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REVIEW

Drugging the 'undruggable' KRAS: breakthroughs, challenges, and opportunities in pancreatic cancer

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ABSTRACT Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with a poor prognosis that is driven primarily by oncogenic KRAS mutations present in > 90% of cases. KRAS mutations, particularly the G12D mutation which dominates in PDAC, fuel tumor initiation, progression, and immune evasion, thereby contributing to therapy resistance. Nevertheless, KRAS has long been considered "undruggable" due to its structure. Recent advances have spurred transformative progress in direct KRAS inhibition. While FDA-approved mutation-specific and pan-KRAS inhibitors show limited efficacy in PDAC, emerging agents (MRTX1133 and RMC-9805) have demonstrated preclinical promise. However, resistance remains a critical hurdle and is driven by pathway reactivation, secondary mutations, and metabolic adaptations. Alternative strategies targeting upstream regulators (SHP2 and SOS1) aim to block KRAS activation and associated resistance mechanisms. Preclinical studies have also highlighted synergistic benefits of combining KRAS inhibitors with MEK, PI3K, or CDK4/6 inhibitors, which are now undergoing clinical evaluation. Immunotherapies, including KRAS-targeted vaccines and adoptive T-cell therapies, have further expanded the therapeutic landscape of enhancing KRAS-targeted therapies in PDAC. The molecular basis of KRAS-driven PDAC, current inhibitors, resistance mechanisms, and innovative strategies are discussed herein to address treatment barriers. Opportunities to improve clinical outcomes are underscored in this challenging malignancy by integrating insights from preclinical and clinical research.

KEYWORDS Pancreatic cancer; KRAS mutations; KRAS inhibitors; therapy resistance; immunotherapy

Introduction

Pancreatic ductal adenocarcinoma (PDAC), representing nearly 90% of pancreatic malignancies, is one of the most aggressive cancers with a dismal 5-year survival rate of approximately 13%[1]. The prognosis for PDAC remains bleak with most patients surviving less than 12 months post-diagnosis[2,3]. Alarmingly, rising incidence rates now exceed survival gains, positioning PDAC to become the second-leading cause of cancer-related deaths in the U.S. by 2030[4]. Surgical resection and chemotherapy form the cornerstone of clinical management for PDAC. Current data indicate that surgical eligibility is limited to 15%–20% of individuals at the time of initial diagnosis[5,6]. This narrow eligibility critically influences prognosis because surgery offers the highest potential for long-term survival. A key challenge arises from the fact that > 80% of PDAC cases are detected in locally advanced or metastatic stages (**Figure 1A**)[1], excluding most patients from curative surgical options. Consequently, systemic chemotherapy has long served as the default therapeutic approach, even for those patients undergoing surgery. However, conventional chemotherapeutic agents often induce debilitating toxicities[7], which markedly reduce patients' functional capacity and quality of life[8]. Recent advances have established two primary regimens for metastatic PDAC: leucovorin, 5-fluorouracil, irinotecan,

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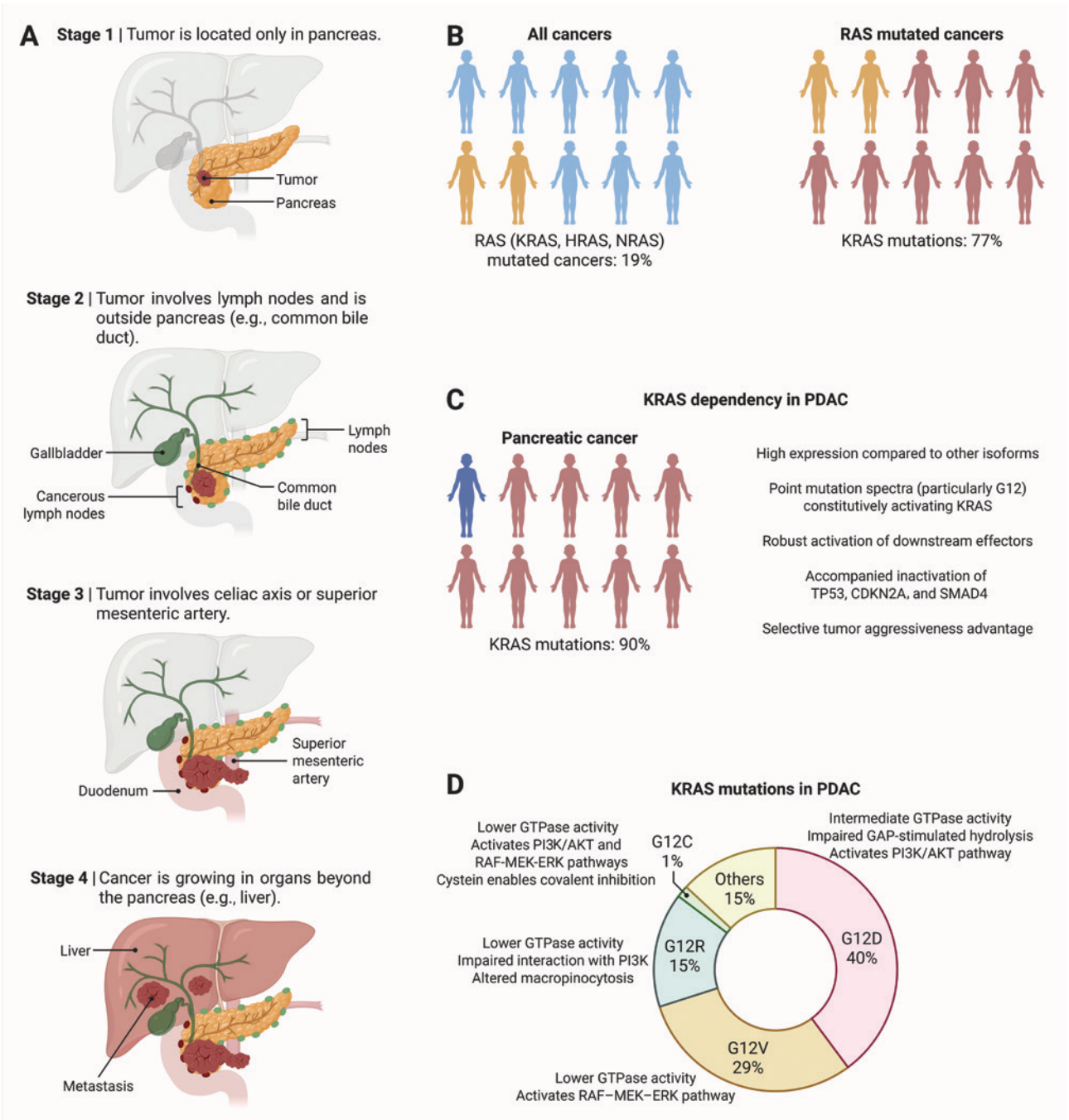


