mer synthetic long chain peptides) with poly-ICLC adjuvant in 8 melanoma patients following definitive resection; six of whom demonstrated peripheral T cell responses [67]. Thirty-two months post-vaccination, half of participants remained disease free, with the 2 patients recurring, who had peripheral T cell response, going on to achieve complete responses after treatment with subsequent anti-PD-1 therapy [67]. Pilot studies in glioblastoma, a low-TMB tumor similar to pMMR PDAC, have shown that neoantigen vaccines can induce peripheral immune response and effector T-cell infiltration [68, 69]. In a very recent combinatorial protocol [73], personalized neoantigen vaccines were added to on-going nivolumab (anti-PD1) treatment in patients with high-TMB tumors (e.g., melanoma, NSCLC, and bladder cancer). The addition of the neoantigen vaccine to ongoing PD1 blockade resulted in robust neoantigen-specific T cell immunity and led to vaccine-induced direct tumor cell killing. Taken together, the pre-clinical and human pilot study data supports the therapeutic synergy of increasing immune activation/expansion with an anti-tumor vaccine and optimizing effector response/countering immunoregulatory signaling with ICB.

With regard to neoantigen vaccine use in PDAC, specifically, a pre-clinical proof of concept study was successfully conducted by Zaidi and colleagues, who generated and administered a neoantigen-targeted long peptide vaccine (PancVAX), with STING adjuvant (ADU-V16), in Panc02 mouse model [74] . Encouragingly, this vaccine led to neoepitope-specific T-cell responses and transient tumor regression that was noted to be significantly more durable when combined with immune checkpoint modulators (e.g., aPD-1 and agonist OX40 mAbs) [74]. These findings formed the basis of two clinical trials. The first, opening later this year, will seek to generate and administer a personalized neoantigen peptide vaccine with poly-ICLC adjuvant along with MGA-012(aPD-1) therapy to metastatic PDAC patients in the maintenance setting. The second, is an ongoing phase 1 clinical trial (NCT04117087) testing the safety and immunogenicity of administering dual ICB (nivolumab and ipilimumab) with a mutant KRAS "off-the shelf" neoantigen vaccine—consisting of six SLPs corresponding to KRAS G12C, G12D, G12V, G12R, G12A, and G13D mutations, respectively, with poly-ICLCadjuvant—in patients with resected mKRAS PDAC following adjuvant chemotherapy. Overall, while currently carrying a high technologic and economic cost to produce, the growing ubiquity and standardization of high-throughput next-generation sequencing and immunogenicity algorithms, neoantigen-targeted vaccination may soon have the feasibility to realize its therapeutic potential in PDAC and other immunologically "cold" tumors types.

3.2 [IO Barrier] sequestration of tumor MHC/HLA I molecules

Effector T-cells directly identify tumor cells as foreign via antigen presentation by MHC (HLA) class I molecules expressed on the surface of tumor cells. However, when examining the tumors of PDAC patients, the locus-specific expression of HLA I was found to be reduced in 61% of PDAC primary tumors and in 93% of tumor metastases [75]. Recently, Yamamoto and colleagues, using a mouse-model of PDAC, observed that, instead of being located of the cell surface, most PDAC antigen-MHC I complexes were sequestered inside the tumor cell within autophagosomes and autolysosomes [76]

3.2.1 [IO strategy] increase tumor HLA class 1 expression by inhibiting autophagy

PDAC cells exhibit constitutive elevated basal autophagy which plays multiple pro-tumorigenic roles, including

promoting immune evasion and supporting tumor metabolic demand in a nutrient-deprived microenvironment [77, 78]. In the same preclinical study mentioned above, the investigators showed that inhibiting an autophagy mediator, NRB1 with chloroquine (CQ) induced an influx of CTLs to the TME and generated robust antitumor clinical responses [76]. While encouraging, this synergy between IO and CQ/hydroxychloroquine(HCQ) has not proven consistent with other preclinical studies suggesting CQ/HCQ attenuates IO response [79]. Clinically, HCQ has not shown significant anti-tumor benefit as a single-agent [80] or in combination with standard chemotherapy in PDAC [81, 82]. This may be, in part, due to off-target systemic immunosuppressive effects of HCQ/CQ's unselective inhibition of endosomal degradation and vesicular trafficking [78, 83, 84]. Given this, the future role of autophagy inhibitors in IO-based regimens will be dependent on the discovery and exploitation of tumor-specificautophagy/metabolic pathways.

3.2.2 [IO strategy] target KRAS signaling to increase sensitivity to autophagy inhibition and IO

Oncogenic KRAS (mKRAS), mutated in 95% of PDAC, has recently been implicated as a mediator of both antitumor immune response and autophagy influx. In models of mKRAS PDAC, inhibition of signaling downstream of RAS (e.g., MEK/ERK) increased tumor cell metabolic reliance on autophagy [85]. Notably, autophagic signaling and transcription of autophagy-associated genes were increased in cells with suppressed m*KRAS* but not in PDAC cells with suppressed wild-type(WT)*KRAS*. This could represent a therapeutic vulnerability for combinatorial targeted therapy, autophagy inhibition, and IO in mKRAS tumors [86]. Based on these preclinical results, a phase I/II(NCT04214418) is underway evaluating combination of cobimetinib (MEK inhibitor), atezolizumab (aPDL-1), and HCQ (autophagy inhibitor) in *KRAS*-mutated advanced malignancies, including PDAC [87].

Furthermore, promising early phase trial results of the first-in-class, KRAS Gly12Cys inhibitor, AMG510, in KRAS G12C-mutated advanced solid tumors [88], particularly in NSCLC [89], shows it is possible to directly target mKRAS. While KRAS G12C mutations are only present in ~2% of PDAC, inhibitors of more common KRAS mutations (e.g., G12A, G12V, or G12A) may soon follow suit. This would have important implications beyond single-agent anti-cancer activity since inhibiting mKRAS may also enhance IO response. In a mouse model of mKRAS PDAC, tumors were unable to evade host immune response after KRAS inactivation. The ongoing phase 1b CodeBreak 101 study (NCT04185883) is examining several combinatorial AMG510-based regimens, including with ICB, in advanced solid tumors harboring mKRAS G12C [90].

