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REVIEW ARTICLE

Treating Pancreatic Ductal Adenocarcinoma: The Targeted Revolution is Here

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies and is a rising cause of morbidity and mortality. An immunosuppressive, hostile tumor microenvironment, and *KRAS*-driven biology have contributed to poor outcomes in PDAC. Recent breakthroughs in targeting tumors with homologous repair deficiency, $KRAS^{G12C}$ mutations, rare gene fusions, and other molecular abnormalities have improved outcomes in subsets of patients. KRAS inhibitors, both allele specific and pan(K)RAS, claudin-targeting biologics, and PRMT5 inhibitors have demonstrated single agent activity in pretreated, biomarker selected PDAC. An improved understanding of the tumor immune microenvironment has facilitated the development of promising cancer vaccines and immunomodulating agents. This review summarizes the current state of PDAC therapeutics and describes drug development targets that will transform outcomes in PDAC in the proximate future.

Key Points

RAS therapeutics are anticipated to improve outcomes in pancreatic cancer and change treatment paradigms.

Other promising biomarker-selected therapeutics are in late-stage development in pancreatic cancer, including agents targeting *MTAP* deletion (PRMT5 inhibitors), claudin, and novel immunomodulatory compounds.

Future challenges include identifying and prioritizing therapeutic combinations of greatest potential for clinical development.

1 Background

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related mortality, following lung and colorectal malignancies. PDAC is arguably the most lethal malignancy with a 5-year survival rate of 8% and incidence rates continue to increase by approximately 1% per year [1]. Despite a revolution in immune-modulatory and targeted therapies, which have transformed outcomes in many cancer types, chemotherapy combinations are the mainstay for most patients with PDAC. However, improvements in molecular characterization and drug development augur the beginning of a more personalized and targeted approach to treatment of PDAC. These advancements have already improved outcomes for patients with germline *BRCA1* and *BRCA2* variants, mismatch repair deficient tumors, and $KRAS^{G12C}$ mutations. Although each of these groups represents a small subset of PDAC, they provide proof of principle that the tumor immune microenvironment (TIME) and PDAC genomic and cellular mechanisms can be successfully targeted.

Activating *KRAS* mutations are the underpinning of PDAC oncogenesis and pathology and are identified in approximately 95% of cases [2]. An additional 3% of cases have alternative mitogen-activated protein kinase (MAPK) pathway alterations, leaving only 2% of cases that are truly $MAPK^{WT}$ [2]. These mutations transform a fundamental regulator of cell survival and

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division, into a constitutively "on" pathway facilitating unregulated tumor cell growth and invasion. Decades of approaches of targeting KRAS directly and indirectly have been unsuccessful, and targeting of other MAPK pathway targets has not shown promise in PDAC outside of *BRAF*^{V600E} mutant disease [3]. However, KRAS^{G12C} inhibitors have recently shown efficacy and gained approval in non-small cell lung cancer (NSCLC) [4, 5], colorectal cancer [6], and guideline endorsement in PDAC [7]. *KRAS*^{G12C} mutations are present in about 1% of PDAC, but KRAS^{G12C} inhibitors have paved the way for the ongoing development of numerous targeted therapies against specific mutant alleles of KRAS (particularly KRAS^{G12D}) and activated KRAS.

In *KRAS* mutant PDAC, the most common comutations of driver oncogenes include *TP53* (78%), *CDKN2A/B* (39%), and *SMAD4* (24%), which have to date not represented promising targets for drug development [2]. However, homozygous deletion of 9p21 resulting in *CKDN2A* and *MTAP* loss, makes tumors susceptible to PRMT5- and MAT2A-inhibition and antifolate therapies [8]. In the *KRAS*^{WT} subtype of PDAC, a more heterogeneous genomic landscape is seen. Such genomic features include actionable targets, including alterations in *BRAF*, *NTRK*, *ALK*, *NRG1,* and higher levels of microsatellite instability (MSI-H) relative to *KRAS* mutant PDAC [2].

Improved understanding of the TIME also has the potential to create novel avenues for antineoplastic therapies. PDAC displays a unique, immunosuppressive TIME that limits penetration by drugs and antineoplastic immune cells. This is due both to a dense, fibrotic stroma that presents a physical barrier and generates high interstitial pressure and hypoxia, and immunosuppressive cells that inhibit cytotoxic T-cell migration, proliferation, and activation [9, 10]. Disruption of the fibrotic stroma [11] and of immunosuppressive signaling [12, 13] has been attempted in PDAC through a variety of approaches, with thus far limited therapeutic success excepting the 1% of patients with mismatch repair deficient (dMMR)/MSI-H tumors [14]. A deeper understanding of the nuances of immunosuppressive signaling in PDAC has the potential to reverse this trend through better understanding of biology, improved target identification, and more efficacious therapeutics. Randomized trials of tumor neoantigen vaccines and agents targeting the immunosuppressive adenosine and CXCL12/CXCR4 pathways are ongoing.

Herein, we summarize the current standard of care in PDAC, and describe the most promising targets for PDAC, that are anticipated to transform outcomes in this recalcitrant disease.

2 Standard of Care Therapies

2.1 Best Available Chemotherapy Regimens for mPDAC

The established standard of care first line therapies in metastatic PDAC (mPDAC) are modified FOLFIRINOX (mFOLFIRINOX, folinic acid [leucovorin, LV], fluorouracil [5-FU], irinotecan, and oxaliplatin) and gemcitabine with nab-paclitaxel (GNP), both of which demonstrated superior median overall survival (mOS) when compared with gemcitabine monotherapy in phase III randomized controlled trials (11.1 versus 6.8 months, hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.45–0.73, $P < 0.001$ for FOLFIRINOX; 8.5 versus 6.7 months, HR 0.72, 95% CI 0.62–0.83, $P < 0.001$ for GNP) [15, 16]. More recently, NALIRIFOX (LV, 5-FU, nanoliposomal irinotecan [nal-IRI], oxaliplatin) gained approval in this population, after demonstrating superior overall survival (OS) when compared with GNP in the NAPOLI 3 trial (11.1 months [95% CI 10.0–12.1] with NALIRIFOX versus 9.2 months [8.3–10.6] with GNP, HR 0.83, 95% CI 0.70–0.99; $P = 0.036$) [17]. Gemcitabine with capecitabine is an alternative first line treatment regimen, but is rarely used [18]. In clinical practice decisions between these three regimens are often based on patient functional status and patient and physician preferences, with GNP having fewer gastrointestinal and neuropathic side effects compared with three-drug regimens, but more alopecia and anemia. Regardless of treatment approach, dose modifications are often necessary to maximize tolerability and time on therapy. Dose adjustments were associated with improved survival in phase III clinical trials of GNP and NALIRIFOX [19, 20]. Although this finding may be confounded as patients who stay on therapy longer have more time to undergo changes in dosing, it suggests that careful dose reductions do not compromise efficacy and can lead to increased time on therapy, cumulative dose received, and improved patient outcomes.

In a second line setting, patients initially treated with FOLFIRINOX and NALIRIFOX are generally treated with GNP. In the NAPOLI-1 trial in patients who had received prior gemcitabine-based therapy, nal-IRI with 5-FU and LV demonstrated superior mOS when compared with LV with 5-FU (6.1 months [95% CI 4.8–8.9] versus 4.2 months [3.3–5.3] with 5-FU, HR 0.67, 95% CI 0.49–0.92; $P = 0.012$) and is currently a standard of care in this setting [21].

Most large, randomized trials have demonstrated a mOS of less than a year regardless of first-line regimen, and second line treatment regimens generally demonstrate mOS of about 6 months. Given these poor outcomes, and the

promising targets described herein, clinical trials represent an appropriate, and often preferred consideration in any treatment setting in PDAC. An algorithm describing approach to mPDAC treatment is illustrated in Fig. 1.

2.2 Best Available Adjuvant and Neoadjuvant Treatment Approaches for PDAC

Nonmetastatic PDAC includes resectable, borderline resectable, and locally advanced disease. The NCCN defines borderline resectable disease as solid tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) > 180° or any contact with contour irregularity or thrombosis of the vein potentially suitable for vascular reconstruction. Locally advanced PDAC is not currently amenable to resection, typically owing to celiac artery (CA) or superior mesenteric artery (SMA) > 180° involvement [22].

For patients with nonmetastatic PDAC, perioperative GNP, FOLFIRINOX, and gemcitabine with capecitabine have demonstrated efficacy without clear data to support superiority of one particular regimen [23, 24]. Six months of perioperative chemotherapy is a standard of care across multiple trials, but the optimal timing of chemotherapy within those 6 months of therapy is a topic of ongoing investigation. In patients with borderline resectable or locally advanced disease, several trials indicate a benefit from receipt of some chemotherapy prior to initial surgery [24, 25]. In patients with resectable disease, subgroup analyses from trials of nonmetastatic PDAC have not demonstrated a clear benefit to neoadjuvant therapy. The NORPACT-1 trial demonstrated superior mOS in patients who underwent upfront surgery compared with initial neoadjuvant mFOLFIRINOX (38.5 months [27.6–not reached (NR)] versus 25.1 months [95% CI 17.2–34.9], HR = 1.52 [95% CI 1.00–2.33], $P = 0.050$) [25, 26] indicating that fit resectable patients may do best with upfront resection and adjuvant FOLFIRINOX [27].

Data from the Italian CASSANDRA trial (Short-course Versus Long-course Pre-operative Chemotherapy With mFOLFIRINOX or PAXG) presented at the 2025 American Society of Clinical Oncology Annual Meeting compared neoadjuvant PAXG (gemcitabine, cisplatin, nab-paclitaxel, capecitabine) with mFOLFIRINOX in 260 patients with resectable or borderline resectable PDAC. The study reported a 16.0 month event free survival (EFS, survival without identification of metastatic disease, 95% CI 12.4–19.8) with PAXG versus 10.2 months (8.6–13.5) with mFOLFIRINOX (HR 0.63, 0.47–0.84, $p = 0.0018$) [28]. Grade 3 neutropenia was more common in PAXG but toxicity profiles were similar [29]. EFS was equivalent between patients treated with 4 versus 6 months of PAXG, although, 6 months of treatment resulted in a higher rate of N0 resection [30]. The use of this regimen may grow with publication of the final results, although to date traction has largely been in Europe.

