Translational advances in pancreatic ductal adenocarcinoma therapy

Abdel Nasser Hosein [1,2,3,4] ✉, Stephanie K. Dougan [5,6] ✉, Andrew J. Aguirre [7,8] ✉ and Anirban Maitra [2,3] ✉

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer that is most frequently detected at advanced stages, limiting treatment options to systemic chemotherapy with modest clinical responses. Here, we review recent advances in targeted therapy and immunotherapy for treating subtypes of PDAC with diverse molecular alterations. We focus on the current preclinical and clinical evidence supporting the potential of these approaches and the promise of combinatorial regimens to improve the lives of patients with PDAC.

PDAC is a devastating disease with a 5-year overall survival (OS) of only 11% (ref. [1]). Recent progress in chemotherapy regimens has improved outcomes in resectable PDAC[2]; however, 80% of patients are diagnosed at an advanced stage, precluding them from curative intent surgery[3]. The past decade has cemented gemcitabine and fluoropyrimidine-based combination regimens as standard of care chemotherapy for patients with metastatic pancreatic cancer[4], although median OS (mOS) rates remain at approximately 1 year (refs. [5,6]). In stark contrast to other tumor types, multiple large-scale trials using targeted agents have been unsuccessful for PDAC[7–9]. However, an improved understanding of the biology and genetics of PDAC have spurred the advent of new targeted and immune-based therapies that may be available for patients with PDAC in the near future. There is a critical unmet need to translate our understanding of PDAC biology to the clinic to improve survival and quality of life. Here, we review our current understanding of the molecular features and immune landscape of PDAC to develop targeted and immune-based therapies and improve outcomes for patients with PDAC.

Targeted approaches to PDAC

Identifying key oncogenic drivers and dependencies may yield novel approaches for PDAC. In this section, we review efforts toward the molecular characterization of PDAC and the strategies aimed at targeting potential vulnerabilities.

The mutational landscape of PDAC. Several large-scale genomic efforts have cataloged potential driver mutations in PDAC, enabling genomic-guided clinical decisions and therapeutic development. Early next-generation sequencing (NGS) studies of resected PDAC tumors revealed that *KRAS*, *TP53*, *CDKN2A* and *SMAD4* displayed the highest mutation frequencies, with >90% of individuals having oncogenic *KRAS* mutations[10,11]. The International Cancer Genome Consortium (ICGC) confirmed these findings and described several structural variations[12]. In addition, The Cancer Genome Atlas

(TCGA) program reported the presence of 20 genes mutated at a frequency of less than 10%, which included chromatin modification genes (such as *ARID1A*, *KMT2D* and *KMT2C*), DNA repair genes (for example, *BRCA1*, *BRCA2* and *PALB2*) and additional oncogenes (*BRAF*, *MYC*, *FGFR1* and others)[13].

Recently, the 'Know Your Tumor' initiative reported that 28% of patients with available clinical outcomes had an actionable mutation, defined as a genetic aberration for which a specific targeted therapy existed[14]. However, only 7% of these individuals had received a matched, precision-based therapy[15]. Notably, even though the OS of patients with or without actionable mutations was comparable, the ones who received matched therapies survived longer than those who received unmatched therapy (2.58 years versus 1.32 years, respectively). The survival of patients with an actionable mutation who did not receive targeted therapy and the survival of those with no actionable mutation were comparable. The vast majority of individuals on matched therapies either had *BRCA* mutations or displayed microsatellite instability-high (MSI-H) status and thus were placed on a poly(ADP-ribose) polymerase (PARP) inhibitor or immune checkpoint blockade (ICB), respectively. In the COMPASS trial, 35 of the 50 evaluable participants with advanced PDAC had progressed on first-line chemotherapy, and, whereas 19 out of 35 went on to receive second-line treatment, these decisions were guided by NGS data in only 5 of those participants[16]. In the PancSeq prospective program, patients with advanced PDAC underwent a biopsy followed by rapid turnaround whole-exome sequencing to allocate them to genomics-guided therapies[17], and 24% (17 out of 71) were treated with off-label use of an approved or experimental agent, highlighting the potential of this integrated multidisciplinary approach. In all of these studies, limitations included the relatively low frequency of actionable alterations beyond *BRCA1*, *BRCA2* or MSI-H and the accessibility of appropriate therapies on or off clinical trials for patients with advanced disease and generally declining performance status. The more recent advent of additional therapies targeting oncogenic driver alterations in both *KRAS*-wild-type and

¹Division of Hematology & Oncology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA. ²Department of Translational Molecular Pathology, University of Texas MD Anderson Cancer Center, Houston, TX, USA. ³Sheikh Ahmed Bin Zayed Al Nahyan Center for Pancreatic Cancer Research, University of Texas MD Anderson Cancer Center, Houston, TX, USA. ⁴Advocate Aurora Health, Vince Lombardi Cancer Clinic, Sheboygan, WI, USA. ⁵Department of Cancer Immunology and Virology, Dana-Farber Cancer Institute, Boston, MA, USA. ⁶Department of Immunology, Harvard Medical School, Boston, MA, USA. ⁷Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA. ⁸Broad Institute of MIT and Harvard, Cambridge, MA, USA. ✉e-mail: abdel.hosein@aah.org; stephanie_dougan@dfci.harvard.edu; andrew_aguirre@dfci.harvard.edu; amaitra@mdanderson.org

KRAS-mutated PDAC will likely improve the number of patients who benefit from genotype-directed therapies in the near future.

Targeting *KRAS* mutations in PDAC. *KRAS*, the most frequently mutated oncogene, transmits signals from receptor tyrosine kinases (RTKs) through the MAPK pathway[18]. Oncogenic *KRAS* mutations occur in over 90% of human PDAC tumors, with different incidences of specific mutated sites, including G12D (41%), G12V (34%), G12R (16%), Q61H (4%) and G12C (~1%)[19,20]. Genetically engineered mouse models (GEMMs) confirmed the role of oncogenic *Kras* in PDAC initiation and tumor maintenance[21–23] through cancer cell autonomous and non-autonomous mechanisms[24]. Expression of the oncogenic *Kras*[G12D] mutation by a pancreas-specific Cre/*loxP* system (that is, the Kras;Cre or 'KC' model) is sufficient to drive precursor pancreatic intraepithelial neoplasia (PanIN) and PDAC[21]. Although the penetrance of PDAC is variable in KC mice, expression of dominant-negative *Trp53* (KPC model) or loss of *Cdkn2a* (encoding p16[Ink4a] and p19[Arf]) results in complete penetrance of PDAC and liver metastases[22,25]. Notably, pancreas-specific *Kras*[A146T] GEMMs do not exhibit PanIN lesions[26], in line with the observation that *KRAS*[A146T] mutations do not typically occur in human PDAC[27], indicating that different *Kras* alleles confer varying oncogenic properties in PDAC[26]. Notably, *KRAS* codon 61 mutations have been associated with decreased downstream phospho-ERK signaling, raising the possibility of an association with improved survival[11,28]. By contrast, *KRAS*[G12D] mutations are associated with worse outcomes than all other *KRAS* mutations and wild-type *KRAS* status in resected PDAC[29].

Despite the high frequency of *KRAS* mutations in PDAC, developing RAS inhibitors has been challenging owing to a lack of drug-accessible pockets amenable to high-affinity binding[30]. However, recent advances in drug development have ushered in an era of mutation-specific KRAS-targeting tools. The *KRAS*[G12C] mutation represents just 1% of PDAC cases[31] but is the first KRAS-mutant protein that could be effectively targeted with a specific small-molecule inhibitor, ARS-1620. This inhibitor was developed through structure-based drug design, and it covalently binds the inactive GDP-bound state of KRAS[G12C], hindering the exchange of GDP for GTP and thereby preventing KRAS activation[32]. In vitro studies demonstrated that ARS-1620 elicits potent, dose-dependent inhibition of phospho-ERK, phospho-S6 and phospho-AKT in *KRAS*[G12C]-mutated, but not *KRAS*[G12D]- or *KRAS*[G12V]-mutated, cell lines. ARS-1620 treatment had antitumor efficacy in in vitro and in vivo models of PDAC. Thus, ARS-1620 provided the first preclinical proof-of-concept evidence for specific KRAS[G12C] inhibition.

