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Actionable mutations in pancreatic cancer: where targeted therapies are making a difference

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest solid tumours, with 5-year survival consistently below 10% and only modest gains from conventional chemotherapy after first-line failure. Although oncogenic *KRAS* mutations dominate the genomic landscape, recent large-scale sequencing has revealed a series of less frequent but therapeutically actionable alterations. This review synthesises evidence from phase I–II trials published through April 2025. It demonstrates that targeting these lesions can yield outcomes that meet or exceed the benchmarks set by the NAPOLI-1 trial (liposomal irinotecan plus 5-fluorouracil and leucovorin), with a median overall survival of 6.2 months and progression-free survival of 3.1 months. Objective response rates reach 33% with adagrasib in *KRAS G12C* PDAC, 22% with olaparib maintenance in germline BRCA1/2 cancers, and over 50% with RET or NTRK inhibitors with fusion alterations; pembrolizumab produces durable benefit in the 1–3% of tumours that are MSI-H/dMMR. Emerging data highlight NRG1 fusions (overall response rate 42% with zenocutuzumab), HER2 amplification, MTAP deletion with PRMT5 dependency and variant-specific (MRTX1133) or pan-RAS (daraxonrasib) inhibitors as the next frontier. Toxicity profiles of targeted agents are generally favourable and often allow prolonged administration compared with cytotoxic regimens. Taken together, these advances represent a substantive therapeutic progress in PDAC over the past decades, even though they currently apply to a minority of patients. These findings underscore the necessity of comprehensive next-generation sequencing for every patient with advanced disease, enabling identification of rare, yet clinically meaningful, targets and moving PDAC management towards a precision-oncology paradigm.

SUMMARY

⇒ Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal cancers, with limited benefit from standard chemotherapy.
⇒ Advances in molecular profiling have identified several rare but actionable alterations—most often in KRAS-wild-type tumors—that offer new therapeutic opportunities.
⇒ Targeted agents directed at KRAS G12C, BRCA1-2, MSI-H/dMMR, NTRK, RET, BRAF, NRG1 and HER2 alterations have demonstrated meaningful activity in early-phase trials.
⇒ Although these mutations represent a small proportion of PDAC, they enable novel personalized treatment approaches supported by growing clinical evidence.
⇒ Systematic genomic testing is therefore essential to identify patients who may benefit from these emerging therapies and to further integrate precision oncology into PDAC treatment.
⇒ *KRAS* (variant specific or pan-inhibitors) and PRMT5 inhibitors (in tumors with homozygous *MTAP* deletion) are showing early efficacy and could redefine pancreatic cancer treatment.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest malignancies, typically diagnosed at advanced stages and associated with poor outcomes. PDAC is currently the fourth leading cause of cancer-related mortality globally and is projected to rank second by 2040.[1] Only 15–20% of patients are eligible for surgery at diagnosis, which is the only potentially curative option. For the majority, with advanced or metastatic disease, outcomes remain dismal despite aggressive chemotherapy, with 5-year survival rates below 10%.[2 3] Chemotherapy regimen, such as FOLFIRINOX or the combination of gemcitabine and Nab-paclitaxel, offers modest improvements in survival but comes at the cost of substantial toxicity and limited long-term benefit. In the second-line setting, the phase III NAPOLI-1 trial compared nanoliposomal irinotecan (Nal-IRI) combined with 5-fluorouracile (5-FU) and leucovorin (LV) to 5-FU/LV in patients with metastatic PDAC, thus demonstrating superior outcomes for the combination of nal-IRI+5-FU/LV with a median overall survival (mOS) of 6.2 months vs 4.2 months and median progression-free survival (mPFS) of 3.1 months vs 1.5 months.

These results serve as a benchmark for second-line systemic treatment efficacy.[4]

While mutations in *KRAS*, *TP53*, *CDKN2A* and *SMAD4* stand as the most common drivers in PDAC, novel but less frequent genetic alterations have been identified as potential therapeutic targets with the advent of next-generation sequencing.[3] Recently, new pharmacological developments have shown promising results by targeting some of these mutations, highlighting the growing importance of molecularly characterising the disease at diagnosis.

This review summarises the clinical benefit evidence from phase I–II trials for targeted therapies directed at actionable molecular alterations in PDAC. We aim to provide gastroenterologists and medical oncologists with a concise and clear overview of current therapeutic options beyond traditional chemotherapy, emphasising the clinical outcomes associated with these targeted strategies.

WHICH MUTATIONS ARE CLINICALLY IMPACTFUL IN 2025 FOR PDAC?