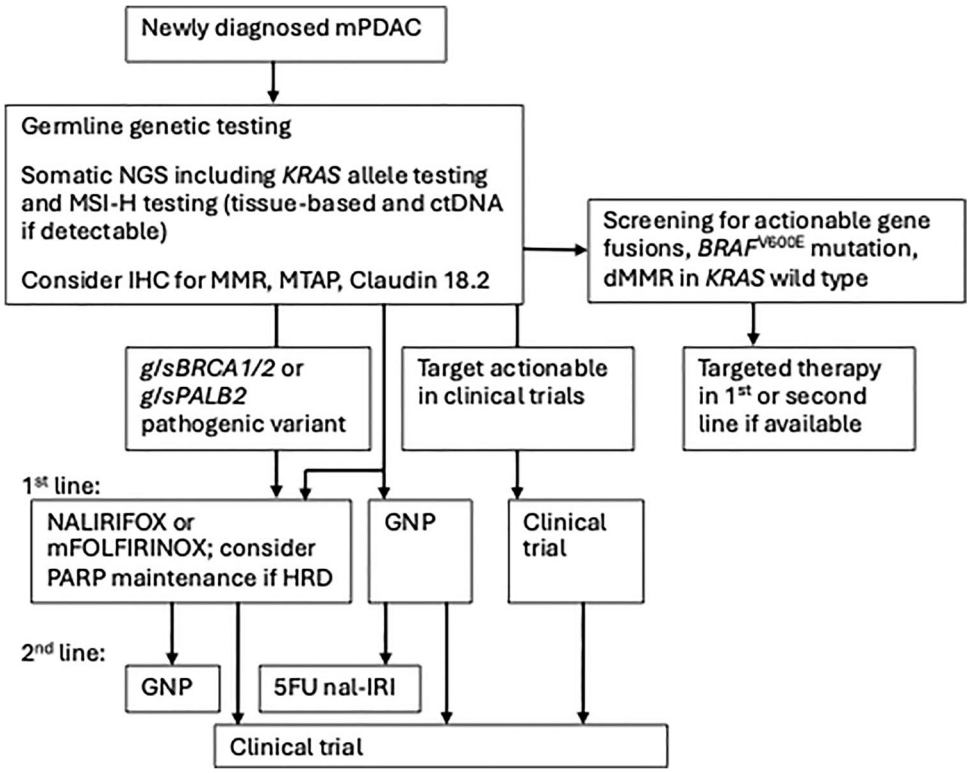

Fig. 1 Flowchart of biomarker testing and current treatment paradigms for metastatic pancreatic ductal adenocarcinoma (mPDAC)

2.3 Locoregional Therapies in Pancreatic Cancer

Surgical resection with pancreaticoduodenectomy or distal pancreatectomy depending on tumor location is the primary method of local tumor control in operable PDAC. The addition of radiation has historically not shown benefit as a routine addition to perioperative chemotherapy, and its use has been primarily limited to palliation and inoperable nonmetastatic disease [24]. However, recent studies have revisited the role of locoregional therapies as part of definitive therapy for PDAC. A single arm study of ablative radiation in patients with technically resectable PDAC with a median age of 80 years demonstrated an OS and distant metastasis-free survival at 2 years of 43.7% (95% CI 27.4–69.5%) and 20.0% (95% CI 9.1–43.8%) [31]. Tumor treating fields (TTFs) deliver low-intensity electric fields that disrupt cancer cellular processes. They are delivered by a device worn on the skin near the tumor and have shown efficacy in lung cancer [32]. A phase 3 trial demonstrated a significant improvement in mOS when TTFs were added to gemcitabine with nab-paclitaxel in locally advanced PDAC (16.2 months [95% CI 15.0–18.0] versus 14.2 months [95% CI 12.8–15.4]; HR 0.82 [95% CI 0.68–0.99]; $P = 0.039$) as well as improvements in distant PFS and pain-free survival [33].

2.4 Comparative Efficacy of Approved Cytotoxic Regimens and Predictive Markers of Response

Given the limited number of available treatment regimens for biomarker unselected PDAC, there has been considerable interest in comparing the efficacy of these regimens. The NAPOLI-3 trial compared NALIRIFOX with GNP in untreated mPDAC and found that NALIRIFOX improved both mOS (11.1 versus 9.2 months) and median progression free survival (mPFS, 7.4 versus 5.6 months) [17]. The mOS noted in this trial closely mirrored the survival from trials leading to the original approval of FOLFIRINOX (11.1 months) [16] and GNP (8.5 months) [15], indicating similar outcomes with FOLFIRNOX and NALIRIFOX with potential superiority over GNP. SWOG S1505 identified equivalent OS between GNP and FOLFIRINOX in a randomized phase II trial in the perioperative setting for resectable PDAC (mOS 23.2 months [95% CI 17.6–45.9] with mFOLFIRINOX versus 23.6 months with GNP [95% CI 17.8–31.7]) [23]. The PASS-01 trial (Pancreatic Adenocarcinoma Signature Stratification for Treatment) compared mFOLFIRINOX and GNP in 160 patients with treatment naive mPDAC. mOS favored GNP (8.5 versus 9.7 months with GNP, HR 1.57 [95% CI 1.08–2.28]; $P = 0.017$), while mPFS was not significantly different between the two arms (4.0 versus 5.3 months for GNP (HR 1.37 [95% CI 0.97–1.92]; $P = 0.069$)) [34]. The GENERATE trial (Modified Fluorouracil, Leucovorin, Irinotecan, and Oxaliplatin or S-1, Irinotecan, and Oxaliplatin Versus Nab-Paclitaxel + Gemcitabine in Metastatic or Recurrent Pancreatic Cancer), terminated early for futility, also found a numerically superior mOS of 17.1 months with GNP, compared with 14.0 months with mFOLFIRINOX (HR 1.31 [95% CI 0.97–1.77]) [35]. The outcomes of trials evaluating the efficacy of mFOLFIRINOX, NALIRIFOX, and GNP in mPDAC are summarized in Table 1.

Table 1 Survival outcomes of patients treated with mFOLFIRINOX, NALIRIFOX and GNP in completed trials in untreated mPDAC

Trial (year of results publication)	# patients in trial	GNP		mFOLFIRINOX/FOLFIRINOX		NALIRIFOX		HR for mOS	*P* value for mOS
		mOS	mPFS	mOS	mPFS	mOS	mPFS		
MPACT (2013) [15]	861	8.5 (7.9–9.5)	5.5 (4.5–5.9)					0.72	< 0.001
PRODIGE (2011) [16]	342			11.1 (9.0–13.1)	6.4 (5.5–7.2)			0.57	< 0.001
NAPOLI-3 (2023) [17]	770	9.2 (8.3–10.6)	5.6 (5.3–5.8)			11.1 (10.0–12.1)	7.4 (6.0–7.7)	0.83	0.036
PASS-01 (2025) [34]	160	9.7 (7.9–16.5)	5.1 (3.9–6.7)	8.5 (7.6–10.4)	4.0 (3.1–6.1)			1.37	0.017
GENERATE (2025) [35]	527	17.1 (14.5–19.2)	6.7 (5.7–7.4)	14.0 (11.3–16.2)	5.8 (5.1–6.9)			1.31	> 0.05

All times are in months; values in parentheses indicate 95% CI; HRs for NAPOLI-3, PASS-01 and GENERATE are for risk of death in mFOLFIRINOX/NALIRIFOX arm compared with GNP arm, HRs for MPACT and PRODIGE are for risk of death with GNP/FOLFIRINOX arm compared with gemcitabine monotherapy arm

GNP gemcitabine nab-paclitaxel, *(m)FOLFIRINOX* (modified) 5-fluorouracil oxaliplatin irinotecan leucovorin, *mOS* median overall survival, *mPDAC* metastatic pancreatic ductal adenocarcinoma, *mPFS* median progression free survival, *NALIRIFOX* nano-liposomal irinotecan leucovorin 5-flurouracil oxaliplatin

A possible explanation for these outcome differences is that different subtypes of PDAC respond differently to particular chemotherapy regimens. Many investigators classify PDAC into two distinct molecular subtypes: "classical" and "basal-like." The "basal-like" subtype has worse outcomes and is molecularly similar to basal tumors in bladder and breast cancers [36]. The "classical" subtype is enriched for genes associated with overexpression of *GATA6*, a gene that promotes epithelial cell differentiation [36]. GATA6 protein expression is often used as a surrogate for the identification of "classical" phenotype PDAC.

The PASS-01 trial incorporated multiple translational endpoints to correlate molecular subtypes with clinical outcomes. Biopsies were used for whole-genome and transcriptome sequencing and GATA6 ISH was performed on baseline histology slides. "Classical" phenotype and high expression of GATA6 ISH were associated with better prognosis, consistent with prior studies [37, 38]. There were trends towards inferior overall response rate (ORR) (19% versus 45%, $P = 0.20$) and mPFS (3.0 months versus 5.5 months (HR 1.76 [95% CI 0.77–4.02]; $P = 0.17$) with mFOLFIRINOX compared with GNP in patients with "basal-like" phenotype tumors. In "classical" tumors mPFS was numerically better with mFOLFIRINOX (6.3 versus 5.4 months; HR 1.26 [95% CI 0.77–2.07]; $P = 0.36$) with equivalent ORR between the groups (33% versus 31% with GNP, $P = 0.55$). Molecular subtype did not significantly modulate mOS in PASS-01 with mFOLFIRINOX associated with numerically worse mOS in both "classical" (9.7 versu 13.9 months; HR 1.80 [95% CI 1.0–3.23], $P = 0.047$) and "basal-like" tumors (7.5 versus 8.9 months; HR 1.14 [95% CI 0.49–2.66]; $P = 0.75$) [34]. This is consistent with data from prior studies indicating that GATA6-low or "basal-like" tumors are more likely to derive benefit from GNP whereas GATA6-high or "classical" tumors may benefit more from mFOLFIRINOX [38, 39]. Given the currently available data, mFOLFIRINOX/NALIRIFOX is often the initial regimen of choice in fit patients with untreated mPDAC, although GNP is increasingly used in a first line treatment setting based on the PASS-01 and GENERATE trial results. It is important to recognize that designation of "classical" and "basal" subtypes need to account for tumor heterogeneity and plasticity, contributing to the challenges of biomarker validation in clinical decision-making.

The toxicity profile of GNP makes it a safe and reasonable choice in patients expected to be at increased risk of toxicity from a triplet chemotherapy regimen. In elderly patients, including those who are frail or have ECOG performance status (PS) 2, multiple studies have demonstrated the efficacy and tolerability of GNP [40, 41]. ECOG-ACRIN EA2186 compared GNP with 5-FU/LV and nal-IRI in vulnerable, elderly patients with mPDAC, a group that has historically been undertreated and underrepresented in clinical trials [42–44]. Outcomes were similar and poor in both treatment groups (mOS 4.7 months GNP versus 4.4 months 5-FU/LV and nal-IRI, $P = 0.72$) [44]. A phase II trial evaluated upfront dose reductions in nab-paclitaxel as part of GNP in patients with PDAC and ECOG PS 2 and found acceptable safety and at either 100 and 125 mg/m^2 [45]. Extrapolating from these results, many providers further modify the GNP regimen to be administered every other week or 2 out of every 3 weeks in patients not expected to tolerate full-dose therapy.