Later, X-ray crystallography studies led to the identification of a cryptic pocket in KRAS[G12C] (H95/Y96/Q99) that was exploited for the development of the first potent clinical-grade KRAS[G12C] inhibitor, AMG-510 (sotorasib)[33,34]. Sotorasib proceeded to clinical trials and demonstrated significant radiographic responses in patients with *KRAS*[G12C]-mutated lung adenocarcinoma[33]. A recent phase 2 clinical trial demonstrated durable clinical benefit, leading to sotorasib becoming the first US Food and Drug Administration (FDA) fasttrack-approved RAS inhibitor[35]. The multicenter, open-label, phase 1/2 CodeBreak 100 clinical trial continues to assess the safety and response rates of sotorasib in a variety of *KRAS*[G12C]-mutated advanced solid cancers (NCT03600883)[36]. Preliminary data demonstrate promising activity in PDAC, with six of eight evaluable participants with PDAC achieving stable disease and three experiencing approximately a 30% reduction in disease burden at 4.3 months median follow-up[37].

A separate KRAS[G12C] inhibitor, MRTX849 (adagrasib), was simultaneously reported[38], and demonstrated efficacy across preclinical models with radiographic responses in both *KRAS*[G12C]-mutated lung and colon adenocarcinomas in a proof-of-concept clinical study. In early results from the KRYSTAL-1 trial, ten patients with

previously treated *KRAS*[G12C]-mutated metastatic PDAC treated with adagrasib were reported[39]. All evaluable individuals demonstrated clinical benefit, including five of ten partial responses (PRs). Progression-free survival (PFS) for this small cohort was 6.6 months, a remarkable observation given that the response rate of second-line chemotherapy for advanced PDAC is only around 10%, with a median PFS of less than 3 months[40]. These preliminary results need to be validated in larger cohorts, and ongoing clinical trials are testing adagrasib as a monotherapy or in combination with other agents, including inhibitors of EGFR, SHP2 and other targets (NCT03785249 and NCT04330664)[41,42].

A small-molecule inhibitor specific for KRAS[G12D], MRTX1133, is currently undergoing preclinical development, with an investigational new drug application pending[43]. In early preclinical work using a panel of *KRAS*[G12D]-mutated PDAC cell line xenograft and patient-derived xenograft (PDX) models, 73% (8 out of 11) of these models demonstrated in vivo tumor regression following treatment with MRTX1133 (refs. [44,45]). Several other groups also have KRAS[G12D] drug development programs underway. Given that the *KRAS*[G12D] mutation is the most common *KRAS* alteration in PDAC with a prevalence of 41% (refs. [19,20]), KRAS[G12D] inhibitors have the potential to make a substantial impact on PDAC treatment.

Beyond allele-selective inhibitors of KRAS, additional small molecules are being developed that target RAS isoforms more broadly. For instance, RMC-6236 was recently reported as a novel clinical-grade pan-RAS inhibitor. This molecule bridges the active, GTP-bound form of RAS to an adjacent chaperone molecule (cyclophilin A), thus forming an inactive 'tricomplex' molecule and preventing RAS interactions with downstream signaling partners[46]. In a recent preclinical report, this molecule demonstrated a reduction in tumor volume across *KRAS* genotypes, including G12D, G12V and G12R mutations[47]. Furthermore, in immunocompetent PDAC mouse models, RMC-6236 treatment increased intratumor CD45+ cell infiltration and decreased numbers of monocytic myeloid-derived suppressor cells (moMDSCs). Additionally, RMC-6236 synergized with anti-PD-1 ICB, leading to durable complete responses in vivo.

SOS1 is a key guanine nucleotide exchange factor for KRAS, which positively regulates its activity at catalytic and allosteric sites[48]. A selective oral small-molecule SOS1 inhibitor, BI-3406, was recently reported to disrupt SOS1–KRAS interaction independent of the *KRAS* mutation. This compound markedly reduced tumor growth and GTP–RAS levels across *KRAS*-driven cancer models[49]. Importantly, combined BI-3406 and MEK inhibitor trametinib treatment led to the regression of established *KRAS*-mutated xenografts through prevention of MAPK feedback reactivation. The clinical SOS1 inhibitor candidate BI-1701963 is currently being investigated in a phase 1 clinical trial of *KRAS*-mutated advanced solid tumors alone or in combination with trametinib (NCT04111458)[50].

Another approach to targeting mutant KRAS in PDAC uses the same lipid nanoparticle-encapsulated mRNA-based vaccine strategy that was used to develop the vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[51]. This mRNA-based vaccine (named mRNA-5671/V941) encodes the four major KRAS mutations seen in cancers: G12D, G12V, G13D and G12C. KRAS epitopes spanning the mutant amino acid have been shown to be presented on multiple alleles of the human version of the major histocompatibility complex class I (human leukocyte antigen; HLA) suggesting that direct T cell recognition of mutant KRAS is a feasible strategy[52,53]. A phase 1 clinical trial is underway and aims to enroll 100 patients with *KRAS*-mutated advanced non-small cell lung cancer (NSCLC), colorectal cancer or PDAC to be treated with mRNA-5671/V941 alone or in combination with the PD-1 antibody pembrolizumab (NCT03948763 (ref. [54]); Fig. 1 and Table 1). Finally, a phase 1 trial is underway at MD Anderson Cancer Center to target the *KRAS*[G12D] allele using synthetic short interfering RNA
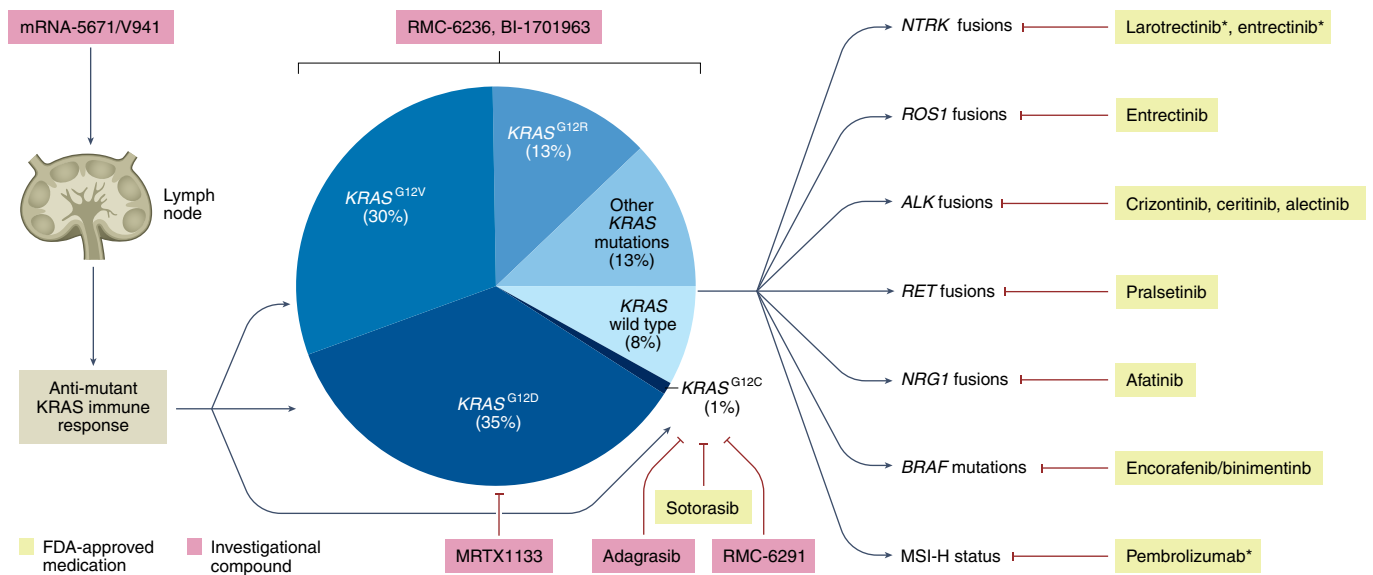
Fig. 1 | Evolving therapeutic landscape of KRAS in PDAC. Relative frequencies of different *KRAS* missense mutations in PDAC. Investigative and FDA-approved precision-based therapies against denoted *KRAS* mutation sites are shown. Therapeutic strategies are also illustrated for *KRAS*-wild-type PDAC based on the presence of alternative driver aberrations. Asterisks indicate FDA-approved molecules with tissue-agnostic indications against the noted molecular alteration.

packaged within mesenchymal stem cell-derived exosomes (iExosomes; NCT03608631)[55,56].