Figure 1 Mutations in KRAS drive PDAC. (A) Illustration depicting different stages of PDAC, in which tumors originating in the pancreas (stage 1) first extend to lymph nodes and bile ducts (stage 2), then invade the superior mesenteric artery (stage 3) and metastasize to other organs, such as the liver (stage 4). (B) Prevalence of RAS mutations in pancreatic cancer. RAS are mutated in 19% of all tumors, whereas 77% of RAS-mutated tumors exhibit KRAS mutations. (C) KRAS dependency in PDAC. In the case of PDACs, 90% of tumors harbor mutations in KRAS with different factors (listed) contributing to this dependency in PDAC. (D) KRAS mutations in PDAC. Among KRAS mutations in PDAC, 40% of mutations are G12D, 29% are G12V, 15% are G12R, and 1% are G12C. All these mutations confer distinct functional impacts on KRAS, leading to aberrant downstream signaling and contributing to disease onset and progression in PDAC.

and oxaliplatin (FOLFIRINOX)[7]; and gemcitabine combined with nab-paclitaxel[9]. Clinicians may transition patients to the alternative regimen when disease progression occurs or toxicity limits tolerability. Standardized protocols for second-line therapy remain undefined and nearly 50% of individuals discontinue active treatment after first-line failure[10]. Notably, patients switching to gemcitabine/nab-paclitaxel following FOLFIRINOX exhibit minimal clinical benefit with a mere 2.9% objective response rate, while 85% endure severe treatment-related complications[11].

Increased PDAC survival has largely been confined to patients with early-stage disease. Enhanced imaging modalities, refined surgical methods, and the strategic application of neoadjuvant chemotherapy to facilitate resection have improved outcomes for localized tumors[5,12,13]. Over the last 8 years, the 5-year survival for regionally confined disease has increased from 38%–60%, while metastatic cases, which represent > 50% of diagnoses, have had minimal improvement (2%–3%)[1,14]. This stark disparity underscores the urgent need for systemic therapies targeting advanced PDAC. KRAS has been a focal point of oncology research for decades due to its central role in tumorigenesis[15]. Given that KRAS mutations serve as both the primary oncogenic driver[16,17] and a sustained dependency in established tumors[18,19], effective KRAS-targeted therapies could revolutionize care, particularly for metastatic patients lacking viable options. However, KRAS has long resisted therapeutic targeting and has therefore earned its reputation as "undruggable"[20,21]. Notably, recent breakthroughs have overturned this narrative with pioneering drugs, like sotorasib and adagrasib, receiving accelerated FDA approval as the first direct KRAS inhibitors[22,23], marking a new era in precision oncology.

This comprehensive review discusses KRAS signaling-driven molecular bases of PDAC onset and progression and highlight clinically developed KRAS inhibitors along with the efficacy and safety profiles from clinical trials. In addition, the molecular mechanisms underlying resistance to KRAS-targeted agents are explored and pinpoint emerging strategies to overcome these barriers. By integrating these perspectives, this review aims to chart a path toward KRAS-targeted transformative therapies for this recalcitrant malignancy.

KRAS and PDAC

Cancer arises from the accumulation of somatic genetic alterations that confer proliferative and survival advantages to cells. Among these alterations, driver mutations in oncogenes and tumor suppressors are central to tumor initiation and progression[24]. Large-scale cancer genome sequencing initiatives have revealed that mutations in a relatively small set of driver genes are responsible for most human cancers. Among these mutations, TP53 mutations are the most frequent and are found in > 50% of tumors across cancer types, serving as a critical gatekeeper of genome integrity and apoptosis[25]. Following TP53, mutations in the RAS family of small GTPases (KRAS, NRAS, and HRAS) collectively represent among the most common oncogenic events, occurring in approximately 19% of cancers (**Figure 1B**)[26]. In this section how KRAS dependency and mutations shape the molecular landscape of PDAC leading to tumor progression, metabolic adaptations, and immune evasion will be explored.

KRAS dependency in PDAC

Despite sharing approximately 85% of the amino acid sequence identity in the GTPase (G) domains, RAS isoforms differ significantly in hypervariable regions (HVRs), post-translational modifications, membrane localization, and tissue-specific expression, which influence distinct biological roles and mutation patterns[27]. Functionally, all RAS isoforms regulate signaling pathways that control cell proliferation, differentiation, and survival (i.e., the RAF–MEK–ERK and PI3K–AKT cascades). However, differential subcellular localization leads to distinct signaling outputs. KRAS is predominantly localized to the plasma membrane with rapid cycling dynamics, while HRAS and NRAS are distributed between the plasma membrane and endomembrane compartments, which contributes to isoform-specific signal regulation[28]. Notably, among RAS-mutated tumors, KRAS dominates by contributing to 77% of RAS-driven malignancies and exhibits pronounced prevalence in the 3 most lethal cancers (lung, colorectal, and pancreatic tumors)[1,27]. Specifically, KRAS alterations are present in approximately 33% of lung carcinomas, 50% of colorectal cancers, and > 90% of pancreatic malignancies (**Figure 1B,C**)[26]. The exceptionally high frequency of KRAS mutations in PDAC highlights the role of KRAS mutations as the principal oncogenic drivers and critical targets for therapeutic intervention[29]. Several factors contribute to the heavy mutation burden of KRAS in PDAC (**Figure 1C**). For example, KRAS is the most abundantly expressed isoform in tissues prone to KRAS-driven cancers, such as the pancreas and lung epithelium, providing a larger mutational target and functional