3 Standard of Care Therapies for Biomarker Selected PDAC

For approximately 10% of patients with PDAC, biomarker selected therapies are approved for treatment. Patients with germline homologous recombination deficiency (HRD) mutations and those with *KRAS*^{WT} PDAC tumors make up the majority of such cases. The trials leading to the approval of these targeted therapies are summarized in Table 2.

3.1 Homologous Recombination Deficiency

Cells with pathogenic mutations in *BRCA1, BRCA2,* or *PALB2* are deficient in homologous recombination (HRD), or the repair of DNA double-strand breaks. This deficiency promotes indirect oncogenesis, and resultant neoplasms are unable to repair double strand breaks properly, amplifying the genotoxicity from DNA damaging agents. These therapies include platinum derivatives and inhibitors of poly (ADP-ribose) polymerase (PARP) [46]. One retrospective cohort of 262 patients with PDAC identified 50 (19%) with HRD (15% germline and 4% somatic). Patients with HRD had improved PFS compared with no HRD when treated with first-line platinum-based chemotherapy (HR 0.44 [95% CI 0.29–0.67], $P < 0.01$), making platinum chemotherapy the recommended first-line therapy [47]. In addition to mFOLFIRINOX, gemcitabine and cisplatin is an acceptable first line regimen in this population. A phase II trial evaluated gemcitabine and cisplatin with or without the PARP inhibitor veliparib in patients with mPDAC and germline *BRCA*/*PALB2* mutations. Although the trial failed to demonstrate improved outcomes with the addition of veliparib, outcomes with gemcitabine and cisplatin were favorable when compared with historical controls, including ORR 65.2%, mPFS of 9.7 months (95% CI 4.2–13.6) and mOS of 16.5 months (95% CI 11.7–23.4). The 3-year OS rate was 17.8% (95% CI 8.1–30.7%) for the full cohort of 50 patients [48].

PARP plays a crucial role in base excision DNA repair and effective blockade can achieve synthetic lethality in HRD-deficient tumors. This phenomenon is best studied patients with *BRCA1*, *BRCA2,* and *PALB2* germline

Table 2 Selected practice-changing completed trials of targeted therapies in PDAC

Trial name (year of publication)	# pts	Patient cohort/ molecular target	Experimental arm				Control arm			HR for mOS (*P* value)	HR for mPFS (*P* value)
			Agent	mOS	mPFS	ORR	Agent	mOS	mPFS		
POLO (2019) [52]	154	g*BRCA* mutation, no progression on platinum chemotherapy	Olaparib	18.9	7.4		Placebo	18.1	3.8	0.92 (0.68)	0.52 (0.004)
NCT03140670 (2021) [53]	46	*BRCA* or *PALB2* mutation, no progression on platinum chemotherapy	Rucaparib	23.5 (20–27)	13.1 (4.4–21.8)		NA				
KEYNOTE-158 (2020) [14]	22	dMMR/MSI-H, progression on prior therapy	Pembrolizumab	4.0	2.1	34.3%	NA				
NCI-MATCH (2020) [71]	2	*BRAF* mutation, progression on prior therapy	Dabrafenib and trametinib			50%	NA				
CodeBreaK 100 (2022) [7]	38	$KRAS^{G12C}$ mutation, progression on prior therapy	Sotorasib	6.9 (5.0–9.1)	4.0 (2.8–5.6)	21% (10-37)	NA				
NCT02650401 (2022) [62]	4	*NTRK* fusion	Entrectinib	22	13	75%	NA				
LIBRETTO-001 (2024) [65]	13	*RET* fusion	Selpercatinib	Immature	5.6 (3.2–NR)	54%	NA				
eNRGy (2025) [67]	36	*NRG1* fusion	Zenocutuzumab	Immature	9.2 (5.5–11.2)	42%	NA				

95% confidence intervals in parentheses (where available); mPFS and mOS are in months; for basket trials number of patients only includes patients with PDAC; # pts, number of patients

HR hazard ratio, *mOS* median overall survival,*mPFS* median progression free survival, *ORR*overall response rate, *PDAC* pancreatic ductal adenocarcinoma

pathogenic variants. PARP inhibitors have demonstrated efficacy in subsets of patients with breast [49], prostate [50], and ovarian cancer [51]. The POLO (Pancreas OLaparib Ongoing) study evaluated patients with germline *BRCA1* or *BRCA2* mutations, mPDAC, and disease that had not progressed during first-line platinum-based chemotherapy. Patients were randomized to receive maintenance olaparib or placebo in a 2:1 fashion. Olaparib demonstrated a superior mPFS to placebo (7.4 versus 3.8 months, HR 0.53 [95% CI 0.35–0.82], $P = 0.004$), but no mOS difference (18.9 versus 18.1 months, HR 0.91 [95% CI 0.56–1.46]; $P = 0.68$) [52]. A key criticism of this trial is the comparison to placebo rather than continuation of systemic chemotherapy. Whether olaparib or maintenance chemotherapy represents the optimal treatment approach is unknown. Rucaparib was also evaluated in the maintenance setting in platinum-sensitive mPDAC with germline or somatic pathogenic variants in *BRCA1*, *BRCA2*, or *PALB2*. In this single-arm study mPFS was 13.1 months (95% CI 4.4–21.8), and mOS was 23.5 months (95% CI 20–27). Only 2/42 patients had somatic HRD mutations so the results of this study may not be generalizable to this population [53]. Single agent PARP inhibition has been evaluated in HRD-phenotype mPDAC with progression on chemotherapy and demonstrates a very low ORR [54, 55].

3.2 Mismatch Repair Deficiency

Tumors with mismatch repair deficiency (dMMR) and/or MSI-H lack the ability to appropriately correct improperly mismatched DNA strands during transcription, leading to hundreds or thousands of somatic mutations and high levels of tumor neoantigens. These findings correlate with improved response to immunotherapy. Such tumors represent < 1% of PDAC cases [56]. The Phase II KEYNOTE-158 evaluated pembrolizumab in 233 patients with noncolorectal dMMR/MSI-H disease and progression on prior therapy. This study included 22 patients with PDAC, demonstrating one complete response, three partial responses, a mPFS of 2.1 months, and mOS of 4.0 months. Amongst the four patients with response, the median duration of response (mDOR) was 13.4 months [14]. Further studies suggest that the underwhelming clinical outcomes for patients with dMMR PDAC in this trial may result from discordance between MSI-H and dMMR in PDAC tumors. Unlike in many other malignancies where concordance between MMR and MSI testing is 95–100% [57], in PDAC the proportion of dMMR tumors that are MSI-H may be significantly lower [58]. In one cohort of 55 patients with pathogenic MMR variants by NGS, 32 had Lynch syndrome and 23 had somatic MMR variants. MSI-H was identified in 49% of patients (59% Lynch syndrome cohort, 43% somatic cohort). A total of 20 patients received immune checkpoint blockade ($n = 17$ MSI-H), the median ICB duration was 27.7 months (95% CI 11.5–NR) and the disease control rate (DCR) was 80%. Amongst 15 patients in this cohort with IHC testing, 33% had preserved MMR expression [58]. A second institutional cohort study corroborates these findings, with a discrepancy between MMR and MSI in 26% of evaluable cases, and ORR of 75% in MSI-H/dMMR PDAC treated with immune checkpoint blockade. This study also found remarkably favorable outcomes for nonmetastatic definitively treated MSI-H/dMMR PDAC recurrence rate of only 3/16 (19%) despite a median follow-up of 25 months [59]. Taken together, these results indicate that there is significant discordance between dMMR and MSI-H in PDAC and that amongst patients with MSI-H durable benefit can be achieved with immune checkpoint blockade, including pembrolizumab or ipilimumab and nivolumab [60, 61].

3.3 Other Rare Pan Tumor, Disease-Agnostic Regulatory Approvals

Several other molecular alterations have targeted therapies approved for use in PDAC. These are generally pan-tumor, disease agnostic regulatory approvals or guideline endorsements for alterations occurring in < 1% of PDAC. Many of these are tyrosine kinase gene fusions that are identified almost exclusively in $KRAS^{WT}$ PDAC, making screening for gene fusions especially important in this population [2].

For patients with mPDAC with neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion, tyrosine receptor kinase inhibitors have approval and demonstrated efficacy. Basket trials of these agents included small numbers of patients with PDAC. In trials of entrectinib, 3 of 4 patients with PDAC responded, with mPFS and mOS of 13 and 22 months, respectively [62]. In trials of Larotrectinib, one of two patients responded with a mDOR of 3.5 months [63].

In the LIBRETTO-001 open-label, basket trial of *RET* fusion solid tumors, selpercatinib demonstrated an ORR in 7 of 13 patients with PDAC including one complete response (CR) with a mDOR of 52.1 months (95% CI 2.5–NR) [64, 65]. In rare *ALK*-fusion positive PDAC, a molecular database review demonstrated an ORR of 2 of 4 evaluable patients to ALK inhibitors. As the ORR and DOR seen with tyrosine kinase inhibitors compare favorably to those normally expected with chemotherapy, these represent appropriate first line treatment options for patients with PDAC and *NTRK*, *ALK* or *RET* fusions, where this information is known at the time of front-line treatment decision-making.

Neuregulin 1 (NRG1) fusion protein binds to human epidermal growth factor 2 (HER2) and creates heterodimerization of HER2/HER3 proteins ultimately leading to uncontrolled cell growth. *NRG1* fusions are present in approximate 0.1% of PDAC cases [66] and the most common fusion partner is *ATP1B1* [67]. In addition to being

overrepresented in *KRAS*^{WT} PDAC, *NRG1* fusions are more commonly observed in early onset PDAC [68]. Zenocutuzumab was recently was FDA approved for *NRG1* fusion-positive PDAC. The eNRGy trial demonstrated responses in 15/36 patients with *NRG1* fusio- positive mPDAC and progression on chemotherapy with a mDOR of 9.1 months (42%; 95% CI 25–59) [67].

Distinct from biliary-tract cancers, there is limited data to support a role for HER2 directed therapy in PDAC [69]. The DESTINY-PanTumor02 trial evaluated trastuzumab deruxtecan in HER2 2+ or 3+ solid tumors following disease progression on initial therapy. A response was seen in only 1 of 25 patients with PDAC, compared with an ORR of 37% in the full cohort [70]. *ERBB2* mutations more commonly co-occur with *KRAS* mutations than many other MAPK alterations, and uncontrolled RAS signaling may limit efficacy of anti-HER2 therapy in patients with *KRAS*^{MUT} and HER2 expressing tumors [2].

Dabrafenib and trametinib is indicated in *BRAF*^{V600E} mutant mPDAC, although a basket trial of this combination in histology agnostic solid *BRAF*^{V600E} tumors enrolled only two patients with PDAC, with one experiencing partial response and the other progressive disease [71].