3.2.3 [IO strategy] bypass absent antigen presentation with NK-cells

PDAC is known to suppress signaling needed to recruit and activate natural killer (NK) cells, and rightly so [91–95]. The innate ability of NK cells to recognize the absence of MHC-proteins and respond rapidly—independent of transcription or proliferation—makes them promising cellular agents to target tumors evading T-cell immunity via mechanisms such as disruption of INF-γ signaling or downregulating MHC-I presentation [96]. NK-cell-based strategies for PDAC include receptor-mediated activation and *ex vivo* expansion of NK cells, chimeric antigen receptor engineering (CAR-NK), adoptive immunotherapy using donor-transformed NK cells, and increasing antibody-dependent cellular cytotoxicity (ADCC) [97].

NK cell checkpoint inhibitors Similar to ICBs, mAbs have been developed to target inhibitory receptors on the surface of NK cells such as the killer-cell Ig-like receptors (KIRs) and Natural Killer Group 2A receptors (NKG2A). Lirilumab (IPH2102/BMS-986015), which targets several inhibitory KIRs, unfortunately has yet to demonstrate a definite improvement in survival outcomes in human trials [98]. IPH2201, a first-in-class mAb targeting NKG2a was shown to be well-tolerated with durvalumab (aPDL-1) in advanced solid tumors (NCT02671435) and demonstrated encouraging preliminary outcomes when add to first-line SOC therapy (mFOLFOX6 + bevacizumab) in pMMR mCRC patients [99].

CAR-NK cell therapy While T cells equipped with chimeric antigen receptors (CAR) have proven highly beneficial in B cell lymphoma and ALL, the required time and difficulty in generating a therapeutic dose of autologous CAR-T cells combined with lack of surface targets in PDAC limits CAR-T cell therapeutic utility. Here, allogenic CAR-NK cells may be a more effective, and more readily available alternative. A novel combinatorial immunotherapy protocol of (1) reduced-dose, metronomic chemotherapy, (2) SBRT, (3) avelumab (anti-PD-L1), (4) N803 (IgG1 Fc-engineeredIL-15-fusion protein), and (5) off-the-shelf, allogeneic (PDL1-targeted), high-affinity NK cell infusion (haNK) resulted in the first reported complete response (CR) to an NK-based immunotherapy combination in advanced PDAC [100]. QUILT-88 (NCT04390399), an ongoing phase 2, randomized, three-cohort study (2 randomized, 1 single-arm) is evaluating PD-L1-targeted haNK cells as part of multimodal treatment regimen combining IO (IL-15 agonist [N-803] and PDL1 t-haNK), SBRT, and SOC chemo in PDAC. Cohort A will test

above experimental combinatorial regimen against gem-NP in the first-line maintenance setting, cohort B will randomize patients to either the experimental regimen or SOC 5-FU + liposomal irinotecan in the second-line setting, and cohort C will be a single arm examining the study therapy in the 3rd-line or later setting (total goal accrual of 250 patients across all cohorts and arms) [101]. Finally, CAR-NK-cell tumor infiltration could be further optimized with an NK cell-recruiting protein-conjugated antibody (NRP-body) that has been shown to enhance tumor-infiltration of *ex vivo* expanded NK cells (via CXCL16 gradient) and increase survival in mouse models of PDAC [97].

3.3 [IO barrier] paucity of mature dendritic cells

A recent study by Hedge and colleagues (2020) demonstrated that a strongly matched pair of an immunogenic neoantigen-MHC complex and CD8+ TCR was not enough to mount an anti-tumor response without functioning conventional dendritic cells (cDC) required for antigen presentation and T-cell priming. In mice bearing PDAC, the rare DCs present in the TME were observed to be phenotypically immature and dysfunctional both in terms of both antigen sampling and trafficking to draining lymph nodes [102]. DC dysfunction is mediated, in part, by dysregulating cytokines (e.g., IL-10, TGFβ) secreted directly by the tumor or tumor-recruited immune subsets [103] .

3.3.1 [IO strategy] optimize dendritic cell recruitment and maturation

CD40 agonism In addition to blockade of negative immune checkpoints (e.g., CTLA-4, PD1-PDL1 axis), immune agonism (e.g., co-stimulatory mAbs targeting CD27, CD137, and CD40) is an area of growing clinical inquiry. Anti-CD40 agonism, to date, has garnered the most translational experience in PDAC. Preclinically, CD40 activation on DCs and monocytes upregulates the expression of other costimulatory molecules (e.g., CD80 and CD86), enhances antigen presentation, licenses DCs, and activates effector T cells [104–107]. The CD40 agonistic monoclonal antibody, APX005M, and SOC chemotherapy (Gem-NP) with or without nivolumab (aPD-1) were recently examined in the first-line setting for advanced PDAC (NCT03214250). Fourteen of the 24 patients enrolled in the initial study phase showed a partial response (58%), and 8 (33%) had stable disease. Compared to a historical mOS for 8.5 - 12.1 months for Gem-NP [5, 108], mOS for the total study cohort was an impressive 20.1 months (12·7 months for cohort B1[0·1 mg/kg APX005M], 20·1 months for cohort B2 [0·3 mg/kg APX005M], 15·9 months for cohort C1 [0·1 mg/kg APX005M + aPD-1], and not evaluable for cohort C2 [0·3 mg/kg APX005M dose + aPD-1]) [109]. In a follow-up phase II study, presented at ASCO 2021, the primary endpoint of 1-year OS > 35% (historical OS rate for Gem-NP) was met when combining chemo with either aPD-1 (1-year OS 57%, mOS 16.7 mo, mPFS 4.8 mo) or APX005M (1-year OS 51%, mOS 14.5 mo, mPFS 5.5 mo); however, it is not with the combination of aCD40 + aPD-1 [1-year OS 41%, mOS 10.7 mo, mPFS 6.7 mo] [110]. Detailed multi-omic immune and tumor biomarker analyses are underway to identify patient subsets that benefit most from these combinations [110]. While these results do temper expectations, aCD40 agonism, along with other immune co-stimulants, are still likely to play a key role in a future effective IO-based regimen(s) for PDAC.

Recombinant FLT3L Recombinant FLT3L has been shown to increase the number of DC precursors and DCs in blood and tissue *in vivo* [111], while CD40 agonism can promote DC maturation [112]. Interim results from a phase I study (NCT03329950) shows that the combination of CDX-1140 (aCD40 mAb agonist) with CDX-301 (recombinant FLT3L) is well-tolerated and in patients with treatment-refractory solid tumors. Additionally, pretreatment of patients with recombinant FLT3L greatly increases the number of circulating and aCD40-responsive DCs [113].