Tackling resistance to KRAS inhibition. Despite these encouraging clinical trial results, it is critical to understand the mechanisms that subvert the efficacy of KRAS inhibition. Studies evaluating multiple *KRAS*[G12C] lung cancer cell lines, xenografts and human-derived xenografts treated with ARS-1620 found newly synthesized KRAS[G12C] through increased EGFR and AURKA signaling[57]. Indeed, ARS-1620 treatment in combination with either EGFR or AURKA small-molecule inhibitors resulted in markedly enhanced suppression of tumors in vivo compared to ARS-1620 monotherapy. In the clinical setting, the combination of sotorasib with the pan-HER inhibitor afatinib in heavily pretreated patients with *KRAS*[G12C]-mutated NSCLC (including those on prior KRAS[G12C] inhibitor therapy) resulted in a 30% PR rate and 73% disease control rate[58]. A large phase 1/2 clinical trial is underway aiming to assess combinations of sotorasib with targeted therapy or immunotherapy in various *KRAS*[G12C]-mutated tumor types (NCT04185883)[59]. Similarly, adagrasib showed increased efficacy in vivo when combined with inhibitors of SHP2, EGFR, mTOR and CDK4/CDK6 (ref. [38]). Multiple mechanisms of resistance to adagrasib have been identified in patients with lung or colorectal tumors, including *KRAS* mutations or amplifications, RTK–RAS–MAPK pathway alterations and histological transformation[60]. Notably, analysis of circulating tumor DNA indicated that multiple mechanisms of resistance had emerged simultaneously in several individuals. Tricomplex inhibitors have demonstrated the ability to overcome second-site KRAS-activating mutations following adagrasib treatment[61]. Future clinical trials assessing the response to KRAS small-molecule inhibitors in PDAC will need to strongly consider the early adoption of concomitant targeting of escape pathways, an approach that has proven effective in targeting other MAPK components in different cancer types[62].

Genetic inhibition of *KRAS* or pharmacologic inhibition of downstream MAPK signaling results in decreased glycolysis and mitochondrial function in human PDAC cells, with an increased dependency on autophagy[63,64]. Indeed, combining ERK or MEK

inhibitors with the autophagy inhibitor hydroxychloroquine leads to marked reduction of PDAC growth in vitro and in vivo. Multiple early-phase clinical trials are underway aimed at seeking a signal of efficacy by combining ERK or MEK inhibitors with hydroxychloroquine in patients with metastatic PDAC (NCT03825289, NCT04132505 and NCT04386057)[65–67].

A useful preclinical system to model potential mechanisms of bypassing KRAS inhibition is the doxycycline-regulated KPC GEMM, where oncogenic *Kras* expression is dependent on doxycycline exposure (iKPC model)[23,68]. In this model, tumors initially regress following doxycycline withdrawal only to relapse 4–5 months later despite the absence of oncogenic *Kras* expression[69]. The surviving tumor cells had decreased reliance on glycolysis and a high dependency on oxidative phosphorylation, supporting the use of oxidative phosphorylation inhibitors to tackle *Kras*-independent 'escaper cells'. Further analysis of escaper-cell subpopulations revealed the acquisition of a mesenchymal phenotype that achieved independence from MAPK signaling through the Smarcb1–Myc signaling network[70]. These escaper cells displayed an anabolic phenotype featuring increased protein metabolism, thus rendering them vulnerable to alterations in the cellular proteostatic machinery, the endoplasmic reticulum stress response and heat shock protein 90 (ref. [71]). *Kras* loss in this model did not induce reactivation of canonical MAPK signaling, but a proportion of tumors underwent an amplification and overexpression of the YAP transcriptional regulator, driving DNA replication and cell cycle progression[72]. These relapsed *Kras*[G12D]-independent tumors also assumed mesenchymal features. Together, these data provide evidence for multiple signaling hubs accounting for putative mechanisms by which PDAC cancer cells may subvert the effect of KRAS inhibition and therefore point to specific strategies to overcome potential escape mechanisms in clinical studies.

Precision approaches for KRAS-wild-type PDAC. Approximately 8–10% of PDAC tumors do not contain *KRAS* mutations[11,13]. Patients with *KRAS*-wild-type tumors have a relatively better prognosis than those with *KRAS*-mutated tumors[29,73]. Patients with wild-type *KRAS* often have alternative oncogenic mutations, most frequently

Table 1 | Precision medicine approaches for PDAC therapy

KRAS-targeting small-molecule therapeutics in preclinical and/or clinical development for the treatment of PDAC

Drug	Target	Mechanism	Phase of trial	Trial design	Cancer type	Primary outcome	Preclinical reference	Clinical reference
Sotorasib[a] (AMG-510)	KRAS[G12C]	Small-molecule binding of GDP-bound state of KRAS[G12C]	I/II	Sequential, dose-finding arms with drug given as a monotherapy and in combination with PD-1	Basket trial with multiple types of solid tumors enrolled (KRAS[G12C] mutation-positive)	Treatment-related adverse events	32,33	36,37
Adagrasib[c] (MRTX849)	KRAS[G12C]	Small-molecule binding of GDP-bound state of KRAS[G12C]	I/II	Sequential, dose-finding arms with drug given as monotherapy	Basket trial with multiple types of solid tumors enrolled (KRAS[G12C] mutation-positive)	Treatment-related adverse events and early clinical activity signal	38	41
			I/II	Sequential, dose-finding arms tested in combination with SHP2 inhibitor (TNO155)	Basket trial with multiple types of solid tumors enrolled (KRAS[G12C] mutation-positive)	Treatment-related adverse events		42
MRTX1133[c]	KRAS[G12D]	Small-molecule binding of GDP and GTP-bound state of KRAS[G12D]	–	–	–	–	43	Pending trial registration
RMC-6291[c]	KRAS[G12C]	Tricomplex inhibitor	–	–	–	–	46	Pending trial registration
RMC-6236[c]	Multi-RAS	Tricomplex inhibitor	–	–	–	–	–	–
BI-1701963[c]	Pan-KRAS	SOS1–KRAS inhibitor	I	Two-arm trial: drug alone and drug plus trametinib	Basket trial with KRAS-mutated advanced solid tumors	MTD[a], ORR in expansion cohort	49	50

Approved and experimental precision medicine approaches in PDAC

Drug(s)	Target	Indication	Frequency of aberration	KRAS wild type or mutant	Responses in PDAC	–	–	References
Pembrolizumab[a]	MMR-deficient/ MSI-H	Advanced MSI-H or MMR-deficient solid tumors[a]	1–2% of PDAC	Strong association with KRAS and TP53 wild type	4/22 patients with PDAC with objective response	–	–	137,141,210,211
Larotrectinib[a], entrectinib[a]	NTRK (gene fusions)	Advanced solid tumor with NTRK gene fusion	Rare event in PDAC (<1%)	KRAS wild type	PR	–	–	86,88,89,212
Encorafenib[b], binimetinib[b]	BRAF	Patients with BRAF[V600E]-mutated PDAC	All BRAF aberrations account for 10% of KRAS-wild-type PDAC	KRAS wild type	Trial ongoing	–	–	74,80
Afatinib[b], zenocutuzumab[c]	NRG1 fusions	NRG1 fusion-positive advanced PDAC	High incidence in KRAS wild type	KRAS wild type	Excellent, durable responses	–	–	92,213–215
Crizotinib[b], ceritinib[b], alectinib[b]	ALK	ALK gene rearranged	0.16% of all patients with PDAC, and 1.3% of all individuals <50 years old	KRAS wild type	Three of four individuals treated with ALK inhibitor had disease control	–	–	93
Entrectinib[b]	ROS1	Approved for ROS1 fusion NSCLC but case report evidence in PDAC	Rare event in PDAC (<1%)	KRAS wild type	One individual with PDAC with minor response	–	–	86
Trastuzumab, deruxtecan[b]	HER2	HER2-overexpressing advanced solid tumor (non-gastric, non-breast)	Amplified in 2% of PDAC cases	KRAS[G12V]	One individual with PDAC tested (PR)	–	–	216,217
Pralsetinib[b] (BLU-667)	RET	RET fusion advanced solid tumors (three patients with PDAC)	Rare event in PDAC (<1%)	KRAS wild type (1.35%) and KRAS mutant (0.22%)	Response in all patients with PDAC tested	–	–	74,91