4 Promising Therapeutics in Late-Stage Development for PDAC

4.1 KRAS-Targeting Therapies

MAPK pathway activation involves binding of an extracellular mitogen to a receptor tyrosine kinase (RTK), such as EGF receptor (EGFR), leading to cellular proliferation and survival. Kirsten rat sarcoma virus protein (KRAS) is a key element in the transduction of RTK signal to the nucleus. KRAS exists in an "off" state bound to guanosine diphosphate (GDP) and an "on" state bound to guanosine triphosphate (GTP). A variety of activating signals can shift KRAS into its "on" form, and KRAS itself contains intrinsic GTPase activity to turn itself off, maintaining a closely regulated feedback loop. *KRAS* activating mutations cluster around the nucleotide-binding pocket, involving exons 2–4 at codons 12, 13, and 61, altering the balance between active

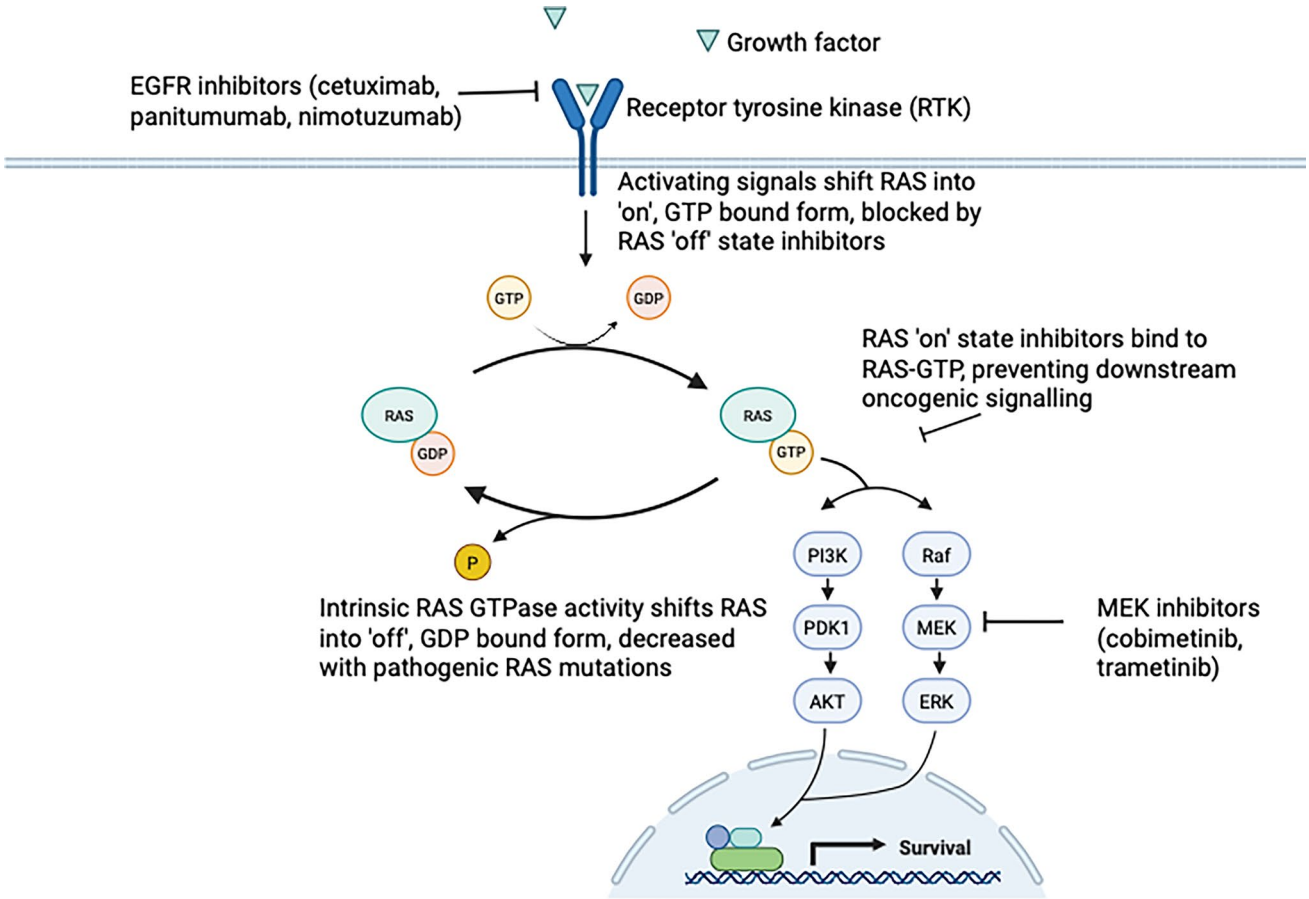

Fig. 2 RAS-MAP kinase signaling pathway (created in BioRender)

and inactive KRAS and leading to constitutive MAPK activation (Fig. 2) [6].

KRAS mutations are present in up to 95% of PDAC and some *KRAS* mutations, e.g. *KRAS*^{G12R}, are pathogenomic of PDAC. *KRAS* mutant dosage is a key predictor of outcomes in PDAC, highlighting the importance of this alteration in shaping the disease course [2]. The most common *KRAS* mutations are G12D (33–39% of all PDAC cases), G12V (25–33%), G12R (15–18%), and Q61mutations (6–8%). Other mutations including G12A and G12C each account for about 1% of cases [2, 6, 72]. The high affinity of mutated KRAS for GTP and its mostly featureless surface has made it a challenging therapeutic target [73]. The first success of direct KRAS targeting derives from the unique biochemistry of the codon 12 glycine-to-cysteine (G12C) mutation. Cysteine thiols are the most nucleophilic amino acid side chains. This is classically seen in the formation of disulfide bonds, in this case enabling disulfide-fragment-based techniques to screen hundreds of potential small-molecule targets of G12C-mutant *KRAS*, leading to the discovery of sotorasib, adagrasib, and a variety of other molecules [74]. Sotorasib and adagrasib were both initially evaluated and approved in NSCLC with very similar clinical outcomes including ORR 37–43% and mPFS 6.5–6.8 months [4, 5]. Sotorasib was evaluated in a phase 1–2 trial of 38 patients with previously treated metastatic *KRAS*^{G12C}-mutant PDAC and found to have an ORR of 21% (95% CI 10–37) with mPFS of 4.0 (95% CI 2.8–5.6) and mOS of 6.9 months (95% CI 5.0–9.1) [7]. A number of *KRAS*^{G12C} inhibitors are currently in development, with divarasib and olmorasib demonstrating improved potency and selectivity when compared with sotorasib and adagrasib in preclinical models [75]. Divarasib was evaluated in a single-arm study in *KRAS*^{G12C} mutant cancers and demonstrated an ORR of 53.4% (95% CI 39.9–66.7) in 60 patients with NSCLC. Amongst seven patients with pancreatic cancer, three had partial response and four had stable disease [76]. Olmorasib demonstrated an ORR of 40% in 88 patients with noncolorectal tumors including 24 patients with PDAC in a heavily pretreated population (median number of prior systemic therapies: 3, 33% with prior KRAS^{G12C} inhibitor receipt) [77].

Although only impactful in the 1% of PDAC with *KRAS*^{G12C} mutations, these agents provided a proof of principle that KRAS could be successfully targeted. A wide variety of other KRAS inhibitors are now in active early, mid, and late phase clinical development. These are broadly classified as allele specific inhibitors or pan-(K)RAS inhibitors, which inhibit the activity of multiple (K)RAS alleles. In theory, allele-specific KRAS inhibitors should have less toxicity, as they avoid targeting wildtype RAS in normal tissues, but increased opportunities for resistance through nucleotide-binding pocket alterations or compensatory activation of wildtype RAS isoforms [78]. RAS inhibitors can be further subdivided into those which bind to the RAS "off" state, preventing conversion to "on" state RAS, and "on" state inhibitors which bind selectively to "on" state RAS and prevent downstream signaling [78]. Tri-complex inhibitors bind to RAS through involvement and remodeling of a third party protein already present in cells, such as cyclophilin A (CypA), preventing mutant KRAS signaling through steric blockade [78].

The pan-RAS "on" inhibitor in the most advanced clinical development is the tri-complex inhibitor daraxonrasib (RMC-6236). Daraxonrasib works by binding CypA, remodeling it to form a complex that binds with high affinity to RAS-GTP. This CypA–drug–RAS–GTP complex sterically hinders RAS-effector interactions and impedes downstream oncogenic signaling [79, 80]. In a phase I clinical trial daraxonrasib (when administered at a clinically active dose of 160–300 mg daily) demonstrated an ORR of 25% (95% CI 14–38), mPFS of 8.0 months (95% CI 5.9–11.1) and mOS of 14.5 months (95% CI 8.8–NR) as second line treatment in 57 patients with *KRAS* mutant mPDAC [81]. A total of 94% of patients showed a > 50% reduction in mutant *KRAS* allele in ctDNA [80]. The most common treatment-related adverse events (TRAEs) were rash (91%), diarrhea (48%), nausea (43%), and vomiting (31%) [81]. In untreated, *KRAS* mutant mPDAC, daraxonrasib elicited an ORR of 47% and DCR 89% [82]. Multiple trials of daraxonrasib are ongoing, including a registration-intent phase III, randomized trial of daraxonrasib versus investigators' choice of standard of care chemotherapy in previously treated mPDAC that recently completed accrual (RASolute 302, NCT06625320) [76]. A three-arm phase III randomized trial comparing daraxonrasib, daraxonrasib with GNP, and GNP alone in the first-line treatment of mPDAC (RASolute 303) is planned [82]. A trial evaluating the benefit of daraxonrasib following adjuvant chemotherapy in resected PDAC has begun accrual (RASolute 304) [83, 84]. These trials will clarify the optimal timing and sequence of KRAS inhibition and evaluate whether pan-RAS inhibition is optimally combined with or sequenced before or after chemotherapy.

Most non-G12C, allele-specific KRAS inhibitors have focused on the most common target, KRAS^{G12D}, present in over 30% of PDAC [2]. As with KRAS^{G12C} inhibitors, KRAS^{G12D} inhibitors take advantage of the unique biochemistry of the amino acid side chain, in this case aspartic acid (D), although approaches vary between inhibitors. Zoldonrasib (RMC-9805) forms a noncovalent bond between KRAS^{G12D} and cyclophilin A that allows the nonreactive covalent "warhead" to slowly bind to the mutant aspartate [85]. GFH375 binds to both the "on" and "off" forms of KRAS^{G12D}. A phase I/II trial evaluated GFH375 in pretreated patients with mPDAC, with 45/68 patients having received at least two prior lines of therapy. ORR in this population was 40.7% with mPFS of 5.5 months [86,

87]. Preliminary data suggests that allele-specific KRAS inhibitors may have a more favorable side effect profile than pan-(K)RAS inhibitors, potentially facilitating tolerable combination with chemotherapy [78]. The $KRAS^{G12D}$ inhibitor HRS-4642 was evaluated in combination with GNP in untreated mPDAC, resulting in an ORR of 60% (95% CI 40.6–77.3), compared with 23% with GNP alone in the MPACT trial [15], without adverse events leading to treatment discontinuation [88].