IL-10 modulation The anti-tumor and systemic immune effects of IL-10 signaling, as is the case with other direct interleukin modulatory treatments, remain complex and, at times, even contradictory. For example, IL-10 agonism and antagonism have been observed to enhance anti-tumor outcomes, preclinically [114, 115]. Despite promising early phase results, IL-10 agonist, pegilodecakin, failed to enhance response to FOLFOX in the 2nd line for mPDAC [116] and led to increased toxicity without enhancing survival when paired with aPD-1 therapy in NSCLC [117]. Human trials with IL-10 inhibition are limited. A phase 1 study (NCT02731742) examining the combination of an IL-10 inhibitor (MK-1966) with a TLR9 agonist (SD-101) was recently halted due to lack of efficacy [118]. More investigation is required to examine context-dependent IL-10 signaling, specifically the effects of blockade on peripheral and tumor-infiltrating T cell activation and expansion [119].

4 Impaired anti-tumor immune cell trafficking to tumor bed

Once primed, activated T cells, primarily the effector subtypes, should traffic to the tumor site via chemotaxis, crossing vasculature, while being maintained by pro-survival growth

factors signaling [120]. However, upon examination of the PDAC TME, we instead observe an "immune desert" with only a small and impotent T cell infiltrate.

4.1 [IO barrier] desmoplastic stroma and dysregulated T cell recruitment

A major factor contributing to this immune exclusion is the dense stromal compartment of PDAC. This a collagenous, desmoplastic hypo-vascular matrix, produced by cancer-induced pancreatic stellate cells and accounts for the vast majority of tumor cellularity [121]. The resultant desmoplasia is known to be responsible for creating a mechanical barrier around the tumor cells, preventing appropriate vascularization and thus limiting exposure to chemotherapy and leading to poor immune cell infiltration. In addition to a physical boundary, PDAC sets up a chemical barrier via disrupted chemokine expression to deregulate signaling involved in effector T-cell recruitment resulting in significantly reduced $CD8^+$T-cell infiltrate. Intratumoral TGFβ signaling via cancer-associated fibroblasts (CAF) appears critical in counteracting anti-tumor immunity via restricting movement of CTLs in the TME. TGFβ signaling also mediates recruitment of immune suppressive cells (e.g., regulatory T cell [Tregs] and myeloid-derived suppressor cell [MDSC]) via downstream signaling targets (e.g., VEGF) further establishing an unfavorable environment for Teff-infiltration [121, 122].

4.1.1 [IO strategy] disrupting the extracellular matrix (ECM)

Non-specific targeting of the ECM with matrix metalloproteinases (MMP) inhibitors such as marimastat and tanomastat failed to demonstrate significant clinical activity in patients with advanced-stage pancreatic cancer [123, 124]. A more specific approach to weakening ECM-scaffolding is targeting hyaluronan (HA), a major component of the PDAC ECM with high levels associated with poor prognosis [125]. In preclinical models, decreasing the hydrostatic pressure in the dense PDAC stroma with PEGPH20, a pegylated hyaluronidase (HA), was shown to increase vascular permeability and increase drug delivery when used in combination with chemotherapy [126] Paradoxically, a phase 1b/II trial of adding PEGPH20 to mFOLFIRINOX resulted in significantly inferior OS, PFS, and ORR with compared to chemotherapy alone [127]. In contrast, PEGPH20 appeared to add a PFS benefit to Gem-NP [128]. However, in a follow-up phase III trial (HALO 109-301), PEGPH20 in combination with chemotherapy failed to improve PFS or OS in metastatic PDAC patients, even among those with HA-high tumor expression [129]. Since it has been observed that PEGPH20 enhances GVAX-induced $CD4^+$ and $CD8^+$T-cell TME infiltration in a preclinical PDAC model [130], it is worth considering whether adding an immunomodulator/ICB to the studied regimen would have led to a change in outcome [131]. Along these lines, the combination of atezolizumab with PEGPH20 is currently being tested in pre-treated advanced PDAC population (NCT03214250).

4.2 [IO strategy] eliminating cancer-associated fibroblasts

Fibroblast activation protein (FAP) found ~90% CAFs and higher levels of tumor expression are associated with poor clinical outcomes in PDAC. Despite preclinical models showing anti-tumor effects of FAP-targeting/ablative strategies [132–134], a FAP antagonist mAb (sibrotuzumab) and small molecule inhibitors (talabostat) have not been able to translate this meaningful benefit to the clinical trial setting [135, 136]. Recently, there has been a growing appreciation for the heterogeneity and plasticity of CAFs and their associated pro- and anti-tumorigenic functioning [136]. This phenotypic complexity may underly the preclinical observations that show depletion of CAFs paradoxically accelerates tumor progression [137, 138]. The next generation of therapies targeting stromal resistance mechanisms in PDAC must account for the functional heterogeneity of CAFs.

4.2.1 [IO strategy] reprogramming cancer-associated fibroblasts

Instead of simply eliminating the stromal fibroblasts from the TME, a more sophisticated approach might be to disrupt crosstalk between tumor-stroma-immune compartments. An example of this is blocking CAF-mediated pro-tolerogenic signaling (e.g., CXCL12/CXCR4) or disrupting CAF–cancer cell immunosuppressive communication loops through blockade of TGFβ and IL-1β.

Targeting CXCL12/CXCR4 chemokine axis CXCL12, produced by CAFs, misdirects effector T cells to the extratumoral stroma, preventing them from entering the tumor [139]. Pre-clinically, disrupting the binding of CXCL12 with its receptor CXCR4 improves the anti-tumor activity of ICB and the combination has been shown to reactivate endogenous TILs in PDAC models [140, 141]. On the basis of this, AMD3100, a small molecule inhibitor of CXCR4, is now being studied in patients with metastatic pancreatic cancer in combination with cemiplimab (aPD-1) in metastatic PDAC (NCT04177810). BL-8040, another CXCR4 antagonist, is being examined in combination with pembrolizumab and chemotherapy for 2nd- or 3rd-line treatment for metastatic PDAC. Preliminary outcomes from the expansion cohort of the COMBAT trial (NCT02826486) showed that the BL-8040 and pembrolizumab added to the NAPOLI-1 regimen (liposomal irinotecan, fluorouracil, and leucovorin) resulted in an encouraging ORR of 32% and a DCR of 77% in PDAC patients

following 1st-line Gem-based treatment [142]. These results compared favorably with the NAPOLI-1's ORR of 17% and DCR of 52% [143] suggesting BL-8040 and pembrolizumab may expand the benefit of chemotherapy in PDAC [142, 143].