dependency[30]. This centrality renders mutations that constitutively activate KRAS particularly advantageous for tumor cells, driving unchecked growth and metabolic reprogramming[18]. This tissue-specific expression and dependency on KRAS, especially in pancreatic epithelial cells, also predispose the tissues to undergo KRAS-driven oncogenesis[31]. In addition, KRAS facilitates stable plasma membrane association and robust activation of downstream effectors, which may potentiate oncogenic signaling more effectively than HRAS or NRAS variants[18,31]. Furthermore, the genomic context of PDAC, which frequently includes loss of tumor suppressors (TP53, CDKN2A, and SMAD4), synergizes with KRAS mutations to facilitate malignant transformation and progression[32]. This gradual loss of tumor suppressor genes serves as a pivotal mechanism driving disease progression, while simultaneously fostering phenotypic diversity among KRAS-driven malignancies[33]. Moreover, differences in mutational processes and the selective advantage conferred by KRAS mutations likely explain why NRAS and HRAS mutations are more frequent in other cancer types, such as melanomas and head and neck cancers, respectively[27]. Finally, mutational processes and DNA repair mechanisms influence the mutation spectra with KRAS codon 12 serving as a mutational hotspot due to its location in the nucleotide-binding pocket, where substitutions markedly impair GTPase activity and stabilize the active GTP-bound form (discussed in detail in Section 2.2)[28]. This combination of functional advantage, tissue-specific vulnerability, and mutational susceptibility explains why KRAS mutations are both frequent and critical in PDAC and other cancers.

Oncogenic KRAS perturbations in PDAC

Oncogenic KRAS mutations predominantly occur at hotspot codons (12, 13, and 61) with approximately 95% of mutations affecting these sites[34]. Codon 12 mutations in PDAC are most common with glycine replaced by aspartate (G12D, 40%), valine (G12V, 29%), arginine (G12R, 15%), or cysteine (G12C, ~1%; **Figure 1D**)[35]. Mutations at codons 13 and 61 are less frequent, although the $KRAS^{Q61H}$ mutation (5% of PDACs) is associated with improved survival[36,37]. In contrast, the $KRAS^{G12D}$ variant correlates with poorer outcomes[38]. Codon 12 mutations are particularly prevalent because this residue lies within the P-loop that interacts directly with the phosphate groups of GTP/GDP[39]. These mutations increase KRAS affinity for GTP and induce conformational changes that hinder GAP-mediated hydrolysis and reduce intrinsic GTPase activity, thereby locking KRAS in its constitutively active GTP-bound state, which drives aberrant downstream signaling[28]. Different substitutions at G12 confer distinct biochemical and signaling properties, which likely reflect both mutational processes (e.g., GGT → GAT transitions in G12D) and selective advantages within specific tissue microenvironments (**Figure 1D**)[40]. For example, G12D exhibits intermediate intrinsic GTPase activity and markedly impaired GAP-stimulated hydrolysis. G12D preferentially activates the PI3K/AKT pathway, which contributes to metabolic reprogramming and survival signaling. G12V displays lower intrinsic GTPase activity compared to G12D and stronger activation of the RAF–MEK–ERK pathway[28]. G12R provides distinct signaling biases, including impaired interaction with PI3Kα and altered macropinocytosis, potentially leading to differential metabolic dependencies[40]. The cysteine residue in G12C introduces a nucleophilic site amenable to covalent inhibition, which underpins the successful development of allele-specific targeted therapies[41]. Functionally, these mutations bias downstream signaling to different extents, affecting cell proliferation, survival, metabolic adaptation, and immune evasion pathways[28,42]. The prevalence of codon 12 mutations in PDAC likely arises from both mutagenic signatures and functional selection. For example, the ability of G12D to support glutamine-driven metabolism may explain its dominance in pancreatic tissue[43]. Different KRAS mutations exhibit distinct biological behaviors as well. For example, codon 12 and 61 mutations are resistant to NF1-mediated hydrolysis[44]. Similarly, among G12 mutants, G12D and G12C exhibit higher intrinsic GTPase activity than G12R and G12V[28]. In return, variations in RAF kinase activation levels influence the prognostic outcomes associated with different KRAS mutant alleles[45]. In addition to point mutations, KRAS signaling can be dysregulated through gene amplifications[46], which can also drive resistance to MAPK inhibitors[47]. As discussed earlier, KRAS mutations in PDAC are frequently accompanied by inactivating alterations in the well-established tumor suppressors, like TP53, CDKN2A, and SMAD4[32]. Concurrent mutations in serine/threonine kinase 11 (STK11) and dysregulation of PI3K/AKT/mTOR signaling are also associated with a poor prognosis in PDAC[48]. Clinically, patient survival trajectories show strong correlation with the total genomic burden of pathogenic variants because each additional cancer-promoting genetic alteration substantially diminishes therapeutic responsiveness and disease management potential, leading to poor survival outcomes[38,49]. In summary, mutations and

amplifications in KRAS, along with co-occurring genetic alterations, contribute to the complexity and heterogeneity of cancers, such as PDAC, underscoring the need for targeted and combination therapeutic strategies.