KRAS mutations

KRAS mutations occur in about 90% of PDAC cases, predominantly involving codon 12, notably *G12D* (35%), *G12V* (20–30%), *G12R* (10–20%) and *G12C* (1–2%). KRAS plays a pivotal role in tumour initiation, appearing early during precursor lesions and often co-occurring with alterations in *TP53* (67%), *CDKN2A* (17%), *SMAD4* (11%) and *ARID1A* (6%). Prognostically, KRAS-mutated (KRASmut) tumours show worse outcomes compared with KRAS wild-type (KRASwt) (mOS 22 months vs 38 months).[5] G12D mutations are more common in metastatic disease and linked to poor outcomes. Conversely, G12R variants are typically found in better-differentiated tumours, with mOS comparable to KRASwt cases.[5] Figure 1 illustrates the main targetable alterations in PDAC, showing their prevalence alongside the corresponding therapies on the right. In KRAS mutations, G12C represents the main alteration for targeted therapies but remains the rarest one (1%). Two inhibitors targeting specifically this alteration have shown moderate efficacy, as illustrated in figure 2 which represents the clinical trials for the targeted therapies in PDAC: sotorasib demonstrated a 21% partial response (PR) with an mPFS of 4 months and mOS of 6.9 months in a phase I–II trial from Strickler *et al*.[6] The second G12C inhibitor, adagrasib, achieved a 33.3% PR rate, mPFS of 5.6 months and mOS of 8 months (figure 2).[7] Toxicities occurring from both inhibitors were mostly manageable gastrointestinal side effects.

BRCA1-2 mutations

Genes involved in homologous recombination repair (HRR)—including *BRCA1*, *BRCA2*, *ATM*, *PALB2* and *CHEK2*—play a key role in maintaining genomic stability by repairing DNA double-strand breaks. Mutations in these genes impair this process, leading to genomic

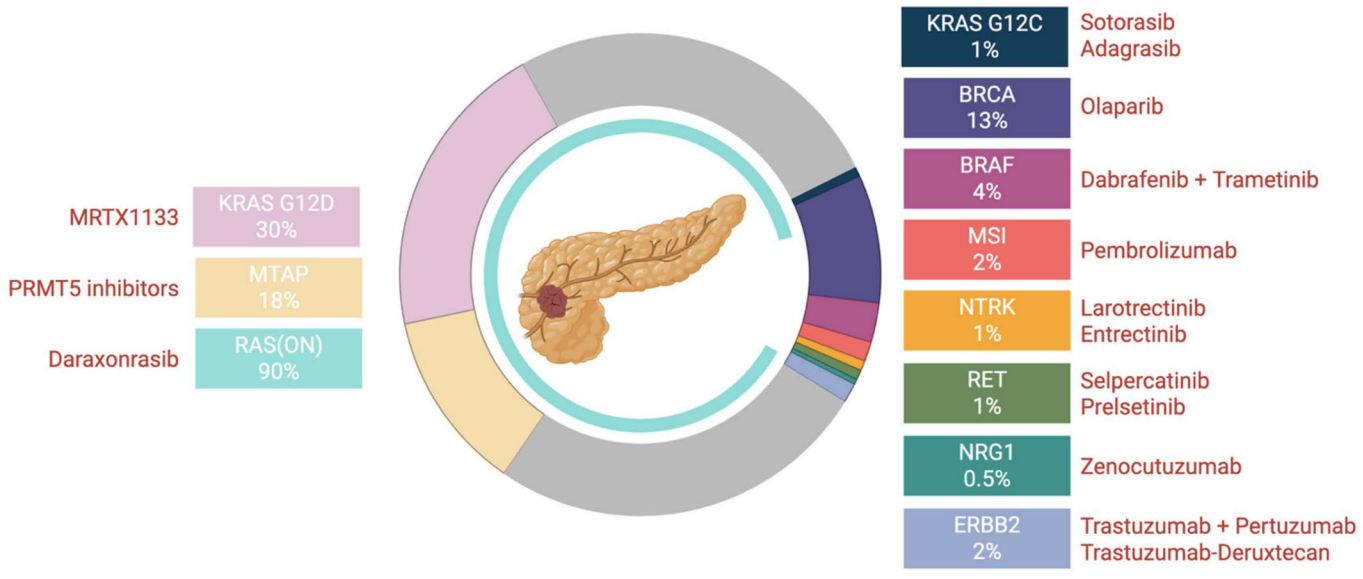
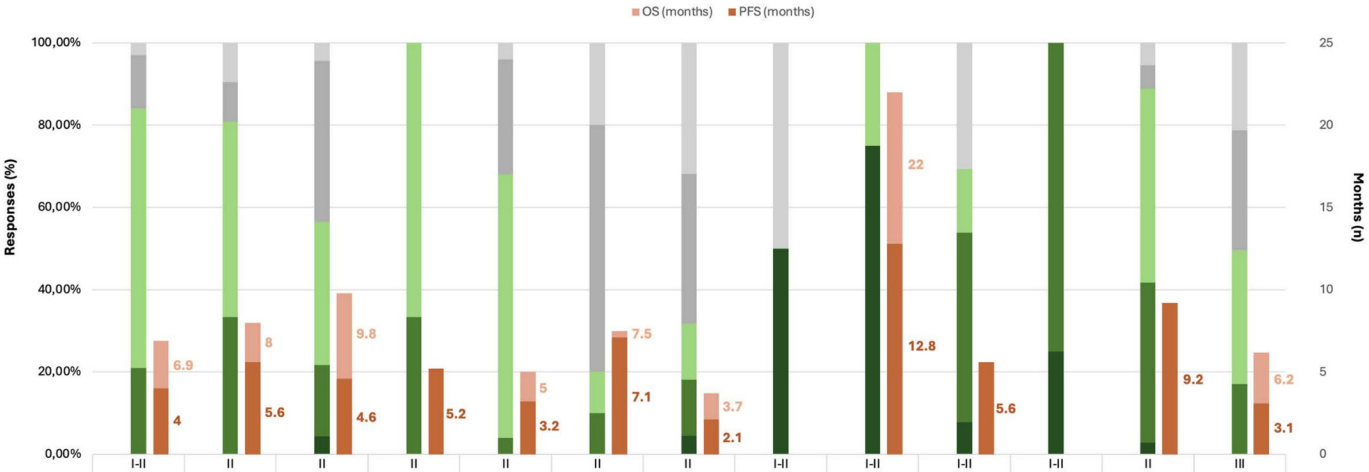