TGFβ inhibition Transforming growth factor beta (TGFβ), released by PDAC tumor cells, stromal fibroblasts, and other cell types in the TME, contributes to the tolerogenic architecture of the TME and suppresses the cytotoxic activities of anti-tumor immune cells [144]. T-cells with constitutively active TGFβ signals remain refractory to full activation [145]. Serum TGFβ have correlated with poor prognosis in pancreatic cancer [146]. Several preclinical models have demonstrated therapeutic synergy of TGFβ signaling inhibition and immunomodulatory agents [147–149]. The combination of gemcitabine and galunisertib, a small molecule inhibitor of TGFβ, enhanced OS compared to chemo alone in first-line treatment in patients with mPDAC (mOS 8.9 and 7.1 months for galunisertib and placebo, respectively [HR = 0.79, 95% CI: 0.59–1.09, posterior probability HR < 1 = 0.93]) [150]. Galunisertib with durvalumab (aPD-L1) was shown to be well-tolerated but had limited in clinical efficacy when used the 3rd or later line for patients with mPDAC [151]. More recently, a bifunctional checkpoint inhibitor comprised of an aPD-L1 mAb fused with a TGFβ ligand trap (M7824, Bintrafusp Alpha) was tested in the phase I setting in a cohort treatment-refractory advanced solid tumor patients. Of the 5 PDAC patients included, there was 1 PR but this patient also had dMMR disease [152]. Expectations for the dual-targeting fusion protein have been further tempered since M7824 fell short of its primary endpoint for second-line treatment in advanced biliary tract cancers (BTC) [153]. However, there are pending results of an ongoing phase II/III trial of M7824 combined with chemo in the 1st line for advanced BTC (NCT04066491), and a similar approach may warrant consideration in PDAC.

IL-1β antagonism High stromal IL-1β expression is associated with poor overall survival of PDAC patients [154]. CAFs are reprogrammed by tumor-derived IL-1β to produce cytokines and chemokines that subvert anti-tumor immunity and further promote cancer growth [154, 155]. Preclinically, the addition of anti-IL-1β antibody significantly enhanced the anti-tumor activity of aPD-1 mAb in the variety of tumor models, including PDAC, and resulted in increased tumor infiltration of CD8+ T cells [155]. In human experience, combination of pembrolizumab and the aIL-1β antagonist, canakinumab, has demonstrated safety in metastatic solid tumor patients [156]. A phase III study (NCT03631199) evaluating the additive impact of canakinumab to SOC first-line immunotherapy and chemotherapy in NSCLC is expected to report final results before the end of the year. A phase II trial of examining dual IL-1β and PD1 blockade in patients' resectable PDAC is in development.

FAK inhibition Another stromal target is focal adhesion kinase-1 (FAK1), a tyrosine kinase expressed on both tumor and stromal cells that has been implicated in driving stromal desmoplasia. Pre-clinically, FAK inhibition decreased tumor cell proliferation, reduced tumor-associated macrophages and CAFs, increased CD8+ T cell infiltration, and sensitized tumors to RT. [157, 158] A phase I trial of defactinib, an oral FAK1 TKI, in combination pembrolizumab and gemcitabine (NCT02546531) showed modest but encouraging efficacy signals in both maintenance and treatment refractory mPDAC settings [159]. Correlative studies with paired biopsies in PDAC patients show increased proliferating CD8+ T cells, while Tregs, macrophages, and stromal density decreased with treatment [159]. FAK inhibition's limited clinical efficacy may be in part related to a resistance mechanism via STAT3 upregulation triggered by FAK-induced stromal depletion, arguing for a combinational approach with direct/indirect STAT3 inhibitors [160, 161].

5 [IO barrier] immunosuppressive cellular TME

Even with sufficient effector T-cell priming, infiltration through the desmoplastic ECM, anti-tumor immune cells are still left to deal with local immunosuppressive cell populations that further dampen and exhaust effector functions. The PDAC TME is populated by multiple types of immunosuppressive cells, including regulatory T (T_{reg}) cells, myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and tumor-associate-neutrophils(TANs) [162].

Tumor-associated macrophages Tumor-associated macrophages (TAMs) are one of the most abundant immune cell populations in the pancreatic tumor stroma due in part to recruitment by oncogenic KRAS [163]. Either via direct tumor-signaling or via tumor-CAF crosstalk, TAMs are generally polarized to the immunosuppressive phenotype (M2) defined by Csf1R, CD206, and IL-10 expression along with reduced expression of MHC class II and Ly6C [155, 164]. These M2 TAMs support tumorigenesis, immune escape (e.g., promoting Th2 cell differentiation), metastasis, and chemotherapeutic resistance [165].

Myeloid-derived suppressor cells Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells that accumulate in the TME, reducing anti-tumor T cell activity and promoting tumor immune escape. These cells can be divided into two general groups termed granulocytic (G-MDSCs) and monocytic (M-MDSCs), phenotypically and morphologically similar to neutrophils and monocytes, respectively. MDSCs suppress effector TILs by

depleting metabolites critical for T cell function (via upregulation of arginases and IDO-mediated sequestration of cysteine), blocking T cell homing (via nitric oxide-mediated downregulation L-selectin expression in T cells), induction of other immunosuppressive cells (e.g., FoxP3+ T reg and M2 TAMs), and upregulating expression of PDL1 to induce T cell anergy [166].

Tumor-associated neutrophils More recently, tumor-associated neutrophils (TANs) have become increasingly recognized for their ability to promote tumor progression, mediate resistance to therapy, regulate immunosuppression, and correlate with poor prognosis numerous cancers in a variety of cancers including PDAC [167–169]. TAN-recruitment to the TME appears to be mediated via the chemokine CXCR2.

5.1 [IO strategy] reprogramming TME myeloid cells

5.1.1 CD40 agonism

As discussed earlier, CD40 is a key mediator of adaptive immune response. Additionally, it may also help reprogram the TME reprograming via effects on myeloid cell populations. Specifically, CD40 agonism potentiates the immunogenic profile of DCs, converts TAMs from a tumor permissive (M2) to a tumoricidal phenotype (M1), and may help reverse stromal desmoplasia [103, 170]. A summary of the current clinical trial data with CD40 agonism can found in Section 3.3.1.