KRAS-driven signaling pathways

KRAS is transcribed from chromosome 12p[50]. The KRAS protein product consists of two main domains (a catalytic "G domain" and a C-terminus variable region)[31]. Inactive KRAS is bound to guanosine di-phosphate (GDP), which prevents downstream signaling. The G domain undergoes conformational changes, resulting in transition of KRAS from the inactive (GDP-bound) state to the active guanosine triphosphate (GTP-bound) state. External stimuli, such as epidermal growth factor (EGF) or cytokines, activate guanine nucleotide exchange factors (GEFs), which reduce KRAS affinity for GDP and permits GTP to bind and switch KRAS to the active state. Key GEFs include Son of sevenless homolog 1 (SOS1), SOS2, growth factor receptor-bound protein 2 (GRB2), and RASGRF2[51]. Src homology region 2-containing protein tyrosine phosphatase (SHP2), a protein tyrosine phosphatase, acts as a scaffold by binding to GRB2, facilitating the formation of the GRB2/SOS1 complex at the cell membrane and promoting KRAS activation[52]. Active KRAS interacts with the RAS-binding domains of effector proteins, initiating downstream signaling cascades. Key effectors include RAF proteins, RALGDS, and PI3Ks. A central pathway activated by KRAS is the RAF–MEK–ERK cascade. KRAS triggers RAF phosphorylation, leading to RAF dimerization, which subsequently activates ERK1 and ERK2[53]. Upon translocation of ERK to the nucleus, phosphorylated ERK activates transcription factors, driving cell cycle progression through G0/G1 mitogenic signals[54]. Another critical downstream signaling axis regulated by KRAS is the PI3K/AKT pathway, which recruits and activates AKT, regulating cell proliferation, apoptosis, and metabolic processes[55]. Feedback phosphorylation involving mTOR targets enhances cell proliferation and inhibits apoptosis *via* enhancing Bcl-XL and Bcl-2 expression[56]. Additionally, RalA and RalB GTPases collaborate with the RAF and PI3K pathways to promote cell migration and proliferation through activation of the Jun-N-terminal kinase (JNK) pathway[57]. GTP on KRAS must be hydrolyzed to GDP to return to an inactive state. While KRAS has limited intrinsic GTPase activity, this process is accelerated by GTPase-activating proteins (GAPs), such as neurofibromin-1 (NF1) and p120-RasGAP (encoded by RASA1; **Figure 2**)[58]. Overall, KRAS signaling has a central role in driving oncogenic processes through multiple downstream pathways, including RAF/MEK/ERK, PI3K/AKT, and Ral effector signaling.

Oncogenic KRAS-driven tumor progression in PDAC

PDAC arises from two main precursor lesions (pancreatic intraepithelial neoplasia [PanIN], accounting for 85%–90% of cases and intraductal papillary mucinous neoplasms [IPMNs], representing 10%–15% of cases). KRAS mutations are detectable, even in early-stage PanIN lesions, emphasizing the pivotal role of KRAS in the initial stages of tumorigenesis. However, the development of invasive PDAC requires additional genetic alterations beyond KRAS mutations. A widely accepted stepwise model describes the progression from precursor lesions to invasive cancer[59,60]. However, emerging evidence suggests that chromothripsis (large-scale genomic rearrangements) may enable rapid disease progression, bypassing the traditional stepwise model[61]. Cystic lesions, which are easily identifiable through imaging, have been increasingly recognized for malignant potential. These lesions often harbor recurrent genetic alterations in KRAS with further mutations observed in invasive PDAC[62,63]. Transcriptional profiling of primary tumors and metastatic samples has identified two major subtypes (basal-like and classical with hybrid phenotypes indicating significant tumor plasticity). The basal-like subtype is more prevalent in metastatic lesions, is associated with pronounced KRAS mutational imbalances[64], and correlates with poor outcomes in PDAC[65,66], suggesting that evolutionary pressures during disease progression favor the emergence of more malignant subtypes.

Oncogenic KRAS-driven metabolic adaptations in PDAC

Metabolic reprogramming is a hallmark of cancer. KRAS mutations in PDAC drive metabolic shift towards aerobic glycolysis that enables the production of glucose, glutamine, and fatty acids, which fuel tumor growth and proliferation. The metabolic effects of KRAS mutations appear to be tumor-specific, influenced by the specific KRAS allele involved[67]. Specifically, KRAS mutations upregulate the GLUT1 transporter and enhance glycolytic enzyme activity, increasing glucose uptake and utilization[19]. Another profound metabolic transformation