Continued

Table 1 | Precision medicine approaches for PDAC therapy (Continued)

KRAS-targeting small-molecule therapeutics in preclinical and/or clinical development for the treatment of PDAC

Drug	Target	Mechanism	Phase of trial	Trial design	Cancer type	Primary outcome	Preclinical reference	Clinical reference
Clinical trials evaluating DNA damage response-targeted therapeutic agents in PDAC								
Drug(s)	Target	Population	Trial status	Trial design	Phase of trial	Primary findings or endpoint	Preclinical reference	Clinical reference
Olaparib	PARP	Patients with *BRCA1*- or *BRCA2*-mutated metastatic PDAC	Completed (FDA approved)	Two-arm, randomized phase control trial	III	PFS: plaparib superior to placebo as maintenance	96,97	99
Rucaparib	PARP	Patients with *BRCA1*-, *BRCA2*- or *PALB2*-mutated metastatic PDAC	Completed	Single-arm study	II	PFS: rucaparib superior to placebo as maintenance	96,97	101
Cisplatin, veliparib	PARP and DNA (alkylation)	Patients with *BRCA1*-, *BRCA2*- or *PALB2*-mutated metastatic PDAC	Completed (NCCN recommendation)	Two-arm, randomized control trial	II	PFS and OS: equivalent between platinum/PARP inhibitor versus platinum arms, and excellent response with platinum	96,97	103
Olaparib	PARP	Patients with *BRCA1*-, *BRCA2*- or *PALB2*-mutated PDAC in the adjuvant setting	Recruiting	Two-arm, randomized control trial	II	PFS	96,97	105
Olaparib, pembrolizumab	PARP and PD-1	Patients with *BRCA1*- or *BRCA2*-mutated metastatic PDAC	Recruiting	Two-arm, randomized control trial	II	PFS	106	107
Niraparib, dostarlimab	PARP and PD-1	Patients with *BRCA1*-, *BRCA2*- or *PALB2*-mutated metastatic PDAC	Recruiting	Single-arm study	II	Disease control rate at 12 months	106	108
BAY 1895344[c]	ATR	Multiple solid tumors including PDAC	Not yet recruiting	Two-arm, non-randomized trial	I	Tolerability of agent, with ORR as an exploratory objective	110	112
AZD6738[c], olaparib	ATR	Multiple solid tumors including PDAC	Recruiting	Two-arm, non-randomized trial	II	ORR	111	113

[a]Tissue-agnostic approval for indicated target [b]Off-label use in PDAC [c]Investigational drug ATR, ataxia telangiectasia and Rad3-related protein; MMR, mismatch repair; MTD, maximum tolerated dose; NCCN, National Comprehensive Cancer Network; ORR, overall response rate.

activating *BRAF* alterations that lead to constitutive MAPK pathway activation and occur in approximately 2% of all PDAC cases[74,75]. BRAF activation may occur as a result of activating in-frame deletions or activating point mutations, such as the V600E mutation (*BRAF*[V600E]) with preclinical models and limited human experience, suggesting that the former may be sensitive to MEK inhibition[17,76]. In a PDAC GEMM, expression of *BRAF*[V600E] in pancreatic progenitor cells produced PanINs with low incidence of progression to PDAC[77]. Similar to the KPC GEMM, the addition of the dominant-negative *Trp53* mutation to *BRAF*[V600E] resulted in full penetrance. In addition, a MEK inhibitor combined with gemcitabine chemotherapy showed regression of orthotopically implanted human-derived xenografts[78]. Despite these findings, a phase 2 clinical trial of 160 patients with metastatic PDAC treated with gemcitabine, or gemcitabine plus the MEK inhibitor trametinib, failed to show any significant differences in OS, PFS or ORR across *KRAS*-mutated or *KRAS*-wild-type individuals, although *BRAF* mutation status was not reported[79]. To apply a precision medicine approach to *KRAS*-wild-type patients with PDAC, *BRAF* mutation status must be confirmed and patients enrolled into BRAF- and MEK-targeting trials. A phase 2 multicenter, single-arm clinical trial is underway in which patients with advanced PDAC and containing a *BRAF*[V600E] mutation will be treated with the BRAF inhibitor encorafenib and the MEK inhibitor binimetinib with ORR as the primary endpoint (NCT04390243)[80]. Dual BRAF–MEK inhibition is approved for *BRAF*[V600E] metastatic melanoma and improves both PFS and OS compared to BRAF inhibition alone[81]. This strategy uses MEK inhibition to suppress MAPK escape mechanisms during BRAF inhibition[82]. Furthermore, a combined analysis of the ICGC and TCGA datasets revealed that 4.2% of *KRAS*-wild-type PDAC tumors had in-frame deletions in *BRAF*, which were confirmed to drive RAF dimerization and increase MAPK signaling in vitro[76]. In preclinical animal models containing in-frame *BRAF* deletions, the pan-RAF inhibitor LY3009120 led to tumor regression, which was not observed with the BRAF[V600E] inhibitor vemurafenib. Unfortunately, an early-phase clinical trial of 51 patients with advanced solid cancer treated with LY3009120, including 5 patients with PDAC, revealed no responses[83].

Neurotrophic RTK (*NTRK*) genes drive mitogenic signaling in the central nervous system[84,85]. Activating *NTRK* fusions occur in <0.5% of all human cancers, including PDAC, and are also observed in *KRAS*-wild-type PDAC tumors[86,87]. In a basket study of patients with advanced solid cancer containing *NTRK* fusions, 75% of individuals responded to single-agent larotrectinib treatment, with 71% of these responders continuing to respond after 1 year of

treatment[88]. This study led to the regulatory approval of larotrectinib for advanced solid cancers containing *NTRK* fusions. Of note, this study included only one individual with PDAC, although this individual did experience a PR. Furthermore, an integrated analysis of three ongoing early-phase clinical trials investigating the *NTRK* inhibitor entrectinib in advanced solid cancers with *NTRK* fusions reported in three evaluable patients with PDAC two and all three with disease control[89]. Moreover, the STARTRK-2 study (NCT02568267)[90] is enrolling patients with advanced cancer that contain *ROS1* fusions, with one individual with PDAC achieving disease stability on entrectinib and remaining on treatment for 7 months (ref. [86]). *KRAS*-wild-type PDAC comprises a minority of cases but features a rich array of druggable non-*KRAS* driver aberrations in genes such as *BRAF* and *NTRK* genes in addition to other fusion events such as *RET*[91], *NRG1* (ref.[92]) and *ALK*[93] (Table 1). Routine tumor sequencing of advanced PDAC tumors is critical in identifying *KRAS*-wild-type individuals likely to benefit from the targeting of alternative driver events.