5.1.2 CD11b modulation

CD11b is almost universally expressed on myeloid cells in PDAC and is an important mediator of myeloid cell migration and functional phenotype. Panni and colleagues developed a small molecule, allosteric agonist of CD11b (ADH-503) that resulted in a partially active CD11b that suppressed myeloid cell infiltration by increasing adhesion to the endothelium, repolarized TAMs to M1 phenotypes, and lead to tumor regression and long-term immune memory when combined with ICB [171, 172]. These preclinical findings are the basis for an early phase clinical trial (NCT04060342) examining safety and tolerance of GB1275, a first-in-class CD11b modulator, alone and in combination with pembrolizumab. Preliminary results from the trial suggest the combination is well-tolerated but responses in PDAC patients included were limited [173].

5.1.3 BTK inhibition

Activation of Bruton's tyrosine kinase (BTK), mediated by PI3Kδ protein kinase, has been linked to M2 macrophages polarization. Blockade of the signaling pathway using BTK inhibitors has resulted in decreased tumor growth, reduced M2-TAMs and B reg TME populations, and increased CD8+ TILs in preclinical models of PDAC [174, 175]. .On the basis of these findings, the BTK inhibitor, acalabrutinib, was studied in a phase II trial as monotherapy and in conjunction pembrolizumab in pretreated advanced PDAC patients (NCT02362048). Though acalabrutinib treatment was associated with reduced circulating MDSCs and the combination induced activation of CD4 and CD8 memory T cells detected in peripheral blood, BTKi plus aPD-1 did not improve PFS/OS [176]. Due to limited on-treatment tumor biopsies, it was not possible to assess treatment-related TME changes [176].

5.1.4 CSF1/CSF-1R inhibition

The colony stimulating factor 1 and colony stimulating factor 1 receptor (CSF-1/CSF-1R) pathway is crucial for the differentiation and survival of pro-tolerogenic M2 macrophages and represents a potential target of reprogramming TAMs from M2 to M1 type [177]. Preclinically, blockade of CSF-1/CSF-1R pathway has shown promising results in repolarizing TAM towards M1 type and induced distinct TME remodeling [178–180]. Although early studies showed potential synergy of cabiralizumab, a humanized IgG4 CSF-1R mAb, with PD1 blockade, the combination when added to SOC chemotherapy-backbone did not improve PFS compared to SOC chemotherapy alone in advanced pretreated PDAC [181]. A small molecule inhibitor of CSF1R, pexidartinib, is being examined in combination with durvalumab in patients with metastatic PDAC or CRC (NCT02777710). Preliminary results from the study showed an ORR of 0% and DCR of 21% with 4 patients achieving SD, two of which happened to be dMMR CRC patients [182].

5.1.5 CCL2/CCR2 inhibition

In mouse models of PDAC, small molecule inhibitors of CCR2 decreased TAM infiltration, increased TIL CD8+Teff to CD4+Treg ratios, and enhanced response to ICB [183, 184]. This led to phase I study of PF-04136309, an oral inhibitor of CCR2, in combination with Gem-NP in patients with mPDAC (NCT02732938). The trial concluded that PF-04136309 was associated with worse pulmonary toxicities and added no clinical benefit compared to gemcitabine and nab-paclitaxel alone [185].

5.1.6 CXCR2 inhibition

Preclinically, inhibiting CXCR2 decreases TAN infiltration, abrogates PDAC metastasis, augments T cell

infiltration and synergizes with aPD-1 and chemotherapy to extend survival [186, 187]. A phase Ib/II clinical trial (NCT02583477) investigating AZD5069, an oral small molecule inhibitor of CXCR2, in combination with aPD-L1, durvalumab, demonstrated limited efficacy in advanced PDAC patients with 8 (40%) of patients experiencing serious adverse events causally related to treatment (3 [15% of patients] requiring study discontinuation, but no reported deaths related to therapy) [188, 189].

5.1.7 Epigenetic therapy

Epigenetic changes are an integral part of PDAC's development, progression, intratumoral heterogeneity, TME makeup, immune escape, and chemoresistance [190]. Revising dynamic epigenetic changes with DNA methyltransferases (DNMT) or histone deacetylases (HDAC) inhibitors may augment immunotherapy [191] by preventing/reversing immune exhaustion [192], increasing tumor antigens and MHC 1 expression [193], and reprogramming local stromal and immune cells to create a more immune permissive TME [194, 195]. Recently, epigenetic regulation of the biologic behavior of MDSCs has emerged as a promising tool in PDAC therapy. In a murine model of PDAC, use of the HDACi, entinostat, changed the polarity of immunosuppressive MDSCs to a nonfunctional phenotype. Additionally, the combination of HDACi plus aPD-1 significantly improved survival as compared with mice treated with either agent [194]. On the basis of these findings, entinostat and nivolumab are under current clinical trial investigation (NCT03250273) for use in pre-treated advanced PDAC patients with preliminary outcomes expected to be reported soon.

5.2 [IO strategy] additional TME-targeted approaches

5.2.1 Reducing T regulatory cells

$CD4^+CD25^+FOXP3^+$ T_{regs}, in the context of PDAC, can limit anti-tumor immune responses and are associated with poor prognosis [196]. However, depletion of Tregs in a preclinical PDAC model failed to relieve immunosuppression and paradoxically led to accelerated tumor progression. Clinically, targeting CCR4, highly expressed on Tregs with Mogamulizumab, reduced intratumoral Tregs, but did not enhance responses to ICB [197].

5.2.2 MEK inhibition

MEK inhibitors have shown immunomodulatory effects and efficacy when combined with PD-(L)1 inhibitors in multiple preclinical models via a variety mechanisms including enhanced MHC I/II expression, increased CD8+ TIL infiltration and survival, and reduced recruitment of mMDSCs, M2 TAMs, and B regs [198, 199, 200. 201, 202, 203, 204, 205]. Unfortunately, the combination of a MEK inhibitor (cobimetinib) plus a aPD-L1 inhibitor (atezolizumab) failed to show compelling immune activity in a large phase III clinical trial in colon cancer [206]. However, a phase II trial of this same combination demonstrated a beneficial PFS therapeutic signal in advanced pretreated BTC patients [207]. One possible explanation for the discrepancy between preclinical and clinical outcomes is that systemic MEK inhibition may impair T cell priming and activation [198]. Dovetailing off of this, multiple pre-clinical models, including PDAC and mKRAS cell lines, have demonstrated synergy between MEKi and immune agonists [199–209]. A clinical trial combining MEKi, ICB, and an aCD27 immune agonism is in development for advanced BTC patients (NCT04941287), and could also represent a future immunotherapeutic strategy in PDAC should it prove successful.