In addition to small molecule KRAS inhibitors, other KRAS-targeting mechanisms of action are being evaluated in the treatment of PDAC. Targeted protein degraders (TPD) represent a novel approach to hard-to-drug targets. Proteolysis targeting chimeras (PROTACs) are heterobifunctional molecules consisting of a ligand for the protein of interest (POI), a ligand for an E3 ligase, and a linker. PROTACs induce the formation of a ternary complex with POI/PROTAC/E3 ligase, leading to ubiquitination of the POI and degradation by the proteasome [89]. ASP3082 is TPD that binds $KRAS^{G12D}$ and E3 ligase, resulting in $KRAS^{G12D}$ degradation [85]. In a phase I dose-escalation study, amongst heavily pretreated patients with PDAC receiving at least 140mg (the anticipated threshold for efficacy based on preclinical studies), ORR was 4/19 (21%) and DCR was 9/19 (47%) [90]. Table 3 summarizes the mechanisms and phase of development of select RAS-targeting agents in clinical development.

Data from sotorasib and adagrasib in $KRAS^{G12C}$ mutant PDAC indicate inevitable development of adaptive and acquired resistance [4, 5, 80]. Resistance to $KRAS^{G12C}$ inhibition can arise through direct modifications to activated RAS signaling ($KRAS^{G12C}$ switch-II pocket mutations, amplification of $KRAS^{G12C}$ allele, secondary *RAS* mutations) or through upregulation of other components of the MAPK pathway (upstream activation of RTK, downstream activation of RAF, MEK, ERK, PI3K) (Fig. 2) [91–93]. pan-RAS inhibitors may overcome resistance mechanisms characterized by alterations in gene product that resist allele-specific inhibitor binding [80, 94]. Early studies of resistance mechanisms to daraxonrasib as well as $KRAS^{G12D}$ inhibitors have implicated upregulation of upstream (RTK) and downstream (MYK) MAPK signaling

Table 3 Selected KRAS inhibitors in development for PDAC

Drug name	Target	Mechanism	Company	Phase
Daraxonrasib	PanRAS	On state tricomplex inhibitor	Revolution Medicines	Phase 3
LUNA018	PanRAS	Off state inhibitor	Chugai	Phase 1
ERAS-0015	PanRAS	On state inhibitor	Erasca	Phase 1
BI-3706674	PanKRAS	Off state inhibitor	Boehringer Ingelheim	Phase 1
QTX3034	PanKRAS	Small molecule inhibitor	Quanta	Phase 1
PF-07934040	PanKRAS	Small molecule inhibitor	Pfizer	Phase 1
BGB-53038	PanKRAS	Small molecule inhibitor	BeiOne	Phase 1
LY4066434	PanKRAS	Small molecule inhibitor	Lilly	Phase 1
JAB-23425	PanKRAS	On and off state inhibitor	Jacobio	Phase 1
AZD0022	G12D	On and off state inhibitor	AstraZeneca	Phase 2
MRTX 1133	G12D	Off state inhibitor	Mirati/BMS	Phase 1
Zoldonrasib/RMC-9805	G12D	On state tricomplex inhibitor	Revolution Medicines	Phase 1
LY3962673	G12D	Off state inhibitor	Eli Lilly	Phase 1
HRS-4642	G12D	Off state inhibitor	Hengrui	Phase 1
QTX3046	G12D	On and off state inhibitor	Quanta	Phase 1
INCB161734	G12D	Off state inhibitor	Incyte	Phase 1
GO45416	G12D	Off state inhibitor	Roche/Genentech	Phase 1
ASP3082	G12D	Degrader (PROTAC)	Astellas	Phase 1
VS-7375	G12D	On and off state inhibitor	Verastem Oncology	Phase 1
GFH375	G12D	On and off state inhibitor	Genfleet Therapeutics	Phase 2
ARV-806	G12D	On and off state inhibitor	Arvinas	Phase 1
Olmorasib	G12C	Off state inhibitor	Eli Lilly	Phase 2
Divarasib	G12C	Off state inhibitor	Roche/Genentech	Phase 1
RMC-5127	G12V	On state tricomplex inhibitor	Revolution Medicines	Preclinical
ELI-002 2P, ELI-002 7P	KRAS G12D G12R, G12V, G12A, G12C, G12S, G13D	KRAS peptide vaccine + immune-stimulatory oligonucleotide	Eli Lilly	Phase 2

This does not represent an exhaustive list as many additional molecules are entering development

and of alternative pathways (YAP-TEAD, cyclin-dependent kinases) [95–101].

In pretreated colorectal cancer, single agent sotorasib demonstrated a response rate of only 9.7% (95% CI 3.6–19.9, $N = 62$) [102]. When combined with the EGFR inhibitor panitumumab, ORR increased to 26.4% (95% CI 15.3–40.3, $N = 53$) with mPFS 5.6 months (95% CI 4.2–6.3) [103]. Adagrasib also demonstrates improved efficacy when combined with upstream EGFR inhibition. In pretreated $KRAS^{G12C}$ mutant colorectal cancer, adagrasib and cetuximab resulted in an ORR of 46% (95% CI 28–66) and mPFS of 6.9 months (95% CI 5.4–8.1), compared with 19% (95% CI 8–33) and 5.6 months (95% CI 4.1–8.3) with adagrasib alone [104].

Trials in PDAC combining inhibition of KRAS and other MAPK targets, as well as dual pan-KRAS and allele specific KRAS inhibition are needed to determine which resistance mechanisms are most clinically relevant and which pharmacologic combinations are most efficacious and tolerable.

Finally, preclinical models indicate that KRAS inhibition has better activity in "basal-like" than in "classical" PDAC cells. With treatment, tumors become enriched for "classical" PDAC cells, with increased expression of the canonical classical state marker claudin 18.2 [80, 101]. Combinations of KRAS inhibition with chemotherapy or claudin 18.2 targeting agents may successfully target both the "basal-like" and "classical" cell states in PDAC. As allele specific KRAS inhibitors are expected to have less activity in normal tissues, which lack the mutant allele, toxicity profiles may be more favorable, thereby enabling tolerable combinations with chemotherapy.

We anticipate the initial approval of KRAS inhibitors will be as a single agent in the pretreated metastatic setting. The ORR to known KRAS inhibitors in this setting are in the 20–40% range in early trial readouts. For patients who have stable disease with tolerable side effects on initial chemotherapy, we would recommend continuing chemotherapy and reserving KRAS inhibition for next line of therapy. The next several years of clinical trials will inform timing and choice of KRAS targeting agents and we anticipate standard treatment paradigms to shift over the coming years to include targeted therapy for nearly all patients diagnosed with PDAC.

4.2 Claudin-Targeting Therapies in PDAC

Beyond RAS, there are many promising targets and novel approaches to PDAC treatment under investigation (Table 4). Claudin 18.2 is a tight-junction molecule predominantly found in the nonmalignant gastric epithelium. In normal tissue it is inaccessible, but during malignant transformation normal cell–cell interactions are disrupted and claudin 18.2 becomes exposed, providing a potential therapeutic target [105]. Zolbetuximab, a monoclonal antibody to claudin 18.2, improved mPFS from 8.67 months (95% CI 8.21–10.28) to 10.61 months (95% CI 8.90–12.48; HR 0.75, 95% CI 0.60–0.94, $P = 0.0066$), also significantly improving mOS (HR 0.75, 95% CI 0.60–0.94; $P = 0.0053$) when added to mFOLFOX6 in HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma and > 75% claudin positivity [106]. Similar results were seen when combining zolbetuximab with capecitabine and oxaliplatin (CAPOX)[107], and zolbetuximab is FDA approved for use in this clinical setting. Ongoing investigation revolves around improving claudin-targeting therapies, for greater efficacy including lower threshold of claudin positivity and expanding claudin therapies to alternative tumor types.

Claudin 18.2 is often ectopically expressed in PDAC and in precancerous pancreatic lesions, suggesting that expression may occur early in PDAC development, potentially as gastric-type differentiation of the pancreatic epithelium [105]. The established efficacy of anti-claudin therapies in gastroesophageal adenocarcinoma makes claudin 18.2 an appealing target in PDAC. Some claudin 18.2 staining is present in up to 95% of PDAC, but strong (> 75% expression or 3+) staining is present in about a third [108, 109]. The proportion of patients who are deemed "positive" for Claudin 18.2 and eligible for trials is therefore strongly dependent on the threshold used. This is guided by the specificity and efficacy of the therapeutic, prompting investigation beyond zolbetuximab to antibody-drug conjugates (ADCs), bispecifics, trispecifics, and CAR-T therapies.

Zolbetuximab is currently being evaluated in combination with GNP (GLEAM trial) or mFOLFIRINOX in the first line treatment of mPDAC (NCT03816163, NCT06396091). An October 2025 press report indicated that the GLEAM trial did not meet the primary end point of improved overall survival when zolbetuximab was added to GNP, although the full details of these results are awaited [110]. This setback highlights the importance of careful selection of patients and biologic modality in ongoing trials targeting claudin 18.2. ADCs against claudin 18.2 have demonstrated single agent activity in PDAC and multiple are currently in development.

SYSA1801 (EO3021) is an anti-Claudin 18.2 ADC that uses a monomethyl auristatin E payload. In a phase I trial, 33 patients with advanced, pretreated gastric or pancreatic cancers with claudin 18.2 expression on ≥ 1% of tumor cells received escalating doses of SYSA1801 monotherapy. The ORR was 38%, although the number of responses in the seven patients with pancreatic cancer is not publicly available [111]. Q-1802, a humanized bispecific antibody against claudin 18.2 and PD-L1 was evaluated in a phase I trials of gastric, pancreatic, or biliary tract cancers, with 16/24 patients achieving a partial response and a phase II trial is underway (NCT04856150) [112].