Targeting DNA damage repair in PDAC. Mutations in DNA damage repair genes result in a deficiency of DNA double-stranded break repair[94]. In a cohort of 2,818 PDAC tissue samples assayed by NGS, somatic *BRCA1*, *BRCA2* and *PALB2* mutations were observed in 1.3%, 3.1% and 0.6% of cases, respectively[95]. In GEMMs, heterozygous germline *Brca2*-inactivating truncations promote PDAC formation on a background of oncogenic *Kras*[96]. Targeting PARP, a critical enzyme for single-stranded DNA repair, in BRCA1- or BRCA2-deficient preclinical cancer models is an effective therapeutic strategy[97,98]. The POLO study demonstrated that the PARP inhibitor olaparib has significant activity in patients with platinum-sensitive metastatic PDAC with germline *BRCA1* or *BRCA2* mutations[99]. In this study, participants on olaparib experienced a 7.4-month PFS compared to 3.8 months for those on placebo (hazard ratio of 0.53; 95% confidence interval of 0.35–0.82). This study led to the FDA approval of olaparib as a maintenance therapy of platinum-sensitive metastatic PDAC that contain germline *BRCA1* or *BRCA2* mutations. Importantly, follow-up analysis of the POLO trial demonstrated no statistically significant difference in median OS between the placebo and olaparib arms[100]. In a single-arm, phase 2 clinical trial, a second PARP inhibitor, rucaparib, also demonstrated clinical activity as a maintenance therapy for patients with platinum-sensitive advanced PDAC and germline or somatic *BRCA1*, *BRCA2* or *PALB2* mutations[101]. Of note, deleterious *BRCA1* and *BRCA2* mutations are often accompanied by inactivation of the second allele and positively correlate with the *BRCA* mutation signature[102], which is associated with response to platinum-based chemotherapy in PDAC[12]. In a recent open-label, randomized, multicenter, two-arm phase 2 clinical trial, patients with advanced PDAC and germline mutations in *BRCA1*, *BRCA2* or *PALB2* were randomized to cisplatin and gemcitabine with or without the PARP inhibitor veliparib[103]. The gemcitabine–cisplatin–veliparib (GCV) arm experienced a 74.1% response rate in comparison to the gemcitabine–cisplatin (GC) arm, which demonstrated a response rate of 65.2% ($P=0.55$). Moreover, the PFS of the GCV and GC arms was 10.1 months and 9.7 months, respectively ($P=0.73$), and the OS was 15.5 months and 16.4 months, respectively ($P=0.60$). Although the addition of PARP inhibition did not improve clinical benefits, the combination of gemcitabine and cisplatin without PARP inhibitor is now considered an effective treatment regimen for this subset of patients[104]. Lastly, a phase 2 randomized trial is investigating the role of adjuvant olaparib in patients with PDAC and germline or somatic *BRCA1*, *BRCA2* or *PALB2* mutations (NCT04858334)[105].

BRCA1 and *BRCA2* mutations positively correlate with increased PD-L1 staining in human PDAC cancer cells[95]. Retrospective data on *BRCA2*-mutated breast cancer revealed a superior response to immune checkpoint inhibition compared to *BRCA2* wild type, in line with results seen in syngeneic mouse models of breast and colon cancer[106], pointing to these as potential candidate biomarkers to stratify patients for ICB. Indeed, an ongoing phase 2 open-label, two-arm clinical trial aims to compare olaparib monotherapy to olaparib plus pembrolizumab as maintenance therapy in patients with metastatic PDAC and germline *BRCA1* or *BRCA2* mutations (NCT04548752)[107]. Another PARP inhibitor–PD-1 doublet (niraparib and dostarlimab, respectively) is also being investigated in a phase 2 clinical trial of patients with metastatic PDAC with either somatic or germline *BRCA1* or *BRCA2* mutations (NCT04493060)[108].

The *ATM* gene is a key regulator of the DNA damage response[109] and is mutated in approximately 5% of PDAC cases[13]. PDAC cells that have mutations in *ATM* are specifically sensitive to PARP inhibition in combination with inhibition of ATR in vivo, whereas PARP inhibitor monotherapy has limited durable activity[110]. A DNA replication stress signature that correlates with the PDAC basal-like transcriptional subtype is predictive of response to ATR inhibition in human PDAC organoids[111]. Multiple early-phase clinical trials testing ATR inhibitors in combination with cytotoxic chemotherapy (NCT04514497)[112] or with PARP inhibitors (NCT03682289)[113] are currently underway (Table 1).

Translational approaches using transcriptionally defined molecular subtypes. Gene expression profiling studies have significantly improved our understanding of the molecular taxonomy of all major cancers over the past two decades[114–117]. The first gene expression-based subtyping study in PDAC revealed the existence of three dominant molecular subtypes of PDAC: quasi-mesenchymal, classical and exocrine-like, with the latter two subtypes displaying a significantly improved survival over quasi-mesenchymal[118]. The quasi-mesenchymal subtype overexpressed mesenchymal-associated genes, whereas the classical subtype overexpressed cell adhesion- and epithelial-related genes. Subsequently, 'virtual microdissection' experiments using expression profiling data revealed the presence of two predominant molecular subtypes of PDAC: basal-like and classical[119]. The basal-like subtype of PDAC was associated with poor survival and resembled the basal subtype in both breast and bladder cancers. Furthermore, the ICGC demonstrated four distinct molecular subtypes by RNA-sequencing gene expression profiling: pancreatic progenitor, immunogenic, aberrantly differentiated endocrine exocrine (ADEX) and squamous, with the latter resembling the basal-like subtype[31]. The squamous subtype displayed an increased frequency of *TP53* and *KDM6A* mutations and displayed a significantly poorer prognosis than all other molecular subtypes. The TCGA team further suggested that samples classified as either ADEX or immunogenic had lower purity of neoplastic epithelium and a higher degree of leukocyte infiltration[13]. After accounting for neoplastic cellularity, all samples were effectively reclassified into either the basal-like/squamous or the classical/progenitor subtypes. More recently, using a cohort of 206 patients with resectable (stages 1 and 2) PDAC and 111 patients with advanced (stages 3 and 4) PDAC, RNA sequencing analysis revealed that 62% of patients with resectable PDAC could be classified as having the classical subtype, whereas in metastatic PDAC, the classical subtype comprised only 46% of individuals[120]. This study also further subdivided basal-like PDAC into two subgroups: basal-like A and basal-like B. Notably, basal-like A made up only 5% of patients with resectable PDAC but 24% of patients with stage 4 PDAC. Furthermore, the basal-like A subtype was shown to be largely chemoresistant, particularly in advanced disease settings. While bulk RNA-sequencing data suggest that the subtypes of PDAC tumors are dichotomous, single-cell RNA-sequencing analysis has revealed the coexistence of populations of cancer cells displaying classical and basal-like signatures within the same tumor, including the presence of 'hybrid' cells bearing features of both subtypes[120–122]. The observed transcriptional

subtype heterogeneity in PDAC may have important implications for development of resistance to therapeutic strategies targeting specific subtypes of the disease.

Gemcitabine/nab-paclitaxel (GnP) and modified FOLFIRINOX (mFOLFIRINOX) are both category one recommended regimens for the treatment of advanced PDAC[104]. Nonetheless, retrospective case series indicated that mFOLFIRINOX may be associated with greater radiographic responses and OS in early[123] and advanced stage disease[124,125]. However, these data may be confounded by the use of mFOLFIRINOX in patients with better performance status. Indeed preliminary evidence from a phase 2 trial (SWOG S1505), in which patients with resectable PDAC were randomized to perioperative chemotherapy with either GnP or mFOLFIRI-NOX, displayed no significant difference in median OS between the two regimens[126]. The PRODIGE-24 study demonstrated a median OS of 54 months in individuals who received adjuvant mFOLFIRINOX in comparison to 35 months in individuals who received only adjuvant gemcitabine. The use of gene expression profiling and molecular classification of patients with PDAC may offer insight into the molecular determinants of response to either chemotherapy regimen.

The COMPASS trial in advanced PDAC assessed the response to chemotherapy in classical and basal-like subtypes[16]. In this trial, 195 participants underwent tumor biopsy followed by RNA sequencing, which classified tumors as either classical (80%) or basal-like (20%)[127]. There was a 60% rate of radiographic progression in participants with basal-like tumors treated with mFOLFIRI-NOX in contrast to a 15% rate of progression in classical tumors. Moreover, *GATA6* expression was significantly increased in classical subtype tumors and may be an appropriate surrogate marker of chemosensitivity across molecular subtypes. Although this was the first report that gene expression profiling may predict response to chemotherapy, the clinical utility of these findings should be prospectively validated. To that end, The Pancreatic Adenocarcinoma Signature Stratification for Treatment (PASS-01) trial is a phase 2, multicenter clinical trial randomizing patients with metastatic PDAC to either mFOLFIRINOX or GnP treatment (NCT04469556)[128]. The primary endpoint is PFS and will provide further insight into comparative efficacies of the two regimens. The correlative studies will provide insight into the responses to both chemotherapy regimens in specific molecular subtypes by integrating the analysis of *GATA6* expression (classical subtype surrogate marker), cytokeratin 5 and cytokeratin 17 expression (basal-like subtype surrogate markers) and the classical–basal subtype gene expression signatures. This and subsequent randomized phase 3 trials may allow clinicians to select first-line mFOLFIRINOX or GnP chemotherapy regimens using expression profiles or surrogate markers of PDAC molecular subtypes.