5.2.3 Targeting B-cells

While contemporary IO is firmly grounded in optimizing cellular immunity, mainly T cell function, the antitumor potential of humoral immunity and B cell modulation is a relatively new area of exploration. In addition to producing antibodies and secreting cytokines, B cells are able to recognize antigens, regulate antigen processing and presentation, and modulate cellular immune response [210]. The latter has been shown clinically in treatment of autoimmune processes. For example, in multiple sclerosis and rheumatoid arthritis, conditions characterized by pathogenic T-cell function, selective B-cell depletion with aCD20 antagonizing mAbs improves symptoms, lowers disease activity, and increases time between disease flares [211, 212]. As with other cellular counterparts, B cell pro- and anti-tumorigenic functions are context-dependent and influenced by the TME milieu. The use of CD20-targeted B cell therapy in patients with advanced solid tumors patients has shown mixed-to-no clinical benefit [213, 214]. Several strategies to antagonize immunosuppressive B-regs have shown promise in the preclinical setting but their clinical utility has yet to be established [215]. Therapies activating of B cells are also under investigation. Beyond optimizing DC function, IL-10 inhibition and CD40 agonism may sustain anti-tumor B cells in the TME as well as promote B-cell-mediatedT-cell activation and memory formation [216, 217]. Additionally, B cell–activating factor (BAFF, BLyS), a B cell–activating cytokine, has been shown to activate B cells expressing high levels of costimulatory molecules (CD40, ICOSL), augment antigen presentation to $CD4^+$ T cells through increased expression of MHC-II, and increases IL-12

Table 1 Selected Clinical Trials Examining Novel Immunotherapy Regimens in Patients with Pancreatic Ductal Adenocarcinoma

Study NCT registry number	Study agent(s)	Standard agent(s)	Subjects	Treatment setting	Phase	Status/results
Multimodal IO regimens						
NCT03329248 NCT03586869	Metronomic chemo (aldoxorubicin, gem, NP, oxal, 5FU, and cy) haNK aPD-L1 PD-L1 t-haNK	SBRT	mPDAC	Metastatic ≤2nd line	Ib/II	Closed mOS 8.0 mo mPFS 6.6 mo 1 CR (treated with PD-L1 t-haNK)
NCT04390399	Aldoxorubicin N-803 (IL-15) PD-L1 t-haNK	Chemo (gem+NP [1st line] or NAPOLI-1 [2nd line]) SBRT	mPDAC	Metastatic Maintenance (group A) 2nd line (group B) ≤3rd line (group C)	II	Open
NCT03767582	CCR2/CCR5i aPD-1 ± GVAX	Chemo SBRT	LA-PDAC	Neoadjuvant & adjuvant	II	Open
NCT03153410	GVAX aPD1 CSF1Ri	Chemo (neoadj) SBRT (neoadj)	BR-PDAC	Neoadjuvant & adjuvant	Pilot	Open
NCT03006302	CRS-207 IDOi aPD-1 ± GVAX		mPDAC	Metastatic ≤2nd line	II	Open
Anti-tumor vaccines						
NCT04853017	Peptide vaccine (shared neoantigen [KRAS], adj AMP-CpG)		rPDAC [KRAS/NRAS mut]	NED maintenance	I/II	Open
NCT03948763	mRNA vaccine (shared neoantigen [KRAS], lipid-based) ± aPD-1		mPDAC [mKRAS]	Not specified	I	Open
NCT04799431	Peptide vaccine (personalized neoantigen, adj pICLC) aPD-1		mPDAC	Maintenance	Pilot/I	Not yet open
NCT02600949	Peptide vaccine (personalized neoantigen, adj imiquimod)		mPDAC	Maintenance ≤2nd line	Pilot	Open
NCT03468244	mRNA vaccine (personalized neoantigen)		Advanced PDAC	≤2nd line	Pilot	Open
NCT03592888	Autologous DC vaccine, (shared KRAS neoantigens)		rPDAC [mKRAS]	Adjuvant	I	Open
NCT04627246	Autologous DC vaccine, (personalized neoantigen) aPD-1	Chemo	rPDAC	Adjuvant	I	Open
NCT04157127	Autologous DC Vaccine* (personalized tumor lysate, adj peg-IFN) *perinodal injection	Chemo	rPDAC	Adjuvant	I	Open
NCT04111172	TAA-encoding viral vaccine (shared, adj *il-PADRE [TH1 epitope])*	Chemo	rPDAC	Adjuvant	II	Open
NCT03806309		± FOLFIRI	LA or mPDAC	Maintenance	II	Open

Table 1 (continued)

Study NCT registry number	Study agent(s)	Standard agent(s)	Subjects	Treatment setting	Phase	Status/results
	Peptide vaccine (shared TAA/TSA, adj *il-PADRE [TH1 epitope*) ± aPD-1					
NCT03376659	TAA-encoding viral vaccine (shared, adj TRICOM) + aPD-L1	Maintenance chemo	mPDAC Maintenance	Maintenance	II	Enrolled Prelim results expected soon
NCT03161379	GVAX aPD1	Chemo SBRT	BR-PDAC	Neoadjuvant	II	Open
NCT03190265	CRS-207 aPD-1 aCTLA4 ± GVAX	Chemo SBRT	mPDAC	≤2nd line	II	Open
NCT02451982	GVAX a4-1BB aPD-1	Chemo SBRT	rPDAC	Neoadjuvant & adjuvant	II	Open Prelim results expected soon
Immune agonists and adjuvants						
NCT04807972	aCD40 agonist ± aPD-1	Chemo	mPDAC	1st line	II	Open
NCT03329950	aCD40 agonist ± aPD-1 ± FLT3L	±Chemo	mPDAC	1st line (aCD40 + chemo arm) Refectory (other groups)	I/II	Open
NCT03214250	aCD40 agonist ± aPD-1	Chemo	mPDAC	1st line	II	[Prelim] No improvement in PFS/OS/ORR when aCD40 added to SOC chemo + PD-1
NCT03193190	aCD40 agonist aPD-L1	Chemo	mPDAC	2nd line	I/II	Open
NCT02376699	aCD40 agonist aPD-1	Chemo	mPDAC	1st line	II	Enrolled Prelim results expected soon
NCT04387071	aOX40 agonist + TLR9 adjuvant (intratumoral)		LA or mPDAC	2nd line	II	Not yet open
NCT04612530	Electroporation CpG adj aPD-1		mPDAC (hepatic mets)	Maintenance	I	Open
NCT04050085	TLR9 agonist (intratumoral) aPD-1	SBRT	mPDAC	Refractory	I	Open
NCT03983954	Superantigen fAb aPD-L1		mPDAC	Refractory	I	Open
NCT03225989	TMZ-CD40L and 4-1BBL- encoded Virus	Chemo	LA or mPDAC	≥1st line	I/II	Open
TME cellular/signaling modulators						
NCT04390763	TGFβ antagonist ± aPD-1	Chemo	mPDAC	1st line	II	Open
NCT03821935	GARP-TGFβ1 antagonist		LA or mPDAC	Refractory	I	Open