Table 4 Selected targeted agents in development in PDAC beyond RAS

Drug name	Target	Mechanism	Available clinical data	Phase
Zolbetuximab	Claudin 18.2	Monoclonal antibody	In gastric cancer improved mOS when added to first line FOLFOX in metastatic HER2-negative, untreated, advanced gastric or gastroesophageal junction adenocarcinoma and > 75% claudin positivity (HR 0.75, 95% CI 0.60–0.94, $P = 0.0053$) [106], trials in PDAC ongoing.	Phase 2
SYSA1801 (EO3021)	Claudin 18.2	Antibody-drug conjugate	ORR of 38% in a phase I trial, 33 patients with advanced, pretreated gastric or pancreatic cancers with claudin 18.2 expression on ≥ 1% of tumor cells [111].	Phase 1
Q-1802	Claudin 18.2	Bispecific antibody	ORR of 67% in phase I trial of gastric, pancreatic or biliary tract cancers [112].	Phase 2
CT041	Claudin 18.2	CAR-T	ORR and DCR were 16.7% and 70.8% in 24 patients with pretreated mPDAC, with median DOR was 9.5 months (95% CI 2.6–NR). Responses all in patients with 60%+ claudin 18.2 expression[113].	Phase 2
Autogene cevumeran	Personalized neoantigens	Cancer vaccine	Autogene cevumeran, atezolizumab and mFOLFIRINOX were evaluated in a phase 1 trial. Responders with vaccine-induced T cells had prolonged median recurrence free survival ($n = 8$, NR), compared with non-responders ($N = 8$, mRFS 13.4 months, $P = 0.007$) [119].	Phase 2
Motixafortide	CXCR4/CXCL12 signaling	Cyclic-peptide CXCR4 inhibitor	Motixafortide, pembrolizumab, nal-IRI, 5-FU, and leucovorin, in the second line treatment of mPDAC, produced outcomes slightly better than seen historically with nal-IRI, 5-FU, and leucovorin alone (ORR 21.1% vs 16%, mPFS 3.8 vs 3.1 months) [21, 127]. Motixafortide, cemiplimab, gemcitabine and nab-paclitaxel resulted in an ORR of 7/11 in untreated mPDAC [131].	Phase 2
Quemliclustat	CD73, adenosine pathway	Small molecule inhibitor	ORR of 38% (95% CI 24–61) with mPFS and mOS of 8.8 (95% CI 6.4–12.6) and 19.4 months (95% CI 12.1–23.0) respectively in phase 1 study of 29 patients treated with GNP and quemliclustat [135].	Phase 3
Enfortumab vedotin	Nectin-4	Antibody-drug conjugate	Improves survival in metastatic bladder cancer. Expressed in up to 71% of PDAC with 13% staining strongly [140].	Phase 1

Table 4 (continued)

Drug name	Target	Mechanism	Available clinical data	Phase
MRG004A	Tissue factor	Antibody-drug conjugate	ORR of 4/12 and DCR of 10/12 when administered at a fully escalated dose of 2mg/kg in mPDAC with progression on prior therapies[141].	Phase 1
Enoblituzumab	B7-H3	Monoclonal antibody	High B7-H3 expression in PDAC, clinical data unpublished.	Phase 1
B7-H3-CAR T	B7-H3	CAR-T	High B7-H3 expression in PDAC, clinical data unpublished.	Phase 1
Saruparib (AZD5305)	PARP1	Small molecule inhibitor	ORR of 7/25 (28%) in a phase I/II trial of patients with advanced breast, ovarian, prostate or pancreatic cancer bearing germline or somatic *BRCA1/2*, *PALB2* or *RAD51C/D* mutations [158].	Phase 2
AMG 193	PRMT5/MTAP	MTA cooperative PRMT5 inhibitor	ORR of 9/42 (21%), including a near-complete response in a patient with PDAC in a phase I trial of AMG 193 in MTAP or CDKN2A deleted, previously treated solid tumors [174, 180].	Phase 2
BMS-986504	PRMT5/MTAP	MTA cooperative PRMT5 inhibitor	ORR, DCR and median duration of response were 23%, 70% and 10.5 months respectively in 133 patients with MTAP loss and progression on prior therapy, including 46 patients with mPDAC [181].	Phase 2
TNG462	PRMT5/MTAP	MTA cooperative PRMT5 inhibitor	ORR of 15% amongst 39 patients treated with active doses of TNG462 in PDAC and *MTAP* loss. Amongst second line patients ORR 25% and mPFS 7.2 months [183].	Phase 2
Nimotuzumab and Panitumumab	EGFR	Monoclonal antibodies	A phase II trial of gemcitabine with or without nimotuzumab (anti-EGFR) in 186 patients with previously untreated advanced KRAS wild type PDAC demonstrated superior mOS (8.6 [95% CI 5.8–10.7] vs 6.0 [95% CI 4.6–7.5] months, HR 0.69, $P = 0.0341$) with nimotuzumab [187, 188]. A SWOG cooperative group study of second-line chemotherapy (GNP or 5FU, nal-IRI and leucovorin) with or without panitumumab in advanced PDAC is planned to start in 2026.	Phase 3

5-FU 5-fluorouracil, *DCR* disease control rate, *DOR* duration of response, *GNP* gemcitabine, *HR* hazard ratio, *(m)FOLFIRINOX* (modified) 5-fluorouracil, oxaliplatin, irinotecan, leucovorin, *mOS* median overall survival, *mPFS* median progression free survival, *ORR* overall response rate, *mPDAC* (metastatic) pancreatic ductal adenocarcinoma

CT041 is a second-generation CAR T cell therapy targeting claudin 18.2. It was evaluated in two phase I trials including 24 patients with advanced, pretreated PDAC. The ORR and DCR were 16.7% and 70.8%. The median PFS and OS were 3.3 (95% CI 1.8–6.2) and 10.0 months (95% CI 5.5–17.6). The mDOR was 9.5 months (95% CI 2.6–NR). Patients with Claudin 1+ or greater were included, but 3+ claudin expression was present for both patients with partial

response lasting > 1 year (60% and 90% of cells positive for expression), indicating that higher levels of expression may be necessary for efficacy even with potent cellular therapies [113]. Further investigation is needed to determine the optimal therapeutic mechanisms of action, claudin 18.2 positivity cutoffs and combinations required for successful claudin-targeting therapy [101, 114].

4.3 Immunomodulatory Agents, Cancer Vaccines and Biologic Therapies

Immunotherapy, including PD-1, PD-L1, and CTLA4 inhibition, has largely failed to improve outcomes in proficient MMR PDAC, regardless of strategy evaluated [115–117]. A unique, fibrotic, and immunosuppressive TIME, characterized by M2 macrophages, regulatory T cells, and immunosuppressive cancer-associated fibroblast subtypes are implicated in resistance to immunotherapy. However, an improved characterization of the TIME has led to refined therapeutic approaches, offering hope that immunomodulatory agents may have an important role in the future treatment of PDAC.

In the perioperative setting, cancer vaccines that prime a patient's immune system against antigens specific to their tumor are a promising therapeutic avenue for the prevention of cancer recurrence. The two most advanced PDAC cancer vaccines are ELI-002 2P and ELI-002 7P, KRAS mutant-specific amphiphile vaccines, and autogene cevumeran, a personalized neoantigen vaccine targeting mostly passenger mutations. Autogene cevumeran, atezolizumab, and mFOLFIRINOX were evaluated in a phase 1 trial in resected PDAC. Responders with vaccine-induced T cells ($n = 8$) had prolonged median recurrence free survival (mRFS, NR), compared with nonresponders ($N = 8$, mRFS 13.4 months, $P = 0.007$). In this trial, 86% of tumor-specific T-cell clones persisted 3 years after vaccination [118]. It is not known whether vaccine response induced improved outcomes, or if responders have better immunologic responses and would have had superior outcomes irrespective of receipt of vaccine. A randomized phase II trial of adjuvant mFOLFIRINOX with or without autogene cevumeran and atezolizumab in patients with resected PDAC and no evidence of residual disease is ongoing, with a primary end point of disease-free survival (NCT05968326). Patients in the experimental arm are primed with autogene cevumeran and atezolizumab followed by standard of care adjuvant mFOLFIRINOX and subsequently by monthly boost doses of autogene cevumeran and atezolizumab for a year [119].

A limitation of autogene cevumeran is the time-consuming, labor-intensive, and expensive process of creating personalized neoantigen vaccines. The presence of *KRAS* mutations in 95% of PDAC offers a prime target for tumor antigen delivery without the need for preselection. Antibodies to KRAS are present in most healthy patients with PDAC, across a diverse HLA background [120]. ELI-002 2P in an amphiphile vaccine that uses modified KRAS G12D and G12R peptide antigens with lipid moieties that facilitate antigen delivery to lymph nodes via endogenous albumin-hitchhiking, resulting in improved antigen-specific T-cell responses [121]. In the phase 1 AMPLIFY-201 trial, ELI-002 2P was evaluated in 20 patients with PDAC and 5 patients with colorectal cancer who had received standard locoregional treatment, with minimal residual mutant *KRAS* disease detected in ctDNA or rising tumor biomarkers. The mOS for the PDAC cohort was 29 months and mRFS was 15.3 months. Patients treated with ELI-002 2P demonstrated increased T-cell reactivity to personalized tumor antigens absent in the initial vaccine, indicative of antigen spreading. In patients with a higher mKRAS-specific T cell response fold change from baseline ($N = 17$), a significantly higher mOS (NR versus 16 months) and mRFS (NR versus 3 months) were noted when compared with the remainder of the cohort ($N = 8$) [122]. These results are promising given historic data indicating an mRFS of 5–7 months in patients with mPDAC and positive ctDNA after curative-intent therapy [118, 123], and require validation in a randomized trial. ELI-002 7P targets six common RAS antigens from codon 12 (G12 D, V, R, C, S, A) and one from codon 13 (G13D). A randomized phase II trial comparing ELI-002 7P with observation after completion of standard of care therapy in resected PDAC, has completed enrolment and results are awaited (NCT05726864) [124]. Further, a translational neoadjuvant trial is planned evaluating ELI-002 7P combined with chemotherapy in two cohorts with or without immune checkpoint blockade.

In the metastatic setting, multiple treatment approaches are under evaluation with the goal of sensitizing the PDAC TIME to immunotherapy. The C-X-C motif chemokine receptor 4 (CXCR4)/C-X-C motif chemokine ligand 12 (CXCL12) axis contributes to the exclusion of antitumor immune cells from the PDAC TIME [125]. Preclinical models indicate that CXCR4 inhibition sensitizes PDAC to immunotherapy [126], but dual inhibition of CXCR4 and PD1 inhibition failed to produce responses in humans [12]. The COMBAT/KEYNOTE-202 trial evaluated motixafortide (CXCR4 inhibitor), pembrolizumab, nal-IRI, 5-FU, and leucovorin in a second line treatment of *de novo* mPDAC [127]. The combination produced slightly better outcomes relative to those seen with nal-IRI, 5-FU, and leucovorin alone in the NAPOLI-1 trial, with ORR 21.1% versus 16%, confirmed ORR 13.2% versus 7.7%, mPFS 3.8 versus 3.1 months, mOS 6.6 versus 6.1 months [21]. However, this was not felt sufficiently promising to proceed with a randomized trial.

A phase I study of motixafortide, cemiplimab, gemcitabine, and nab-paclitaxel (MCGN) in patients with treatment-naive mPDAC revisited CXCR4/CXCL12 pathway

inhibition with the hypothesis that first line treatment and combination with gemcitabine fostered a better setting for this immunomodulatory combination [128]. MCGN demonstrated an ORR of 7/11 (64%, 95% CI 31–89) and mPFS of 9.7 months (95% CI 5.8–NR) [129]. Increased levels of CXCL12-producing cancer-associated fibroblasts correlated with response to MCGN, potentially identifying patients more reliant on CXCR4/CXCL12 pathway signaling and likely to benefit from CXCR4 inhibition [130]. A phase II randomized trial of gemcitabine and nab-paclitaxel with or without motixafortide and cemiplimab is ongoing (NCT04543071) [131].