Immunotherapeutic approaches to PDAC

Immunotherapies are transforming cancer therapy across tumor types. In this section, we review recent advances and challenges in PDAC immunotherapy and ongoing strategies to reprogram the tumor microenvironment in PDAC.

Immunotherapy trials in PDAC. ICB therapies have revolutionized cancer treatment and clinical prospects[129], as monoclonal antibodies targeting PD-1/PD-L1 and CTLA-4 have proven highly effective across numerous solid tumors[130–135]. Although anti-PD-1 antibodies have a tissue-agnostic indication for all metastatic solid tumors with MSI-H status[136], this occurs in approximately 1–2% of PDAC[137]. ICB has otherwise proven ineffective in the treatment of PDAC in several early-phase clinical trials[138,139]. Most recently, a phase 2 clinical trial tested durvalumab (anti-PD-L1 monoclonal antibody) plus tremelimumab (anti-CTLA-4 monoclonal antibody) versus durvalumab monotherapy in individuals previously treated with chemotherapy for metastatic PDAC[140]. Both arms displayed

favorable toxicity profiles, but the objective response rates were 3.1% and 0%, respectively. These disappointing results highlight the need for translational studies seeking to understand and reverse the recalcitrant nature of the PDAC tumor immune microenvironment.

The immune landscape of PDAC. T cell-targeted immunotherapy strategies have been largely unsuccessful in PDAC beyond the ~1% of patients with MSI-H tumors[141,142]. Nevertheless, new efforts to augment T cell function using vaccines, adoptive cell therapies and novel checkpoint blockade targets and efforts aimed at increasing major histocompatibility (MHC) class I expression on tumor cells could offer new paths forward for enhancing antitumor immunity in PDAC[143–145]. Although CD8^{+} T cells are present at relatively high frequencies in approximately one-third of PDAC primary tumors, spatial analysis revealed that T cells are rarely located adjacent to the tumor cell nests[146,147]. Instead, neoplastic cells are surrounded by macrophages and fibroblasts, and close proximity of alternatively activated macrophages correlates with poor prognosis[147]. Both malignant cells and fibroblasts secrete chemokines and growth factors that attract monocytes and granulocytes to the tumor microenvironment, thereby replenishing a short-lived pool of immunosuppressive myeloid cells. These include CXCL2, CCL2, granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF)[148,149]. Tumor-associated macrophages, derived either from infiltrating monocytes or from pancreas-resident macrophages, can directly support malignant cells through growth factors such as transforming growth factor-β (TGFβ) and provision of metabolites that interfere with nucleoside analog-based chemotherapies[150–152]. Given the complex immunosuppressive landscape of the PDAC microenvironment[143–145], we will focus here on immune targeting strategies with three primary aims: (1) removing short-lived immunosuppressive myeloid cells; (2) reprogramming dendritic cells (DCs) to better prime tumor-specific T cell responses, particularly in the context of KRAS vaccines; and (3) targeting macrophage and fibroblast stromal support networks (Fig. 2 and Tables 2 and 3).

Targeting short-lived immunosuppressive myeloid cells. The importance of the chemokine receptors CXCR2 and CCR2 and their ligands in regulating neutrophil and monocyte cell trafficking to tumors is well established[153]. Given the short-lived nature of these cells, blocking their influx rapidly leads to a decline in intratumoral moMDSCs and gMDSCs. In mice, transient depletion of neutrophils or selective interference of neutrophil trafficking can lead to reduction in PDAC tumor burden, although such strategies cannot be maintained long term due to the critical importance of neutrophils for host defense[154–156]. Agonism of the pan-myeloid integrin CD11b prevents accumulation of most myeloid cell types in PDAC mouse models and strongly synergizes with PD-1 blockade[157]. Similarly, mice treated with inhibitors of CCR2 that targeted circulating monocytes showed reduced PDAC tumor burden[158]. In humans, a landmark clinical trial of FOLFIRINOX combined with a small-molecule inhibitor of CCR2 versus FOLFIRINOX alone in patients with locally advanced PDAC[159] demonstrated a retention of monocytes in the bone marrow, correlating with a notable drop in monocytes from circulation and moMDSCs from the tumor microenvironment in CCR2 inhibitor-treated individuals. This was accompanied by impressive reductions in primary tumor burden, leading to downstaging of disease and eligibility for surgery in 39% of the cohort[159]. Unfortunately, a similar study of a CCR2 inhibitor combined with GnP in metastatic PDAC failed for both safety and efficacy[160]. One possible interpretation is that blockade of monocyte trafficking may be suited as an adjunct to neoadjuvant chemotherapy or to immunotherapies that engage tumor-specific T cells but could result in therapy-related adverse events when used long term. Currently, an early-phase clinical trial
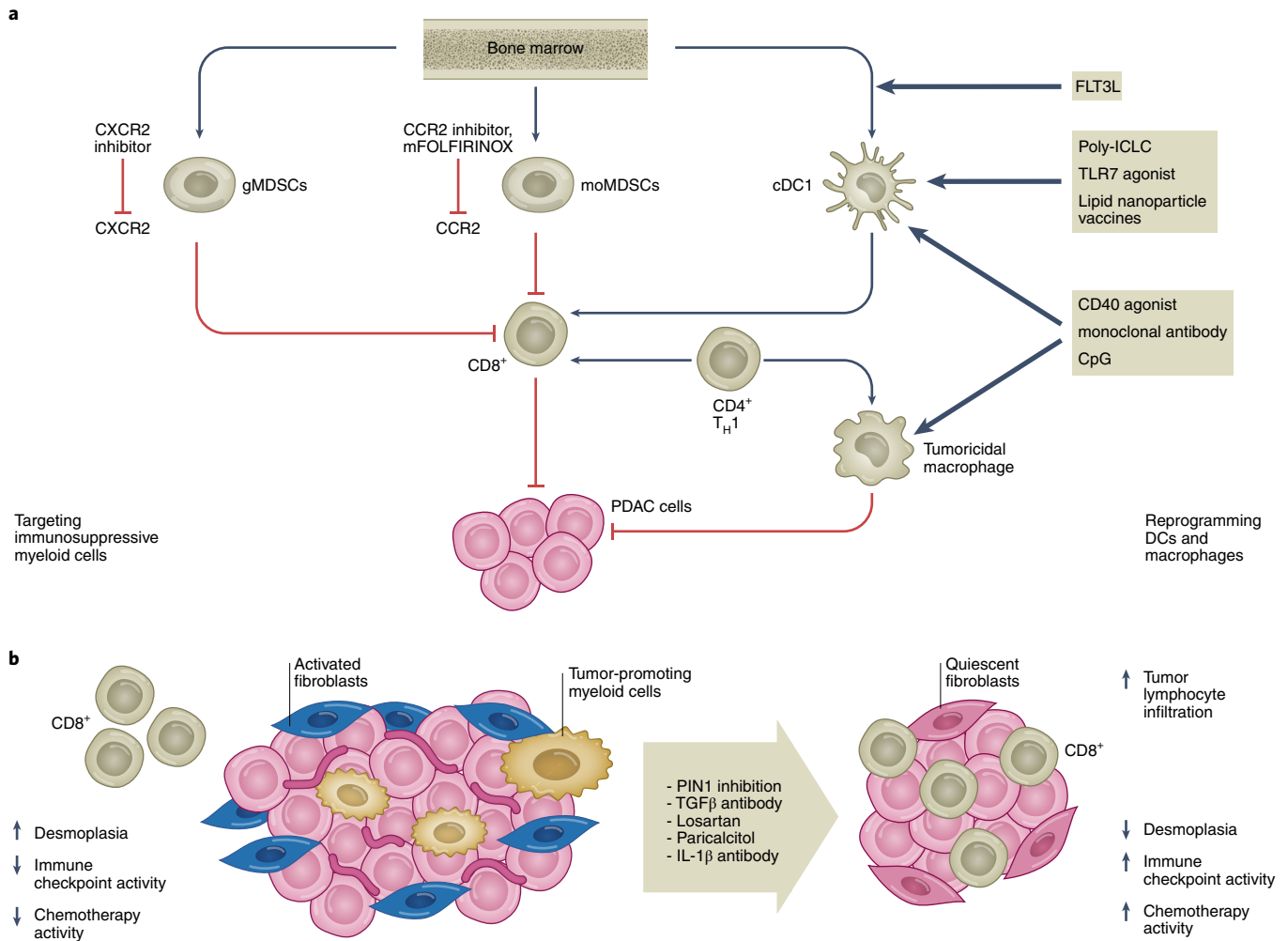
Fig. 2 | Translational immunotherapeutic approaches to PDAC. a, Schematic representation of two immunotherapy approaches to PDAC: targeting immunosuppressive myeloid cells and reprogramming DCs and macrophages, with both strategies converging on increased CD8^{+} lymphocyte activity against PDAC cancer cells. Specific receptors amenable to therapeutic intervention on the immunosuppressive myeloid cells granulocytic MDSCs (gMDSCs) and moMDSCs are CXCR2 and CCR2, respectively. FLT3 ligand (FLT3L) promotes the recruitment of cDC1s from the bone marrow, while agonistic anti-CD40 monolonal antibody and CpG promote cDC1 and tumoricidal macrophage activity. Three other denoted molecules (polyinosinic–polycytidylic acid and poly-L-lysine (poly-ICLC), Toll-like receptor 7 (TLR7) agonist and lipid nanoparticle vaccines) exert potential anti-PDAC antibody activity primarily through increased activity of cDC1s. **b**, The PDAC microenvironment features poor infiltration of cytotoxic T cells and a desmoplastic stroma with an abundance of activated fibroblasts, extracellular matrix proteins and tumor-promoting myeloid cells. Reprogramming of activated fibroblasts through one of several investigational approaches may attenuate the desmoplastic stroma and improve PDAC chemotherapy and ICB sensitivity. IL-1β, interleukin-1β; PIN1, peptidyl-prolyl *cis-trans* isomerase NIMA-interacting 1; T_H1 cell, type 1 helper T cell.