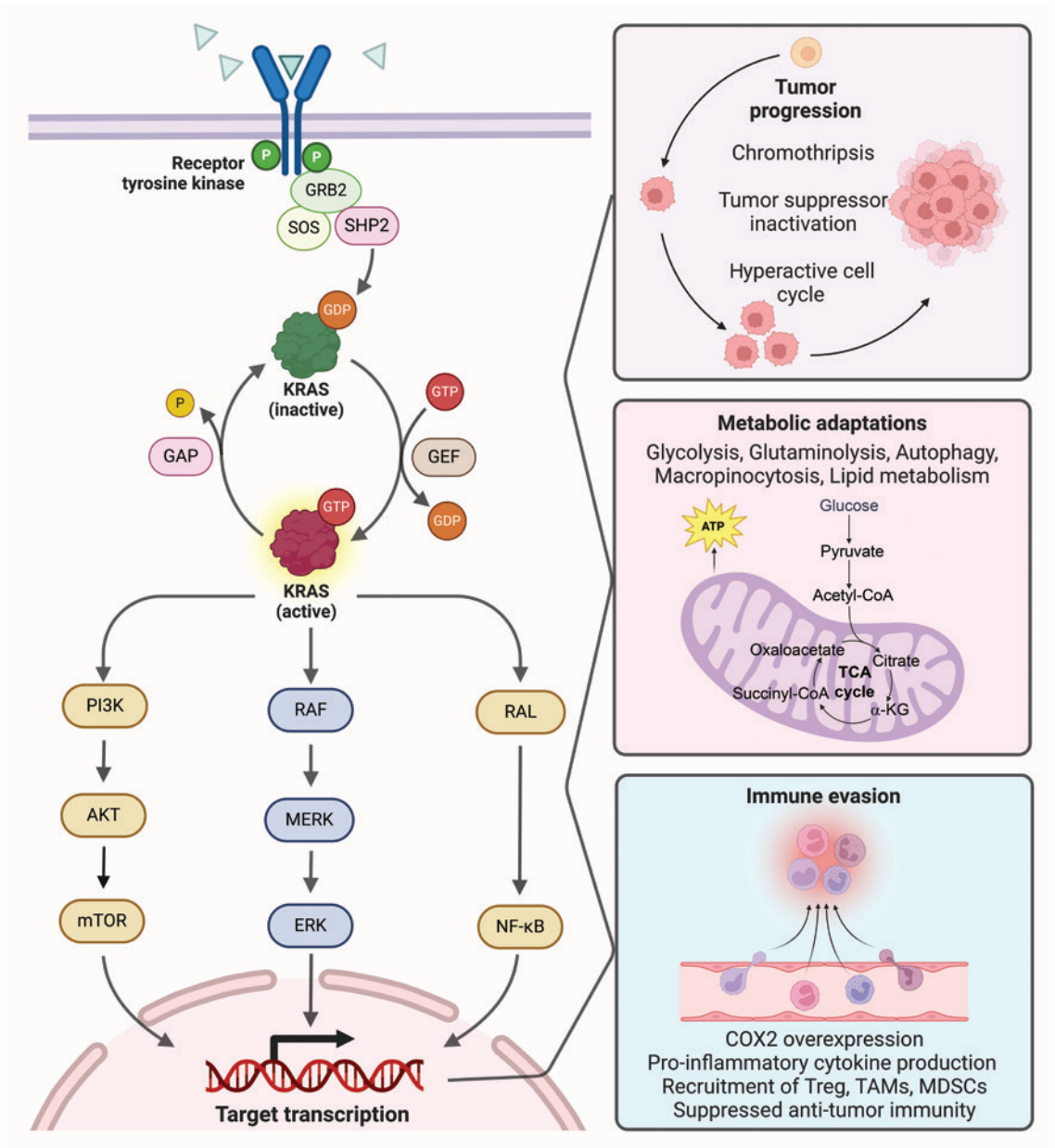


Figure 2 Oncogenic KRAS in PDAC. Receptor tyrosine kinases activate KRAS (wild type or mutated) driving various signaling cascades, like PI3K/AKT/mTOR, RAF/MERK/ERK, and RAL/NFkB signaling promoting tumor aggressiveness. Oncogenic KRAS signaling in PDAC drives tumor progression by hyperactivating cell cycle progression in conjunction with chromothripsis and tumor suppressor inactivation by fueling metabolic adaptations, such as glycolysis, glutaminolysis, autophagy, macorpinocytosis, and enhanced lipid metabolism, and by promoting immune evasion *via* COX2 overexpression, pro-inflammatory cytokine production, and recruitment of inhibitory immune cells, thereby suppressing anti-tumor immunity.

in KRAS-mutated tumors is the heightened reliance on glutamine to fuel survival and growth. Glutamine metabolism has a vital role in maintaining cellular redox balance by regulating the NADP+/NADPH ratio and thereby maintaining tumor viability[68]. KRAS mutations in PDAC rewire cellular processes to prioritize glutamine absorption and breakdown *via* the enzyme, glutaminase (GLS), generating glutamate that directly fuels the tricarboxylic acid (TCA) cycle. This adaptation enables KRAS-mutated cells to sustain energy production and generate biosynthetic precursors essential for rapid

proliferation (**Figure 2**)[69,70]. KRAS-driven synthesis of aspartate from glutamine fuels nucleotide production, a prerequisite for unchecked cell division[71]. To optimize this process, KRAS suppresses glutamate dehydrogenase (GDH) while upregulating glutamate-oxaloacetate transaminase (GOT), redirecting aspartate to the cytoplasm. Aspartate contributes to redox balance through NADPH generation *via* malic enzyme 1, linking metabolic activity to cellular defense mechanisms[72]. KRAS mutations further amplify tumor resilience by stabilizing nuclear factor erythroid 2-related factor 2 (NRF2), a master regulator of antioxidant and metabolic genes. NRF2 activation boosts glutaminolysis by elevating enzymes, like GLS1 and GOT1, while enhancing cellular defenses against reactive oxygen species. This dual mechanism sustains metabolic flux and fosters resistance to chemotherapy in PDAC, complicating treatment outcomes[73,74]. The interplay between these metabolic adaptations and PDAC progression extends to sirtuin 5 (SIRT5), a modulator of glutamine utilization. Loss of SIRT5 activity shifts glutamine metabolism toward non-canonical pathways involving GOT1, inadvertently accelerating tumor formation[75]. Additionally, KRAS-driven PDAC tumors exploit ornithine aminotransferase (OAT) to convert glutamine into polyamines, molecules critical for tumor progression[76].

Nutrient scavenging pathways, such as autophagy, are often upregulated in PDAC, sustaining the TCA cycle and supporting tumor growth[77,78]. Autophagy is induced downstream of oncogenic KRAS *via* activation of signaling cascades involving AMPK, which phosphorylates ULK1 to initiate autophagosome formation, while simultaneously inhibiting mTORC1 to relieve autophagy suppression[78]. This coordinated activation sustains cellular bioenergetics and macromolecular turnover under nutrient deprivation, conferring metabolic plasticity critical for PDAC progression[79]. The transcription factor, MYC, which is stabilized downstream of KRAS *via* ERK signaling, transcriptionally upregulates genes essential for autophagy and lysosome biogenesis, such as TFEB and lysosomal hydrolases, and enhances lysosomal degradation capacity and recycling efficiency[80,81]. This MYC-driven autophagy modulation couples metabolic demand with intracellular resource recycling, enabling tumor survival and resistance to chemotherapy. Targeting RAS effector pathways, such as ERK signaling, may increase tumor dependence on autophagy, necessitating combination therapies[82]. Another critical nutrient scavenging metabolic process in PDAC is macropinocytosis, which allows cells to engulf extracellular material to meet metabolic demands (**Figure 2**)[83,84]. KRAS mutations promote macropinocytosis through activation of downstream effectors, such as RAC1 and PAK1, which regulate actin cytoskeletal dynamics critical for macropinosome formation[85,86]. MYC also has a pivotal role by enhancing expression of genes involved in nutrient uptake and vesicle trafficking, thereby promoting efficient macropinocytic nutrient acquisition[82]. Recent studies have revealed allele-specific differences in micropinocytosis, such as tumors with the $KRAS^{G12R}$ mutation, have been shown to exhibit impaired activation of the p110α PI3K effector, which reduces macropinocytic uptake, suggesting a functional heterogeneity among KRAS mutants in regulating nutrient scavenging pathways[67].