Figure 1 Donut charts illustrating the main targetable mutations in pancreatic ductal adenocarcinoma (PDAC), along with their reported prevalence and corresponding therapies (in red) that have been evaluated in clinical trials for safety and efficacy (as detailed in the main text). The light blue segment denotes other PDAC-associated mutations that are currently non-targetable, or for which limited clinical data are available. Prevalence estimates are derived from genomic studies referenced in the review (see References [5–35]). BRAF, B-raf proto-oncogene; ERBB2/HER2, erb-b2 receptor tyrosine kinase 2/human epidermal growth factor 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; MSI, microsatellite instability; MTAP, methylthioadenosine phosphorylase; NTRK, neurotrophic tyrosine receptor kinase; NRG1, neuregulin 1; RET, rearranged during transfection proto-oncogene; RET, rearranged during transfection proto-oncogene; RAS(ON), rat sarcoma (on).



	I-II	II	II	II	II	II	II	I-II	I-II	I-II	I-II	II	III
	38	21	23	3	25	10	22	2	4	13	4	36	117
	CodeBreaK 100	KRYSTAL-1	NCT01078662	BELIEVE	DESTINY-PanTumor02	MyPathway	KEYNOTE-158	NCT02122913; NCT02637687; NCT02576431	STARTRK-1; STARTRK-2; ALKA-372-001	LIBRETTO-001	ARROW	eNRGy	NAPOLI-1
	Sotorasib	Adagrasib	Olaparib	Dabrafenib + Trametinib	Trastuzumab + Deruxtecan	Pertuzumab + Trastuzumab	Pembro-lizumab	Larotrectinib	Entrectinib	Selpercatinib	Pralsetinib	Zeno-cutuzumab	nal-IRI+5-FU/LV
	KRASG12C		BRCA1/2	BRAFV600E	HER2		MSI-H status	NTRK fusions		RET fusions		NRG1 fusions	2nd-line treatment
Other/NE %	3,00%	9,50%	4,30%	0,00%	4,00%	20,00%	31,80%	50,00%	0,00%	30,80%	0,00%	5,60%	21,40%
PD %	13,00%	9,50%	39,10%	0,00%	28,00%	60,00%	36,40%	0,00%	0,00%	0,00%	0,00%	5,60%	29,10%
SD %	63,00%	47,60%	34,80%	66,70%	64,00%	10,00%	13,60%	0,00%	25,00%	15,40%	0,00%	47,20%	32,50%
PR %	21,00%	33,30%	17,40%	33,30%	4,00%	10,00%	13,60%			46,20%	75,00%	38,90%	17,10%
CR %	0,00%	0,00%	4,30%	0,00%	0,00%	0,00%	4,50%	50,00%	75,00%	7,70%	25,00%	2,80%	0,00%