Adenosine plays a role in mediating the immunosuppressive PDAC TIME and CD73 is an enzyme involved in the generation of adenosine. CD73 may be overexpressed on tumor-associated immune and fibroblast cells, leading to accumulation of adenosine, activation of the adenosine receptor and dampening of T cell-mediated antitumor immunity [132]. Quemliclustat is a small-molecule CD73 inhibitor [133]. A phase 1 study that included 29 patients treated with quemliclustat and GNP demonstrated a promising confirmed ORR of 38% (95% CI 24–61) with mPFS an mOS 8.8 (95% CI 6.4–12.6) and 19.4 months (95% CI 12.1–23.0), respectively [134]. A phase III randomized, placebo-controlled trial of GNP with or without quemliclustat has completed accrual (NCT06608927) [135].

CD40 is a costimulatory receptor expressed on the surface of B cells, monocytes, macrophages, and dendritic cells. CD40 agonists may alter the tumor stroma to induce a more immune-activated and chemotherapy sensitive phenotype, including redirection of tumor-infiltrating macrophages from M2 to M1phenotype [136]. The CD40 agonist mitazalimab was combined with mFOLFIRINOX in untreated mPDAC in the phase 1b/2 OPTIMIZE-1 trial. This study met its primary end point with an ORR of 40% (one-sided 90% CI ≥ 32%) in 57 patients. The combination also produced a promising mPFS of 7.7 months, mOS of 14.3 months, and mDOR of 12.5 months and a phase III randomized, controlled trial is planned [137].

Oncolytic viruses selectively infect, replicate in, and lyse cancer cells initiating antitumor immune responses. At least 20 trials of these viruses in PDAC are recently completed, ongoing, or planned, mostly using adenovirus or herpesvirus vectors [138]. The most advanced of these viruses is VCN-01, an oncolytic adenovirus expressing hyaluronidase to degrade tumor stroma, facilitate chemotherapy, and enhance the antitumor immune response. VCN-01 was recently evaluated in the phase IIb VIRAGE trial. A total of 112 patients with untreated mPDAC were randomized 1:1 to GNP with or without VCN-01. The most common VCN-01-related serious adverse events were flu-like symptoms (13,2%), transaminase increase (5.7%), and drug-induced liver injury (3.8%). mDOR was improved in the experimental arm (5.4 versus 11.2 months, HR = 0.22 [95% CI 0.08–0.62] $P = 0.004$), and there was a trend towards improved mOS (8.6 versus 10.8 months, HR = 0.57 [95% CI 0.34–0.96] $P = 0.055$) and mPFS (4.6 versus 7.0 months, HR = 0.55 [0.34–0.88], $P = 0.011$), meriting further investigation of this combination [139].

A series of novel biologic agents are under investigation in mPDAC, including ADCs, bispecifics, trispecifics, and CAR-T cells. Bispecifics and trispecifics bind multiple epitopes, generally on immune and tumor cells, bringing immune cells directly to the tumor to facilitate inflammation and neoplastic cell death. A key aspect of these therapeutic classes is identifying the right antigen with sufficient and accessible presentation in tumor cells and low enough levels of expression in normal cells to avoid excessive toxicity. Enfortumab vedotin (EV) is an ADC targeting nectin-4 and is part of the first-line, standard of care for treatment of metastatic bladder cancer. Nectin-4 is expressed in up to 71% of PDAC with 13% staining strongly, and EV is currently under evaluation in a phase II trial of patients with previously treated mPDAC (NCT05915351) [140]. Tissue factor, a molecule increased in PDAC carcinogenesis and a driver of increased thrombotic risk, is targeted by MRG004A, an ADC with monomethyl auristatin E payload. A phase I, dose expansion study of MRG004A demonstrated an ORR of 9/37 when administered at a fully escalated dose of 2mg/kg in mPDAC with progression on prior therapies. In the cohort of patients treated as second line therapy, ORR was 4/10, DCR was 8/10, mPFS was 5.8 months (95% CI 1.3–8.5), and mOS was 13.2 months [141]. Higher intensity or expression positive area for tissue factor did not clearly associate with the response of TF-ADC MRG004A [142]. This highlights that understanding of the biology of target turnover and heterogeneity is still limited. A phase III trial of MRG004A in pretreated mPDAC is underway in China [143].

There are many other targets of interest for biologic therapy development with strong scientific rationale and preclinical data that are under investigation. B7-H3 is a transmembrane receptor highly expressed on a variety of malignant cells including PDAC [144]. Several B7-H3 biologic therapies are currently under evaluation in clinical trials including the monoclonal antibody enoblituzumab (NCT02982941) [145, 146] and a CAR-T cell product (B7-H3-CAR T, NCT06500819) [147].

Trophoblast cell surface antigen 2 (TROP2) is a cell surface antigen overexpressed in more than half of PDAC cases. The TROP2 targeting ADCs sacituzumab govitecan and datopotamab deruxtecan are approved for use in breast cancer on the basis of phase 3 trials demonstrating improvement in mPFS [148]. A phase 1/2 trial of sacituzumab tirumotecan in gastrointestinal malignancies including mPDAC ($N = 40$) is currently ongoing [149]. MUC1 is a protein that can carry the CA 19-9 antigen, often found in

pancreatic cancer. MUC1 ADCs have produced promising tumor responses in mouse models of pancreatic cancer [150, 151]. CEA-related cell adhesion molecules (CEACAMs) are highly glycosylated cell surface anchored, intracellular, and intercellular signaling molecules, some of which are overexpressed in PDAC [152]. In a phase 1 trial EBC-129, an anti-N256-glycosylated CEACAM5 and CEACAM6 ADC, demonstrated an ORR of 19% in 21 patients with pretreated mPDAC [153]. Further clinical data from trials involving these promising targets are eagerly awaited.

4.4 Homologous Recombination Deficiency

About 5% of patients with PDAC have germline or somatic pathogenic *BRCA1*, *BRCA2,* or *PALB2* mutations and 10–25% of PDAC have a detectable HRD-phenotype [154]. This subset includes patients with germline and somatic mutations in *BRCA1*, *BRCA2*, *PALB2*, *RAD51*, genes involved in the BCDX2 protein complex (*RAD51*), and defines a cohort of patients who may benefit from platinum chemotherapy, PARP inhibition, and other therapies targeting genomic instability associated with HRD [155]. In two phase II trials of olaparib in pretreated mPDAC with HRD phenotype, only 1/46 patients had a partial response. A total of 33 out of 46 had stable disease with a mPFS of 3.7 months [54]. The POLO trial built upon these findings, identifying PARP inhibition as a potential mechanism of maintaining preexisting tumor control in patients with the highest level of HRD-phenotype [52]. The ongoing APOLLO study (A Randomized Phase II Double-Blind Study of Olaparib Versus Placebo Following Curative Intent Therapy in Patients With Resected Pancreatic Cancer and a Pathogenic *BRCA1*, *BRCA2,* or *PALB2* mutation) is evaluating the addition of olaparib to adjuvant therapy in patients with resected PDAC and pathogenic *BRCA1*, *BRCA2,* or *PALB2* mutations (NCT04858334) [156].

Current PARP inhibitors inhibit both PARP1 and PARP2, but PARP1 inhibition is primarily responsible for induction of synthetic lethality and PARP2 inhibition is responsible for most hematologic toxicity, limiting tolerability and combinability with chemotherapy [157]. A variety of selective PARP1 inhibitors are in development [157]. Saruparib (AZD5305), a highly selective PARP1 inhibitor, was evaluated in a phase I/II trial of patients with advanced breast, ovarian, prostate, or pancreatic cancer bearing germline or somatic *BRCA1/2*, *PALB2,* or *RAD51C/D* mutations. Patients had received a median of 3.5 prior lines of therapy and 43.5% had prior PARP inhibition. ORR was 7/25 (28%) and early safety data indicate that saruparib may be more tolerable than first generation PARP inhibitors [158].

HRD-phenotype may predispose tumors to immunotherapy response [159, 160]. A single institution retrospective review of 12 patients with chemotherapy-refractory mPDAC (N =10), ampullary (N = 1), or biliary (N = 1) cancer and germline pathogenic variants in HRD genes treated with ipilimumab and nivolumab noted a complete response in four patients, partial response in one patient, and stable disease in two (ORR 42%). The four patients who achieved CR remained without evidence of disease after 11 to 41 months. Responses were seen in three patients with PDAC (two with *BRCA1* mutation, one with *RAD51C* mutation) [161].

The phase II POLAR trial evaluated maintenance olaparib and pembrolizumab in patients with mPDAC without progression. Patients were selected on the basis of HRD-phenotype genes or exceptional platinum response. In the cohort of patients with *BRCA1*, *BRCA2,* or *PALB2* mutations (core HRD mutations) mPFS on maintenance therapy was 8.3 months (95% CI 5.3–NR) and mOS was 28 months (95% CI 12–NR) (mPFS 7.4 months and mOS 18.9 months in with olaparib alone in POLO trial) [52, 162, 163]. Additional cohorts of patients with pathogenic germline or somatic mutations in non-core HRD genes (*ATM*, *BAP1*, *BARD1*, *BLM*, *BRIP1*, *CHEK2*, *FAM175A*, *FANCA*, *FANCC*, *NBN*, *RAD50*, *RAD51*, *RTEL1*, *MUTYH*), and of patients with platinum sensitivity of at least 6 months had significantly poorer outcomes with mPFS of 4.8 months (95% CI 4–12) and 3.3 months (95% CI 1.9–4.8), respectively [163]. Tumor molecular characterization indicated that higher tumor-infiltrating lymphocyte density, and increased abundance of frameshift indels and neoantigens were seen in the cohort of core HRD mutations and associated with clinical benefit [163]. SWOG S2001 is evaluating maintenance olaparib with or without pembrolizumab in patients with germline *BRCA1* or *BRCA2* mutations without progression on 4–6 months of platinum chemotherapy and will further clarify whether the addition of pembrolizumab adds clinical benefit in this setting (NCT04548752) [164].

Because of the deficient repair of double-strand breaks HRD tumors, these tumors may more susceptible to chemotherapy drugs that induce double-strand DNA breaks, such as melphalan [165, 166]. However, reversion mutations in *BRCA* can cause resistance to melphalan. Bis-chloroethylnitrosourea (BCNU), vitamin B12, and vitamin C can increase glutathione disulfide levels to inhibit DNA repair and sensitize wild-type cancer cells to melphalan. A phase I trial of melphalan, BCNU, vitamin B12b, and vitamin C and hematopoietic stem cell transplantation in *BRCA* mutant mPDAC is ongoing (NCT04150042) [167]. Enrollment was permitted with or without recent progression. For patients with mPDAC and stable/responding disease at time of enrollment (N = 5), mPFS was not reached with a median follow-up time of 14.2 months and N = 3 (25%) were free of disease and off all therapy at 11, 23, and 42 months [168].