Table 1 (continued)

Study NCT registry number	Study agent(s)	Standard agent(s)	Subjects	Treatment setting	Phase	Status/results
	± aPD-1					
NCT04581343	aIL-1β antagonist aPD-1	Chemo	mPDAC	1st line	I	Open
NCT04543071	CXCR4i aPD-1	aPD1 Chemo	mPDAC	1st line	II	Open
NCT02826486	CXCR4i aPD-1	± Chemo	mPDAC	≥2nd line	I/II	Enrolled [Prelim] DCR 77%, ORR 32% w/chemo DCR 34%, ORR 3% w/o chemo
NCT03193190	CXCR4i aPD-L1		mPDAC	≥2nd line	II	
NCT04477343	CXCR1|2i aPD-1		mPDAC	Maintenance	I	Open
NCT03257761	Epigenetic modifier (DNMTi) aPD-L1		mPDAC	≥2nd line	Ib	Open
NCT03250273	Epigenetic modifier (HDACi) aPD-1		mPDAC	≥2nd line	II	Enrolled Interim results expected soon
NCT04060342	CD11b modulator ± aPD-1	± Chemo	mPDAC	1st line (for chemo combo)	I/II	Open
NCT03193190	aIL-6 antagonist aPD-L1	Chemo	mPDAC	1st line	II	Open
NCT03727880	FAKi aPD-L1	Chemo	rPDAC	Neoadjuvant & adjuvant	II	Open
NCT03496662	CCR2/CCR5i aPD-1	Chemo	BR or LA-PDAC	Neoadjuvant 1st line	I/II	Open

Key (selected terms): *adj*, vaccine/immune adjuvant; *AMP-CpG*, amphiphilic-CpG (pathogen-associated molecular pattern); *BR-PDAC*, borderline resectable pancreatic ductal adenocarcinoma; *CRS-207*, live, attenuated double-deleted*Listeria* vaccine targeting mesothelin; *CSF-1R*, colony-stimulating factor-1 receptor; *Cy*, cyclophosphamide; *DC*, dendritic cell; *DCR*, disease control rate; *DNMTi*, DNA methyltransferase inhibitor; *FAKi*, focal adhesion kinase inhibitor; *Gem*, gemcitabine; *GVAX*, GM-CSF secreting allogeneic pancreatic tumor cell vaccine; *haNK*, high affinity natural killer cells; *HDACi*, histone deacetylase inhibitor; *IDOi*, indolamine 2,3-dioxygenase inhibitor; *IO*, immunotherapy, immuno-oncology;*LA-PDAC*, locally advanced pancreatic ductal adenocarcinoma; *mPDAC*, metastatic pancreatic ductal adenocarcinoma; *NAPOLI-1*, 5FU and leucovorin plus liposomal irinotecan; *NP*, nab-paclitaxel;*ORR*, objective responsive rate; *OS*, overall survival; *Oxal*, oxaliplatin; *PD-L1 t-haNK*, PD-L1 targeted high affinity natural killer cells; *PFS*, progression-free survival; *pICLC*, polyinosinic-polycytidylic acid; *rPDAC*, resected pancreatic ductal adenocarcinoma; *SOC*, standard of care; *TAA*, tumor-associated antigen; *TLR*, toll-like receptor; *TME*, tumor microenvironment; *TSA*, tumor-specific antigen or neoantigen