Figure 2 Table with bar plots illustrating the principal molecular alterations, their corresponding targeted therapies and the clinical outcomes and response rate found in the various clinical trials discussed in the previous section. For each mutation-therapy pair, the bars depict treatment responses categorised as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Patients who were not evaluable or not included in trial outcomes are shown in the uppermost segment of each bar (Other/NE). A colour gradient is applied to enhance visualisation—darker green shades indicate more favourable responses, while darker grey tones denote disease progression or cases that remain unevaluated. On the right side of each panel, bar plots represent survival outcomes: progression-free survival (PFS) in orange and overall survival (OS) in salmon. The left y-axis corresponds to response rates (in percentages), while the right y-axis indicates survival durations (in months). Note: For larotrectinib and entrectinib, trial publications combined CR and PR rates, although they are separated in the summary table for clarity. The NAPOLI-1 trial (far right) is shown for context, as a comparison to the targeted therapies.

instability and tumourigenesis. BRCA1 and 2 alterations are found in approximately 5–10% of familial PDAC cases and about 3% of sporadic ones (figure 1). These mutations are more commonly associated with KRAS wild-type tumours and exhibit lower frequencies of other PDAC canonical alterations such as TP53, CDKN2A and SMAD4. Among other HRR-related genes, ATM and PALB2 mutations occur in approximately 2–6% and 0.5% of PDAC cases, respectively,[8] thus expanding the pool of potential candidates for DNA repair-targeted therapies. BRCA-mutated patients tend to be diagnosed at a younger age and often present distinct molecular features. HRR gene deficiency, whether germline or somatic, has been linked to an increased sensitivity to platinum-based chemotherapy and is also associated with a more favourable prognosis.[9 10] Based on genomic instability, poly (ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, have emerged as promising therapies by exploiting deficiencies in DNA repair through the inhibition of base excision repair and the trapping of the PARP enzyme.[11] Initially studied as potential therapeutic treatment in breast and ovarian cancer, they have also demonstrated clinical activity as first-line or maintenance therapy in PDAC, especially in BRCA1/2, ATM and PALB2-mutated tumours.[11] In a phase II study by Kaufman *et al*,[12] olaparib as second-line monotherapy showed a 27% response rate and stable disease (SD) in 35% of patients, with a mOS of 9.8 months and mPFS of 4.6 months as represented in figure 2. Adverse events consisted principally of fatigue and gastrointestinal toxicity. Additionally, the phase III POLO trial evaluated olaparib as maintenance therapy, demonstrating a longer mPFS (7.4 months vs 3.8 months) without a significant OS benefit.[13]

BRAF mutations

B-raf proto-oncogene (BRAF) mutations are found in 2–4% of patients with advanced PDAC as illustrated in figure 1, with a higher incidence in KRASwt tumours (10–30%) than in KRASmut (1.5–3%).[14] The most frequent variant, BRAFV600E, initiates tumourigenesis and promotes tumour growth by activating the MAPK pathway. Combination therapy with dabrafenib and trametinib was evaluated in the phase II BELIEVE basket trial, which included three patients with PDAC and BRAFV600E mutations.[15] One achieved a PR, while the other two demonstrated SD under treatment, resulting in an overall response rate (ORR) of 33.3% and a disease control rate (DCR) of 100%, with an mPFS of 5.2 months

(figure 2). Reported adverse events included fever, anaemia and elevated transaminases, mostly grade 1–2.

MSI-H/dMMR

Microsatellite instability-high (MSI-H) and mismatch repair deficiency (dMMR) are found in about 1–3% of PDAC cases (figure 1). These tumours typically exhibit elevated tumour mutational burden, increased neoantigen load and prominent CD8+ tumour-infiltrating lymphocytes, contributing to their immunogenicity and sensitivity to immune checkpoint inhibitors. Pembrolizumab, an anti-PD-1 antibody, has demonstrated clinical benefit in this tumour subset. Based on data from KEYNOTE-158 and other studies, pembrolizumab received tumour-agnostic Food and Drug Administration (FDA) approval for MSI-H/dMMR solid tumours. In figure 2, the results of the KEYNOTE-158 trial are presented where 22 patients with PDAC achieved an ORR of 18.2%, with an mPFS of 2.1 months and mOS of 3.7 months.[16] Common adverse events included fatigue, diarrhoea and pruritus. Pembrolizumab maintained a durable and clinically significant antitumour activity with a manageable safety profile in patients with advanced MSI-H/dMMR malignancies.