is seeking to assess the response of CCR2 inhibition in combination with the anti-PD-1 monoclonal antibody nivolumab plus chemotherapy (NCT03496662)[161]. However, because chemotherapy affects hematopoietic cell survival and differentiation, as do concurrent therapies, such as a recombinant G-CSF, how these treatments affect MDSCs should be thoroughly investigated.

Reprogramming DCs. Given the limited efficacy of strategies aimed at reinvigorating exhausted T cells in pancreatic cancer, whether the central issue in patients with PDAC is endogenous T cell exhaustion or a lack of T cell priming remains an open question[162]. Studies in mice have revealed the importance of cross-presenting type 1 conventional dendritic cells (cDC1s) in priming tumor-specific CD8^{+} T cell responses and the dearth of these cells in pancreatic cancer[163,164]. Indeed, a direct comparison of mouse models of PDAC versus lung adenocarcinoma showed a distinct lack of CD103^{+}

cDC1s in PDAC. FLT3L treatment increases intratumoral cDC1s and restores sensitivity to CD40 agonist antibody and radiation therapy in PDAC mouse models[164]. Ongoing early-phase clinical trials will soon determine the tolerability and efficacy of CD40 agonist antibody in combination with FLT3L in PDAC and other solid tumors (NCT04536077 and NCT03329950)[165,166].

DCs phagocytose tumor cell fragments and present antigenic peptides on MHC class I and class II. Following activation, DCs express costimulatory ligands and upregulate CCR7 to travel to draining lymph nodes and prime naive CD8^{+} and CD4^{+} T cells[129]. This process is dependent on the presence of innate immune adjuvants, including damage-associated molecules, such as ATP or HMGB1, released from dying tumor cells[157]. Although tumor cell death can activate DCs, phagocytosis of tumor cell fragments also induces regulatory programs in DCs that hinder their subsequent engagement with T cells[167]. This regulatory program can be

Table 2 | Selected vaccine clinical trials in PDAC

Vaccine candidate	Molecular targets	Mechanism	Phase of trial	Trial design	Population	Primary endpoints	Number of individuals	Clinical trial reference
mRNA-5671/V941	KRAS^{G12D}, KRAS^{G12V}, KRAS^{G13D}, KRAS^{G12C}	mRNA against *KRAS* elicits T cell response	1	Two-arm trial: drug alone and drug plus pembrolizumab	Basket trial with *KRAS*-mutated NSCLC, colorectal cancer or pancreatic adenocarcinoma	Dose-limiting toxicities, adverse events	N/A	54
ELI-002	KRAS^{G12D}, KRAS^{G12R}	Lipid-conjugated immune-stimulatory oligonucleotide plus a mixture of lipid-conjugated peptide-based antigens	1/2	The phase 2 component will include 90 patients with PDAC randomized to vaccine or observation	Basket trial with *KRAS*-mutated PDAC, colorectal cancer, NSCLC, ovarian cancer, cholangiocarcinoma bile duct cancer or gallbladder carcinoma. Individuals will have a positive circulating tumor DNA assay after definitive therapy	Dose-limiting toxicities (phase 1 component), relapse-free survival (phase 2 component)	158 total (90 PDAC in phase 2 component)	218
KRAS peptide vaccine + poly-ICLC		Targeted long peptide vaccine elicits immune response against mutant KRAS	1	Single-arm, sequential assignment of individuals	Individuals at high risk of developing PDAC by family history or germline mutation status	Drug-related toxicities, interferon-producing mutant KRAS-specific CD4$^+$ and CD8$^+$ T cells	25	219
KRAS peptide vaccine plus poly-ICLC	KRAS^{G12C}, KRAS^{G12V}, KRAS^{G12D}, KRAS^{G12A}, KRAS^{G13D}, KRAS^{G12R}	Targeted long peptide vaccine elicits immune response against mutant KRAS with the addition of enhanced cell-mediated immune response through ICB	1	Single-arm study of individuals given vaccine candidate in combination with anti-PD-1 and anti-CTLA-4 ICB	Patients with resected PDAC after neoadjuvant and/or adjuvant chemotherapy and/or radiation	Drug-related toxicities and interferon-producing mutant KRAS-specific CD8$^+$ and CD4$^+$ T cells	30	220
Neoantigen peptide vaccine plus poly-ICLC	Prioritized neoantigens and personalized mesothelin epitopes	Neoantigen peptide vaccine will be capable of generating neoantigen-specific CD4$^+$ and CD8$^+$ T cell responses	1	Single-arm study of patients with PDAC	Patients with PDAC following surgical resection and adjuvant chemotherapy	Safety of neoantigen peptide vaccine	15	221
RO7198457 (mRNA-based personalized tumor vaccine)	Tumor-associated antigens	Antigen-presenting cells take up mRNA-based vaccine and express tumor-associated antigens, leading to cytotoxic and memory T cell immune responses against the tumor-associated antigens	1	Single-arm study in which patients with PDAC undergo surgical resection followed by atezolizumab treatment, a personalized cancer vaccine and FOLFIRINOX chemotherapy	Patients with PDAC undergoing curative intent resection	Safety of a personalized tumor vaccine combined with atezolizumab and FOLFIRINOX	20	222
Synthetic personalized tumor-associated peptide vaccine therapy	Tumor-associated antigens	Antigen-presenting cells take up mRNA-based vaccine and express tumor-associated antigens, leading to cytotoxic and memory T cell immune responses against the tumor-associated antigens	I	Single-arm study in which individuals are treated with imiquimod (TLR7 agonist), pembrolizumab and vaccine therapy	Patients with advanced PDAC and colorectal cancer	Demonstrate feasibility of custom vaccine. Demonstrate that the custom peptide-based vaccine in combination with pembrolizumab is safe	60	223

N/A, not applicable.

overcome by exposure of DCs to microbial products that engage TLR signaling, such as the viral nucleic acid mimetic pIpC or CpG DNA, and these innate immune adjuvants are being incorporated into vaccine strategies[168]. Other approaches include targeted agents that affect DNA replication and repair pathways, which activate the STING pathway, leading to type I interferon production, which in turn promotes DC activation[169].