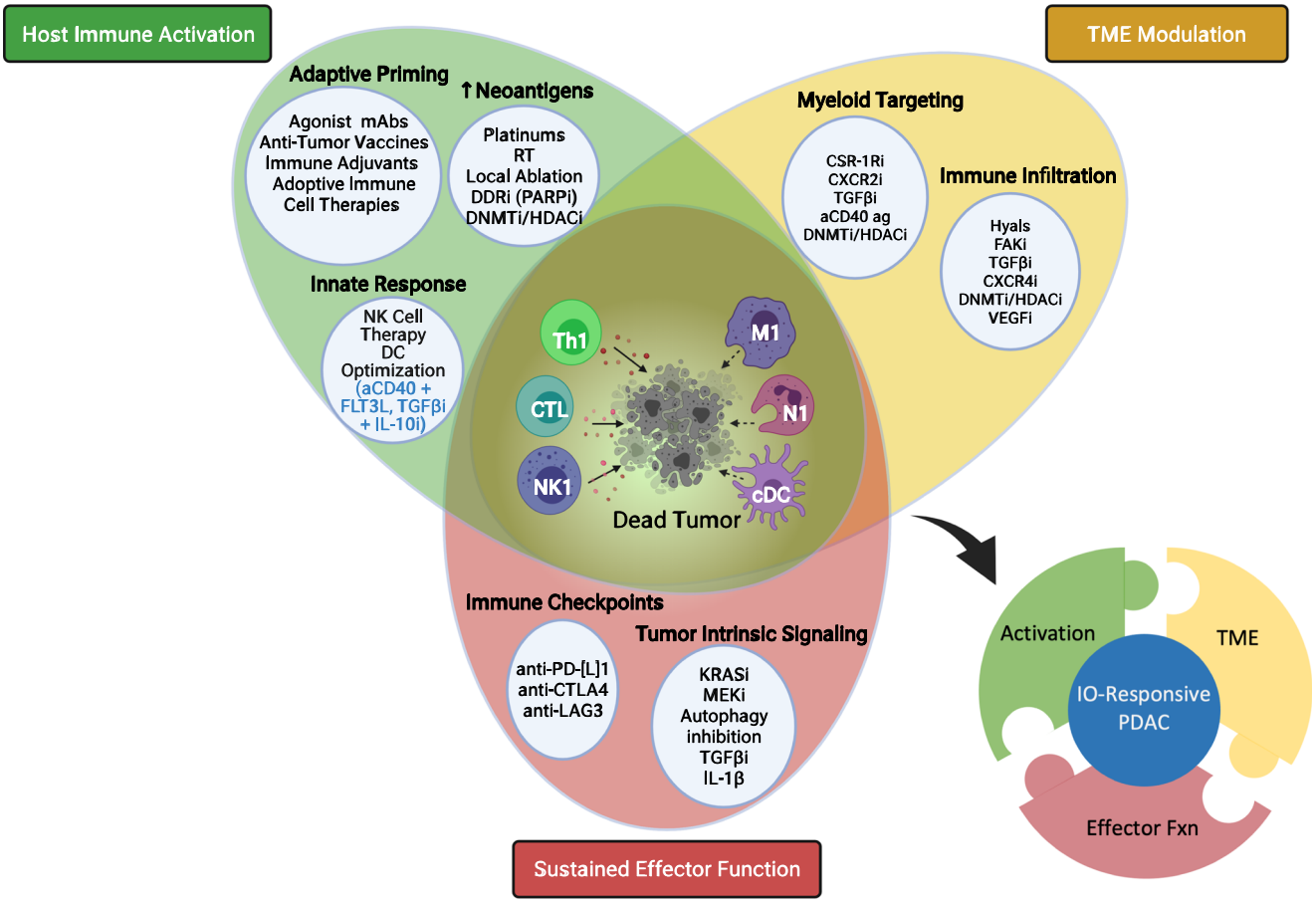

Fig. 3 A Framework for Successful IO-based Treatment in PDAC To block immune escape, next generation IO-based approaches for PDAC must be built on targeting immune priming/activation pathways simultaneously with modulating local TME immunosuppression and blocking immune checkpoints blockade for effective sustained anti-tumor immune trafficking and sustained cytotoxic response. This will require several IO and targeted agents on top of conventional therapies. Standard chemotherapy with combinatorial cocktail of an anti-tumor vaccine, co-stimulatory agent (aCD40), TME crosstalk modulator (CXC4Ri or TGFb trap), and ICB (aPD-1) is one such potential combination. Key (selected terms): [cDC] conventional dendritic cell; [CSF-1Ri] colony-stimulating factor-1 receptor inhibitor; [CTL] cytotoxic T lymphocyte; [CTLA-4] cytotoxic T lymphocyte antigen 4; [DDRi] DNA damage repair inhibitor; [DNMTi] DNA methyltransferase inhibitor; [FAKi] focal adhesion kinase inhibitor; [FLT3L] Fms-related receptor tyrosine kinase 3; [HDACi] histone deacetylase inhibitor; [Hyals] hyalanurinases; [LAG3] lymphocyte activating 3; [M1] tumor associated macrophage, type I phenotype; [mAbs] monoclonal antibodies; [N1] Neutrophil, type 1 phenotype; [NK] – natural killer; [NK1] natural killer cell, type 1 phenotype; [PARPi] Poly (ADP-ribose) polymerase inhibitor; [PD-L1] – programmed death-ligand 1; [RT] radiation therapy; [TGFb] transforming growth factor beta; [Th1] T helper cell, type 1 phenotype; [VEGFi] Vascular endothelial growth factor inhibitor. Created with BioRender.com

expression to promote the differentiation of Th1 cells and T memory cells [218]. BAFF/BLyS was safely tolerated in a clinical trial for treatment of IgA deficiency (NCT00024934) may be valuable adjuvant for CD40 targeted and/orvaccine-based regimens [218, 219].

6 Conclusions and perspectives

Pancreatic adenocarcinoma has multiple layers of immune-resistance to overcome, but it is not an immune-refractory tumor [56]. A growing understanding of its resistance mechanisms and intricate tumor microenvironment dynamics are revealing novel IO therapeutic targets and combinatorial approaches (see Table 1 for a selection ongoing clinical trials examining novel IO-based regimens). Specifically, immune agonists, such as aCD40 agonism, and anti-tumor vaccines represent promising strategies to stimulate host immune response via activation and expansion of anti-tumor effector cells. With the advancement of high-throughput multi-omics technologies accurately characterizing tumor-specific antigens and their respective immunogenicity, neoantigen-targeting strategies may enhance the effectiveness of current systemic immunotherapies, minimize off-target toxicities, and lead to formation of long-term anti-tumor memory. Furthermore, off-the-shelfNK-cell therapies may be an effective method for bypassing downregulated antigen-MHC complex presentation on PDAC cells. Optimization of anti-tumor

lymphocyte activation will need to be coupled with strategies that disrupt tumor-myeloid immunosuppressive communication loops within the TME to promote anti-tumor effector infiltration and prevent immune exhaustion. This will require a sophisticated and nuanced approach to targeting the TME that focuses more on reprogramming (e.g., inhibiting CXCL12/CXCR4 chemokine signaling, or blocking tumor-CAF pro-tolerogenic crosstalk mediated via TGFβ and IL-1β) rather than simply depleting cellular targets.

Looking ahead, the template for successful immunotherapy in PDAC will be built on multipronged targeting of immune priming/activation pathways in parallel with TME modulation and immune checkpoint blockade to ensure sustained anti-tumor responses (Fig. 3). Given the numerous barriers preventing a robust and durable anti-tumor immune response, it is not surprising that the vast majority of the clinical trials discussed in this review have returned largely negative, or, at best, modest outcomes because the IO strategies examined, at their core, are incomplete. An effective IO regimen for pMMR PDAC will require several IO and molecular agents on top of conventional therapies. Standard chemotherapy with combinatorial cocktail of an anti-tumor vaccine, co-stimulatory agent (aCD40), TME crosstalk modulator (CXC4Ri or TGFβ trap), and ICB (aPD-1) is one such potential combination. The IO breakthrough that PDAC needs will take the form of regimen that takes this comprehensive approach to immune response while accounting for compensatory signaling pathways, and context-dependent immunomodulatory roles of therapeutic targets.

Declarations

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