NTRK fusions

TRK receptors, encoded by *NTRK* (*Neurotrophic Tyrosine Receptor Kinase*) genes, are expressed in neural tissue and play key roles in development and cellular signalling, particularly in the nervous system. *NTRK* gene fusions, although extremely rare in PDAC (<1%) as shown in figure 1, result in chimeric oncoproteins that drive tumourigenesis independently of KRAS and other common mutations.[17] Larotrectinib, a selective TRK inhibitor, received tumour-agnostic FDA approval after demonstrating a 75% ORR across various tumour types in early-phase trials.[18] In a pooled analysis including two evaluable PDAC cases, one achieved a PR for 3.5 months (figure 2).[19] Entrectinib, another TRK inhibitor showcased in figure 2, demonstrated similarly encouraging results in pooled analyses of STARTRK-1, STARTRK-2 and ALKA-372-001 trials. Among four patients with PDAC, the ORR was 75%, with an mPFS of 12.8 months and mOS of 22 months.[20 21] No treatment discontinuations occurred due to toxicity, with most adverse events being manageable and reversible with dose modification.

RET fusions

RET (REarranged during Transfection proto-oncogene) fusions occur in fewer than 1% of PDAC (figure 1) and lead to constitutive activation of RET tyrosine kinase.[22] Selpercatinib, a selective RET inhibitor included in figure 2, was evaluated in a phase I–II basket trial by Subbiah *et al* and demonstrated a 54.5% ORR among patients with PDAC harbouring RET fusions.[22] Although the median duration of response was not reached, the therapy showed evidence of disease control. In a 2024 ASCO gastrointestinal cancer update of the same trial, 7 of 13 patients with PDAC responded to selpercatinib, including one CR and two additional patients with SD, resulting in a disease control rate of 69.2% (figure 2).[23] Pralsetinib, another selective RET inhibitor that we included in figure 2, showed a 100% RR within the four patients with PDAC in the ARROW phase I–II trial, including one CR lasting over 33 months.[24] The most common reported adverse events included elevated liver enzymes and neutropenia, with grade ≥3 events occurring in a subset of patients.

HER2 alterations

The *Human Epidermal growth factor Receptor 2* (*HER2/ERBB2*) gene encodes the HER2 protein. Amplification, overexpression or activating mutations are found in about 1–7% of PDAC cases as illustrated in figure 1. These alterations frequently co-occur with KRAS mutation—observed in nearly 72%—which have been associated with resistance to HER2-targeted therapies in other tumour types.[25] Moreover, HER2 amplification and overexpression have been linked to poorer clinical outcomes in PDAC.[26] Clinical activity from HER2-directed therapy has been modest. In the MyPathway basket trial, trastuzumab and pertuzumab produced a 10% ORR and 20% DCR among 10 evaluable patients with PDAC, with median PFS and OS of 7.1 and 7.5 months, respectively (see figure 2).[27] Notably, these responses were observed exclusively in patients with KRASwt PDAC, whereas no responses were reported in KRAS-mutated cases, highlighting the impact of KRAS status on therapeutic efficacy. The DESTINY-PanTumor02 study tested the antibody–drug conjugate trastuzumab-deruxtecan (T-DXd), reporting a 4% response rate but SD in 64% of patients, translating to median PFS 3.2 months and OS 5 months (figure 2).[28] Treatment-related adverse events ≥G3 were observed in 12.1% of patients in MyPathway, but 40.8% with T-DXd.

NRG1 fusions

Neuregulin 1 (NRG1) fusions are identified in approximately 0.5% of PDAC (figure 1), almost exclusively in KRASwt tumours. By driving aberrant ERBB2/3 signalling, they act as oncogenic drivers promoting tumour progression. The detection of NRG1 fusions was improved with the introduction of RNA-sequencing, as the complexity and variability of these fusions may be missed by DNA-sequencing.[29] Figure 2 displays the phase II eNRGy trial where the bispecific HER2/HER3 antibody zenocutuzumab produced an ORR of 41.7% including 1 CR and 14 PR in 36 evaluable patients with PDAC. The median PFS was evaluated at 9.2 months.[30] Additionally, 17 other patients achieved SD, resulting in a DCR of 88.9%. These findings establish NRG1 fusions as actionable targets, with zenocutuzumab emerging as a promising treatment for this molecular subset. Consequently, the FDA approved this therapy in December 2024, making it the first targeted treatment for NRG1 fusion tumours, especially in NSCLC and PDAC.[31 32] Toxicity related to treatment of

any grade consisted mainly of gastrointestinal side effects and fatigue. Supportive evidence also comes from case reports of the pan-ERBB inhibitor afatinib, which has induced meaningful tumour shrinkage and symptomatic benefit, warranting formal prospective evaluation.[29]