Lipid metabolic pathways are also hijacked in KRAS-mutant cancers. For example, ATP-citrate lyase, which converts citrate into acetyl-CoA, is upregulated to fuel fatty acid and cholesterol synthesis[87]. This pathway becomes hyperactive in PDACs, supporting the lipid demands of proliferating cells. Concurrently, these tumors suppress hormone-sensitive lipase (HSL), an enzyme responsible for breaking down lipid droplets, leading to lipid accumulation that fuels metastasis and acts as a signaling nexus[88]. Upregulation of fatty acid synthase (FASN), a driver of lipid synthesis, is also common in KRAS-mutant PDAC tumors, further underscoring the role of lipid reprogramming in this malignancy[89]. Overall, oncogenic KRAS drives comprehensive metabolic adaptations in PDAC that could be targeted to disrupt KRAS-driven tumor growth and improve therapeutic efficacy in these tumors.

Oncogenic KRAS-driven immune evasion in PDAC

An immunosuppressive tumor microenvironment is a characteristic of PDAC. The dense stroma in the PDAC tumor microenvironment is largely maintained by cancer-associated fibroblasts (CAFs), which exhibit significant heterogeneity but are broadly categorized into immunosuppressive and immune-enhancing subtypes[90]. KRAS mutations exert cell-extrinsic effects, promoting early immune evasion through the infiltration of immunosuppressive cells[64,91]. Studies using genetically engineered mouse models have demonstrated that KRAS-driven PanIN lesions are associated with an inflammatory tumor microenvironment marked by COX2 overexpression and early recruitment of regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressor cells [MDSCs] (**Figure 2**)[91,92], underscoring the role of KRAS mutations in fostering immune evasion. KRAS-driven

cytokine production, including interleukin 6 (IL-6), activates the JAK1/STAT3 pathway and creates a pro-inflammatory tumor microenvironment that supports tumorigenesis[93,94]. Additionally, KRAS mutations induce the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF), which recruits MDSCs and suppresses anti-tumor immunity[95,96]. Oncogenic KRAS reprograms CAFs in a non-cell-autonomous manner, enabling CAFs to secrete cytokines that recruit immune cells into the tumor microenvironment[97]. Mesenchymal stem cells within the stroma further contribute to tumor invasion and metastasis by secreting factors that sustain this tumor-promoting environment[98]. RAS signaling also upregulates chemokines, such as IL-8[99] and C-X-C motif chemokine receptor 2 (CXCR2)[100], along with NF-κB, which amplify inflammation[101]. Immune escape is further facilitated by PD-L1 upregulation and the conversion of CD4+ cells into regulatory T cells, a process driven by ERK activation and the secretion of IL-10 and transforming growth factor β1 (TGF-β1)[102]. However, some chemokine signatures (e.g., C-X-C motif chemokine ligand 4 [CCL4], CCL5, CXCL9, and CXCL10) are associated with T cell infiltration and may predict responses to immune checkpoint inhibitors in specific PDAC genotypes (**Figure 2**)[103,104]. Overall, KRAS mutations have a central role in PDAC progression by orchestrating an immunosuppressive tumor microenvironment, a deeper understanding of which is critical for developing effective therapeutic strategies.

Targeting KRAS in PDAC

Targeting KRAS directly with drugs has historically been a formidable challenge because designing a reversible inhibitor capable of competing with GTP, to which KRAS binds with picomolar affinity, remains an insurmountable hurdle for drug discovery. Additionally, KRAS lacks deep structural pockets beyond the nucleotide-binding site, making KRAS poorly suited for allosteric inhibition[105]. These obstacles, coupled with the failure of early efforts, such as farnesyltransferase inhibitors[106,107], have cemented the KRAS reputation as "undruggable." As a result, therapeutic strategies have predominantly focused on indirect methods to inhibit mutant KRAS signaling[108]. Unfortunately, these approaches have provided only marginal clinical benefits for PDAC patients. For example, erlotinib, an EGFR inhibitor used with gemcitabine, remains the only approved targeted therapy for PDAC but extends survival by a mere 12 d[109]. Recent breakthroughs have spurred the development of numerous KRAS inhibitors[110]. Beyond the 2 $KRAS^{G12C}$ inhibitors that have received accelerated FDA approval, at least 17 additional $KRAS^{G12C}$ inhibitors, 5 $KRAS^{G12D}$ inhibitors, and 3 pan-RAS inhibitors targeting various mutations are currently in clinical trials[111]. Herein the groundbreaking progress that has been made thus far in PCAC KRAS inhibition is discussed.

Mutation-specific KRAS inhibition in PDAC

In this section current progress in mutation-specific inhibition of KRAS in PDAC with a focus on $KRAS^{G12C}$ and $KRAS^{G12D}$ mutations is explored.

$KRAS^{G12D}$ inhibitors

$KRAS^{G12D}$ is the most prevalent KRAS mutation in PDAC and present in approximately 40% of patients. Cell lines harboring $KRAS^{G12D}$ exhibit a strong dependence on KRAS for survival[112], suggesting that effective $KRAS^{G12D}$ inhibitors could significantly benefit patients with this mutation. Unlike $KRAS^{G12C}$, $KRAS^{G12D}$ lacks a reactive cysteine residue, precluding covalent modification. However, leveraging insights from adagrasib development, Mirati Therapeutics (San Diego, CA, USA) discovered MRTX1133, a reversible $KRAS^{G12D}$ inhibitor that binds to the GDP-bound form through extensive structure-based drug optimization. MRTX1133 is now in clinical trials (NCT05737706)[113,114]. While MRTX1133 favors the GDP-bound state, MRTX1133 also interacts with GTP-bound KRAS by blocking RAF-RAS interactions with active $KRAS^{G12D}$ (**Figure 3**)[114]. MRTX1133 has demonstrated significant antitumor activity in preclinical studies. MRTX1133 was shown to induce dose-dependent reductions in cell viability and suppress oncogenic KRAS signaling in $KRAS^{G12D}$-mutant PDAC cell lines [114,115]. Intraperitoneal administration of MRTX1133 resulted in dose-dependent tumor regression in mouse xenograft models using $KRAS^{G12D}$-mutant HPAC cells with near-complete responses (approximately 85% tumor reduction) without obvious toxicities. In contrast, Revolution Medicines (Redwood City, CA, USA) has advanced RMC-9805, a covalent tri-complex inhibitor targeting active RAS^{G12D}[116,117]. Preclinical models have indicated that RMC-9805 effectively inhibits cell proliferation and suppresses RAS pathway activity *in vitro*. In mouse xenograft models of $KRAS^{G12D}$-mutant tumors, RMC-9805 elicited objective responses in 7 of 9 PDAC models[118]. RMC-9805 is currently being evaluated in a phase I trial for patients with advanced $KRAS^{G12D}$-mutant solid tumors (NCT06040541).