Beyond PARP inhibition, novel therapies are in development to target tumors with DNA repair deficiencies. DNA

polymerase θ (POLθ) has minimal expression in normal cells, but is overexpressed in many cancers with DNA repair deficiencies, including HRD and nonhomologous end joining (NHEJ) deficiencies [169]. In preclinical models, inhibition of POLθ leads to synthetic lethality including after acquired resistance to PARP inhibitors, and may synergize with PARP inhibition in HRD tumors [170, 171]. Clinical trials evaluating POLθ inhibitors both alone and in combination with PARP inhibition are ongoing (NCT06077877) [172].

4.5 Targeting *MTAP* Loss

Methylthioadenosine phosphorylase (*MTAP*) is involved in methionine and adenine salvage and loss of MTAP activity leads to metabolic reprogramming from glycolysis to purine synthesis to meet cellular demands for nucleic acids and adenosine triphosphate (ATP) [173]. This leads cancer cells with *MTAP* deletion to rely on protein arginine methyltransferase 5 (PRMT5) and inhibition of PRMT5 can then induce synthetic lethality in these cells [174]. *MTAP* is located in close proximity to *CDKN2A*, so there is a high rate of concordance between homozygous deletion of the two genes [175, 176]. *MTAP* loss can be detected either through NGS or immunohistochemical staining for the MTAP protein (S-methyl-5'-thioadenosine phosphorylase). The prevenance of MTAP loss in PDAC varies significantly between cohorts, but is likely present in 20–40% of cases [8, 177, 178].

Methylthioadenosine (MTA) is present at increased levels in patients with MTAP deficiency. MTA is a weak, inhibitor of PRMT5 that binds competitively with S-adenosylmethionine (SAM). Compounds that bind PRMT5 cooperatively with MTA, and not with SAM, can selectively inhibit PRMT5 cells with *MTAP* loss, while sparing *MTAP* wild type cells given their low MTA levels, potentially improving toxicity profile over other PRMT5 inhibitors [179]. Multiple MTA cooperative PRMT5 inhibitors are currently in trials including AMG 193, BMS-986504, and TNG462.

AMG 193 inhibits PRMT5 and induces synthetic lethality in tumors with MTAP loss [174]. A phase I trial evaluated AMG 193 in *MTAP* or *CDKN2A* deleted, previously treated solid tumors. In patients receiving doses of at least 800 mg, ORR was 9/42 (21%), including a near-complete response in a patient with PDAC [180]. Another PRMT5 inhibitor, BMS-986504, was evaluated in 133 patients with *MTAP* loss and progression on prior therapy, including 46 patients with mPDAC. Across tumor types ORR, DCR, and mDOR were 23%, 70%, and 10.5 months, respectively [181]. A phase 1 trial of patients with PDAC and *MTAP* loss included 39 patients treated with active doses of TNG462. Amongst these patients ORR was 15% and 25% for patients treated in the second line. mPFS in the second line was 7.2 months. Based on these findings, a phase III trial of TNG462 in the second line treatment of mPDAC with *MTAP* loss is planned [182].

Trials evaluating PRMT5 inhibition with chemotherapy are ongoing (NCT06360354). In addition, given the high rates of *KRAS* mutation and *CDKN2A* loss in MTAP deleted PDAC, there is interest in combining PRMT5 inhibition with inhibition of KRAS or CDK4/6, with preclinical data indicating potential synergy with this approach [183]. Multiple trials of combined PRMT5 and KRAS inhibition are currently ongoing (NCT06360354, NCT06922591).

4.6 *KRAS* Wild Type PDAC

KRAS wild type PDAC has a unique genomic landscape relative to *KRAS* mutant PDAC, although a high proportion of these tumors retain MAPK signaling dependencies [184]. These tumors may be more vulnerable to targeting other parts of the MAPK pathway. In colorectal cancer, EGFR inhibition has demonstrated benefit in *RAS* wild type disease [185] and there may be a role for EGFR inhibition in *RAS* wild type PDAC. A 2013 trial of adjuvant gemcitabine and cetuximab in PDAC observed a trend towards improved outcomes with the regimen in *KRAS* wild type PDAC (median disease-free survival 11.5 versus 9.3 months, $P = 0.57$) [186]. A phase II trial of gemcitabine with or without nimotuzumab (anti-EGFR) in 186 patients with previously untreated locally advanced or metastatic *KRAS* wild type PDAC demonstrated superior mOS (8.6 [95% CI 5.8–10.7] versus 6.0 [95% CI 4.6–7.5] months, HR 0.69, $P = 0.0341$), and mPFS (5.1 [95% CI 3.7–6.8] versus 3.4 [95% CI 2.5–4.0] months, HR 0.68, $P = 0.0163$) with nimotuzumab [187]. A follow-up phase III trial made the same comparison in 82 patients and corroborated these findings with superior mOS (10.9 versus 8.5 months, HR 0.66, 95% CI 0.42–1.05; $P = 0.08$) and mPFS (4.2 versus 3.6 months, HR 0.60 [95% CI 0.37–0.99], $P = 0.04$) in the group receiving nimotuzumab [188]. These data provide strong evidence that EGFR inhibition may have a role in *KRAS* wild type PDAC. A SWOG cooperative group study of second-line chemotherapy (GNP or 5FU, nal-IRI, and leucovorin) with or without panitumumab in locally advanced, unresectable, or metastatic *KRAS* wild type PDAC is planned to start in late 2025 (NCT06998940) [189].

4.7 Metastasis Directed Therapy

Patients with mPDAC are almost never curable, and local therapies have therefore not been a central aspect of care in these patients. The phase II EXTEND trial evaluated the addition of metastasis directed therapy (mostly radiation to liver metastases) in oligometastatic PDAC. This intervention extended mPFS from 2.5 (95% CI 1.7–5.1) to 10.2 months (95% CI 4.6–14.0), without a significant extension of mOS.

Exploratory subgroup analyses indicated that patients with more activated T-cells and greater T cell receptor diversity, may derive an OS benefit. Even in the absence of an OS benefit, a mPFS benefit without much added toxicity may be clinically meaningful, given the significant symptom burden often associated with progressive PDA [190]. Metastasis directed therapy may have a particularly compelling role in patients with lung metastases. Lung-only metastatic disease is characterized by a mOS approximately twice as long as liver-only metastatic disease [191–194]. Small cohorts have demonstrated long-term survival after resection of lung metastases in oligometastatic PDA [195–197]. The role of metastasis directed therapy in mPDAC will likely continue to evolve as systemic therapies improve.

5 Supportive, Adjunctive Care in PDAC

PDAC can result in challenging secondary physical and psychosocial problems for patients, including pancreatic insufficiency, biliary tract obstruction, duodenal obstruction, anorexia, diabetes, tumor-associated pain, thrombosis, and anxiety/depression. The management of these complications is beyond the scope of this review and has been effectively summarized in several manuscripts [198, 199]. Multidisciplinary management and early intervention are critical to optimize symptom control and improve outcomes.

6 Biomarker Testing, Disease monitoring—ctDNA and Emerging Tools

As mPDAC treatment is individualized on the basis of biomarker testing, the reliable identification of these biomarkers is increasingly important. For patients who may have clinical trial opportunities, this should ideally include somatic NGS or targeted gene sequencing including *KRAS* allele testing, testing for relevant gene fusions in *KRAS* wild type PDAC, testing for *MTAP* loss by NGS, and/or immunohistochemistry, immunohistochemistry for claudin 18.2 expression and MMR and/or MSI testing. In addition, all patients should undergo germline genetic testing for HRD-associated mutations. Given the typically aggressive nature and advanced presentation of mPDAC, this testing must be done efficiently to avoid delays of care. Pancreatic tissue specimens are often fine needle aspirates which may be too limited for NGS testing and are unsuitable for evaluation of Claudin 18.2 expression. Because of these limitations, core biopsy of a metastatic site may be the preferred method of tissue acquisition in many patients with mPDAC. For patients in whom tissue is insufficient for molecular testing, circulating tumor DNA (ctDNA) may aide in tumor genomic profiling at diagnosis, and potentially at time of disease progression. In patients with stage IV disease, ctDNA has high sensitivity for tumor DNA and concordance with somatic mutational testing on tumor tissue [200, 201].

ctDNA may also have a role for disease monitoring in PDAC, although currently available data does not support its routine use in this setting. Currently tumor marker surveillance represents a standard aspect of disease monitoring in PDAC, most commonly with CA 19-9 which is detected in approximately 80% of cases [202]. ctDNA has an established role in adjuvant disease monitoring in colorectal cancer and its use is an area of active investigation across oncology [203, 204]. Typically, ctDNA used in this setting is tumor-informed, using a known tumor mutational profile to detect the presence of that same profile the patient's serum. This contrasts with nontumor informed ctDNA which detects all mutations potentially associated with malignancy. Retrospective data indicates that ctDNA detection and clearance has strong prognostic value in both the adjuvant and metastatic disease settings, but prospective clinical trial data is needed to determine how to use this data to escalate or deescalate therapy on the basis of patient risk [205–208]. One study of resected pT1-T3 PDAC involved tumor-informed ctDNA testing with the option of deescalating to 3 months of adjuvant chemotherapy in the case of ctDNA negativity. Of 102 patients, 54 (53%) were ctDNA negative after resection and 24 (44%) of these were deescalated to receive a planned 3 months of adjuvant chemotherapy. With a median follow-up of 36 months, the median recurrence free survival in ctDNA positive patients was 13 months, compared with 22 months for ctDNA negative patients (HR 0.52, $P = 0.003$). Amongst ctDNA negative patients, mRFS nonsignificantly favored 6 months of chemotherapy (26 versus 18.5 months, HR 0.64, $P = 0.159$) [209]. As more data becomes available regarding ctDNA as a marker of "minimal residual disease" in nonmetastatic PDAC and of response to therapy in mPDAC, ctDNA is likely to be further incorporated into clinical practice and PDAC clinical trial design.

7 Conclusions

The current therapeutic standard for PDAC remains multiagent chemotherapy. However, recent bioengineering developments have led to an explosion in RAS directed therapies, which have shown significant early promise and are now in late-stage development in all stages of PDAC. Phase 3 trials are evaluating the role for pan-RAS inhibition in untreated and pretreated mPDAC and following standard adjuvant therapy. Other promising strategies include next generation immunotherapeutics, vaccines, and therapies against emerging targets including claudin 18.2 and MTAP. In parallel, associated technologic developments for biomarker testing

and monitoring are rapidly moving PDAC to a disease that may be highly actionable for personalized medicine approaches in the next 2–5 years.

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