Therapeutic cancer vaccines have historically been unsuccessful, although recent developments have reignited interest in this topic (Table 2). Mutant KRAS epitopes are presented on multiple human

Table 3 | Selected immunotherapy trials in PDAC

Strategy	Molecular target	Cell targets	Preclinical/clinical reference	Active clinical trial(s)
Removing short-lived immunosuppressive myeloid cells	CCR2	Infiltrating monocytic immunosuppressive cells	158,224	161
	CXCR2	Infiltrating granulocytic immunosuppressive cells	156	225
Reprogramming DCs to better prime tumor-specific T cell responses	FLT3L and CD40 (agonism)	FLT3L mobilizes conventional DC from bone marrow. CD40 agonism activates cDCs within the tumor microenvironment	163,164	165,166
Reprogramming PDAC-associated fibroblasts	Vitamin D receptor	PDAC-associated fibroblasts	226	198,199
Blocking immunosuppressive TGFβ signaling	Angiotensin II receptor	PDAC-associated fibroblasts	197	196
Blocking immunosuppressive TGFβ signaling	TGFβ	PDAC-associated fibroblasts	192,194	195
Blocking immunosuppressive IL-1β signaling	IL-1β	PDAC-associated fibroblasts	189,205	207

HLA alleles and can elicit antitumor T cell responses in patients with cancer, suggesting that direct T cell recognition of mutant KRAS is possible in at least a subset of individuals[52,53]. Analysis of blood from healthy donors with diverse *HLA* haplotypes revealed that mutant *KRAS*-specific T cells could be readily expanded from the naive repertoire[170]. Given the early emergence of *KRAS* mutations in preneoplastic lesions, *KRAS*-mutant-specific T cells may acquire tolerance early in the oncogenic process. However, the near-ubiquitous presence of mutant *KRAS* in PDAC and its known role as a key oncogenic driver makes KRAS an ideal target for personalized vaccine approaches. Moreover, the development of better computational tools for candidate neoantigen prioritization and the emergence of improved vaccine delivery platforms will spur the development of efficacious personalized vaccines for PDAC[171,172].

Targeting macrophages. Macrophages are highly abundant in PDAC, and they participate in tissue repair, support epithelial cell growth and have tumor-promoting properties[158]. Nevertheless, macrophage depletion strategies in solid tumors have limited efficacy due to compensatory increases in other myeloid cell populations[157]. Therapies aimed at reprogramming macrophages to phagocytose and kill live tumor cells may provide an interesting twist to this approach. Tumoricidal macrophages were first identified in PDAC treated with agonistic anti-CD40, an antibody that activates the phagocytic program in macrophages[173]. Anti-CD40 antibody seemed to operate independently of T cells, although it was later found to activate DCs and enhance T cell priming in addition to its effects on macrophages[174–176]. A recent phase 2 trial testing anti-CD40 antibody, anti-PD-1 antibody and GnP revealed no benefit of inclusion of anti-CD40 antibody, suggesting that the T cell-priming role of anti-CD40 antibody in human PDAC may not be its central mechanism of action[177]. Determining how to better exploit the macrophage-potentiating role of anti-CD40 in combination therapy for PDAC may prove fruitful. Tumoricidal macrophages were also reported in mice treated with the NF-κB modulator LCL-161, which induced lymphotoxin production from T cells that reprogrammed macrophages to phagocytose and kill live pancreatic tumor cells[178,179], indicating potential alternate pathways for tumoricidal macrophage induction.

The receptor–ligand interactions that govern macrophage uptake of live tumor cells are still largely unknown. The 'don't eat me' ligand CD47 on tumor cells can engage SIRPα on macrophages and prevent phagocytosis, although blockade of CD47 alone has little effect in most solid tumors without provision of a prophagocytic signal[180–183]. Activation of macrophages with the TLR9 ligand CpG can induce phagocytosis even of tumor cells expressing CD47 (ref. [184]). Antibodies of IgG1 subclasses engage Fc receptors on macrophages and can strongly induce phagocytosis[185]. These translational approaches inducing tumoricidal macrophages are of great interest, and only clinical testing will inform of their actual efficacy in patients with PDAC.

Targeting cancer-associated fibroblasts. Activated fibroblasts are a major source of myeloid cell-recruiting chemokines. Although broad targeting of PDAC cancer-associated fibroblasts has been unsuccessful[186,187], increased understanding of the heterogeneity of the fibroblast compartment has led to a resurgence in interest in targeting subsets of fibroblasts or their secreted products[188–191].

Antibodies that target TGFβ result in pleiotropic phenotypes, including decreased intratumoral fibroblasts, relieved CD8+ T cell suppression and reduced myeloid cell infiltration[192–194]. An anti-TGFβ monoclonal antibody (NIS793) in combination with GnP and PD-1 blockade is currently being evaluated in a phase 2 clinical trial (NCT04390763)[195]. The angiotensin II receptor antagonist losartan acts partly via decreased TGFβ levels and is also being tested in combination with PD-1 blockade and chemoradiation in resectable PDAC (NCT03563248)[196,197]. Fibroblast quiescence may also be achieved using vitamin D[157], and two phase 2 clinical trials of paricalcitrol with GnP (NCT03520790)[198] and with PD-1 blockade plus GnP/cisplatin (NCT02754726)[199] in patients with metastatic PDAC are underway.

PIN1 mediates the phosphorylation and activation of >60 oncoproteins and inactivation of >30 tumor suppressor genes, many of which are downstream of oncogenic *KRAS*[200]. A high-throughput small-molecule screen identified all-trans retinoic acid (ATRA) to directly bind, inhibit and degrade PIN1 in vivo[201]. A selective inhibitor of PIN1, sulfopin, has also demonstrated efficacy in orthotopic mouse models[202]. ATRA plus arsenic trioxide or sulfopin treatment in PDAC models promotes a quiescent cancer-associated fibroblast state and thereby diminishes the PDAC desmoplastic response; additionally, PIN1 inhibition leads to decreased degradation of the gemcitabine plasma membrane transporter (ENT1), enhancing chemosensitivity, and it may synergize with immunotherapy[202,203]. Finally, chemotherapy plus ATRA showed promise in a phase 1 clinical trial in metastatic PDAC[204], indicating that PIN1-based stromal reprogramming strategies are worth further investigation.

IL-1β is actively produced by macrophages and granulocytes in PDAC and has pleiotropic effects on the tumor microenvironment, including supporting inflammatory cancer-associated fibroblasts, which produce IL-6 and have been shown to support

an immunosuppressive microenvironment and tumor cell survival[189,205]. IL-1β may also be produced by PDAC tumor cells, and blockade of IL-1β in preclinical models synergizes with PD-1 blockade[206]. The IL-1β-blocking antibody canakinumab and PD-1-blocking antibody spartalizumab are currently being evaluated in combination with GnP in a phase 1 clinical trial (NCT04581343)[207]. Canakinumab limits the incidence of lung adenocarcinoma[208], and the role of innate inflammatory cytokines in tumor-promoting inflammation is recognized[209]. Whether blockade of IL-1β will be effective in established tumors remains to be determined.

Future directions

Over the past decade, we have gained a deep understanding of recurrent driver mutations in PDAC by in-depth analyses of human samples and GEMMs. These tools have delineated specific vulnerabilities in PDAC and have improved our understanding of the tumor microenvironment. Future translational studies using PDAC GEMMs will need to account for the real-world presence of multiple driver genes. As we have seen with the recent successful approvals of PARP inhibitors and PD-1 blockade for molecularly defined subclasses of PDAC, precision-based and immunotherapy-based preclinical and clinical pipelines open new therapeutic avenues. The ongoing developments in KRAS-specific inhibitors is especially encouraging for PDAC. As encountered in other major malignancies, once these therapies reach the clinic, we will need to address how they will be given in concert with current standard of care chemotherapy. In addition, understanding the mechanisms of chemotherapy resistance in PDAC is essential to control this systemic illness. Lastly, as PDAC treatment approaches hopefully advance, attention will also need to focus on measures aimed at improving the quality of life of patients, such as cancer-associated cachexia. We predict that the next decade will feature an abundance of precision oncology approaches to this recalcitrant cancer, which will benefit an ever-larger group of patients.

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Competing interests

Additional information