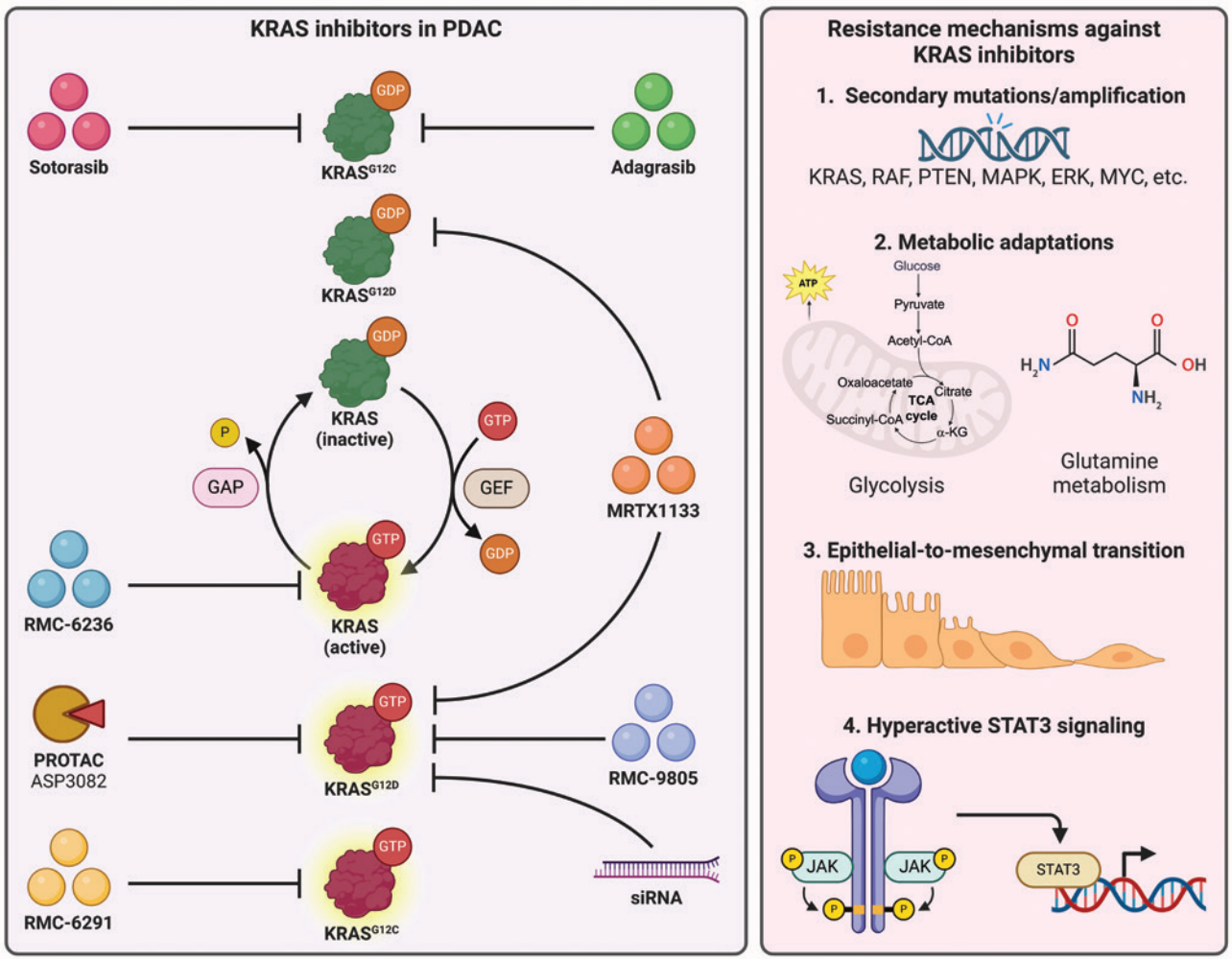


Figure 3 Emerging KRAS inhibitors in PDAC and resistance mechanisms underlying these inhibitors. Different KRAS inhibitors (mutation-specific and general) are being tested in clinical trials for efficacy in limiting tumor burden in PDAC. Among these inhibitors, sotorasib and adagrasib target inactive form of $KRAS^{G12C}$, whereas RMC-6291 is a potent inhibitor of active form of $KRAS^{G12C}$. In contrast, MRTX1133 inhibits active and inactive forms of $KRAS^{G12D}$, whereas RMC-6236 and RMC-9805 only inhibit active form of $KRAS^{G12D}$. In addition, PROTACs and siRNA-based approaches are also being developed to target KRAS in clinical settings. While these approaches have shown promise, resistance against these therapies evolve over time. Secondary mutations and amplifications, metabolic adaptations, epithelial-to-mesenchymal transition, and hyperactive STAT3 signaling represent key resistance mechanisms against KRAS inhibition in PDAC.

Small interfering RNAs (siRNAs) are being actively explored as a way to silence KRAS expression (**Figure 3**). These short RNA molecules are designed to bind to specific messenger RNAs (mRNAs), effectively blocking gene expression[119,120]. Despite high specificity, delivering siRNAs to target cells remains a significant challenge due to rapid degradation, quick renal clearance, and the dense stromal environment of PDAC tumors[121]. One potential solution is the local delivery of siRNA directly into tumors. Fifteen patients with locally advanced PDAC received biodegradable implants (Local Drug EluteR [LODER]; Silenseed Ltd., Jerusalem, Israel) containing siRNA targeting $KRAS^{G12D}$ with systemic chemotherapy in a phase I/IIa study. Among the 12 evaluable patients, 2 had a positive response, while 10 had stable disease with a median overall survival of 15.1 months. However, five patients experienced serious treatment-related adverse events[122]. Exosomes, which are natural nanoscale vesicles capable of delivering molecular cargo, offer another promising delivery method. These vesicles, which express CD47 on the surface, exhibit enhanced efficiency and longer half-lives compared to synthetic liposomes[123]. Exosomes carrying siRNA targeting $KRAS^{G12D}$ have exhibited significant tumor growth inhibition and improved