DISCUSSION

Over the past decade, the molecular profile of PDAC has been more clearly characterised, uncovering a variety of new potential target alterations as illustrated in figure 1. However, despite these advancements, the integration of this knowledge into clinical benefit has remained a challenge. While the majority of PDAC tumours express mutations that are not currently actionable, a small subset of tumours, particularly those harbouring KRAS wild type, carry alterations that can be targeted with clinically meaningful outcomes.

The evidence presented in this review highlights that even though targeted therapies apply to a small subset of patients, their impact should not be underestimated. Figure 2 provides an overview of the clinical trials reviewed in this article that investigated targeted therapies for KRASG12C, BRCA1/2, MSI-H/dMMR, NTRK, RET, BRAF, NRG1 and ERBB2 alterations in PDAC. Reported response rates and survival outcomes frequently matched or surpassed those achieved with standard chemotherapy. For comparison, data from the NAPOLI-1 trial—considered a benchmark for second-line chemotherapy in PDAC—are included on the far right of figure 2. Many of the targeted therapies discussed here demonstrate comparable or better outcomes with potentially improved tolerability.

While these results offer promising outcomes for patients with PDAC, it is important to acknowledge several limitations that constrain the generalisability of these findings. Most of the clinical trials discussed are early-phase, often non-randomised or basket trials that involve a small number of selected patients with PDAC. Such trial designs inherently carry a risk of selection bias and lack the robustness of randomised, prospective controlled trials. Consequently, the extrapolation of these results to the broader PDAC population must be made cautiously. Additionally, despite encouraging response rates for some alterations—particularly RET and NTRK fusions, which reported ORR above 50%—most targeted therapies are still under early investigation and require validation in larger, controlled studies. Moreover, reported outcomes were predominantly constituted of partial response or stable disease, often with limited durations of benefit. Nevertheless, these different trials represent the most meaningful advances seen in PDAC treatment in recent years. Precision oncology in PDAC is no longer a future idea; it is beginning to transform treatment approaches, with systematic and comprehensive molecular profiling now a vital component of care in advanced stages of PDAC. Identifying these rare but actionable mutations offers patients an opportunity for more personalised and potentially more effective treatments.

Several emerging targets of biological and therapeutic relevance are highlighted on the left side of figure 1. Methylthioadenosine phosphorylase (MTAP) deletions, present in about 18.4% of PDAC, often co-occur with mutations in CDKN2A/B and KRAS, correlating to a worse prognosis. The homozygous loss of MTAP disrupts the methionine salvage pathway, resulting in a reliance on PRMT5. Early-phase trials are exploring PRMT5 inhibitors within this patient group, potentially leading to innovative treatments for tumours with MTAP deletion.[33] Finally, KRAS, long described as undruggable, is now being targeted with specific inhibitors for variants or broader categories. MRTX1133, a selective non-covalent inhibitor of KRAS G12D, the most prevalent KRAS mutation in PDAC (34%), has shown promising preclinical results, with tumour regression in 73% of PDAC xenograft models, supporting future clinical development.[34] Rat sarcoma (RAS) (ON) inhibitors are designed to inhibit RAS signalling directly. Daraxonrasib is currently being evaluated in a phase I trial for KRAS-mutated PDAC, reporting an ORR of 27% and a DCR of 95% among the 37 patients included.[35] These results are encouraging and deserve careful consideration, as they could significantly expand our therapeutic options if larger studies confirm clinical efficacy.

CONCLUSION

In this review, we have compiled clinically significant data on actionable mutations in PDAC. Although the range of targetable alterations in PDAC is limited due to their rarity and resistance to treatment, the development of targeted therapies and tumour-agnostic agents creates new opportunities for personalised strategies in a disease that remains aggressive with minimal clinical progress over recent decades. Systematic genomic profiling is essential for identifying clinically significant targets to expand therapeutic options and improve patient outcomes.

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