survival in PDAC mouse models[124]. Targeted degradation of mutant KRAS proteins is another groundbreaking approach in tackling KRAS mutant cancers[125]. Proteolysis targeting chimeras (PROTACs) are a novel class of molecules that leverage the body's natural protein degradation machinery. These bifunctional compounds bind to the mutant KRAS protein and an E3 ubiquitin ligase, tagging the mutant protein for destruction[126]. One such PROTAC, ASP3082, specifically targets $KRAS^{G12D}$ and has demonstrated encouraging preclinical results in suppressing the growth of PDAC cells (**Figure 3**). A phase I clinical trial is currently evaluating the therapeutic potential of ASP3082 in PDACs[125]. Although PROTACs may pose higher toxicity risks, PROTACS represent a unique therapeutic option, particularly for cancers driven by KRAS amplification.

$KRAS^{G12C}$ inhibitors

In the case of $KRAS^{G12C}$-mutant tumors, a selective small molecule was first introduced in 2013 that irreversibly and covalently binds to $KRAS^{G12C}$ in the GDP-bound state by targeting the reactive cysteine residue[42]. This breakthrough paved the way for sotorasib (Amgen, Thousand Oaks, CA, USA) and adagrasib (Mirati Therapeutics), the first KRAS inhibitors to gain accelerated FDA approval in 2021 and 2022, respectively, for $KRAS^{G12C}$-mutant non-small cell lung cancer (NSCLC)[22,23]. These inhibitors are unique because the inhibitors covalently modify $KRAS^{G12C}$, trapping KRAS in an inactive GDP-bound conformation. Notably, $KRAS^{G12C}$ retains intrinsic GTP hydrolysis rates like wild-type KRAS, distinguishing $KRAS^{G12C}$ from other KRAS mutations[28]. RMC-6291 (Revolution Medicine), which is currently undergoing clinical evaluation (NCT05462717), represents a novel class of $KRAS^{G12C}$ inhibitors with a unique mechanism of action. Unlike sotorasib and adagrasib, RMC-6291 and its counterpart (RMC-4998) use a tri-complex, covalent strategy that specifically targets the GTP-bound state of $KRAS^{G12C}$, preventing an interaction with downstream effectors (**Figure 3**)[127]. These inhibitors first bind to cyclophilin A, a chaperone protein that does not normally interact with RAS. The resulting binary complex undergoes a conformational change, enabling the binary complex to attach to GTP-bound $KRAS^{G12C}$ and covalently modify the critical cysteine residue, thereby blocking effector signaling. This approach achieves faster, more potent, and more selective target engagement compared to current FDA-approved $KRAS^{G12C}$ inhibitors[127]. In summary, the development of mutation-specific KRAS inhibitors represents a significant leap forward in cancer therapeutics. While challenges remain, particularly for non-^{G12C} mutations, innovative strategies, such as tri-complex inhibitors and reversible binding mechanisms, offer promising avenues for treating KRAS-driven cancers, like PDAC.

Pan-KRAS inhibition in PDAC

Although the $KRAS^{G12D}$ mutation is the most common mutation in PDAC, a substantial number of patients have non-^{G12D} KRAS alterations[112]. Therefore, a therapeutic agent capable of targeting a wide range of KRAS mutations could provide the broadest clinical benefit for PDAC patients. In this regard, identification and exploitation of a previously unknown shallow pocket in $KRAS^{G12C42}$ has substantially favored the development of non-^{G12C}, reversible, and pan-KRAS inhibitors now entering clinical trials[113,114]. Recently, Boehringer Ingelheim (Ingelheim am Rhein, Mainz-Bingen, Rhineland-Palatinate, Germany) developed BI-2865, a non-covalent pan-KRAS inhibitor that binds to multiple KRAS mutations[113]. Derived from the same lineage as sotorasib, BI-2865 selectively targets the inactive form of wild-type KRAS and its mutant variants, while sparing NRAS and HRAS isoforms, a feature expected to enhance tolerability in patients. In experiments involving 39 KRAS cell lines, including 7 with wild-type KRAS, 24 with mutant KRAS, and 8 wild type with upstream signaling alterations from lung, colorectal, or pancreatic cancers, BI-2865 effectively blocked KRAS activation and downstream signaling across all models. The compound showed the highest potency in $KRAS^{G12C}$-mutant cells, followed by $KRAS^{G12D}$, $KRAS^{G12V}$, and $KRAS^{G12R/Q61X}$ mutations. This hierarchy of potency aligns with the degree of KRAS dependency (G12D > G12V > G12R) and is thought to be linked to the BI-2865 mechanism by which KRAS is trapped in an inactive, GDP-bound state. The rate at which different KRAS mutations transition into this state likely determines the sensitivity, mirroring intrinsic GTP hydrolysis rates across mutants (G12C > G12D > G12V > G12R > Q61L)[28]. Consistent with these findings, BI-2865 has also been shown to have robust activity in KRAS wild-type cell lines[113].

Pan-RAS inhibition in PDAC

Revolution Medicine has developed reversible, GTP-binding, multi-selective inhibitors (RMC-7977 and RMC-6236; **Figure 3**)[128,129]. These agents function as tri-complex inhibitors and are designed to inhibit not only mutant KRAS but also hotspot

mutations in NRAS and HRAS, extending the activity to wild-type RAS isoforms. RMC-7977 and RMC-6236 first form a binary complex with cyclophilin A, which then undergoes a conformational change enabling the binary complex to bind active RAS and block downstream effector interactions. Given the presumed necessity of wild-type RAS signaling in normal cells[130], targeting all three wild-type RAS isoforms initially raised concerns about potential toxicity. However, preliminary data suggested that RMC-7977 is well-tolerated, causing minimal toxicity at doses that produce significant tumor regression in multiple mouse models[128,131]. This favorable safety profile may be attributed to factors, such as intermittent inhibition of RAS/MAPK signaling in healthy cells compared to sustained inhibition in tumor cells, the enrichment of cyclophilin A in malignant tissue, or the selective engagement of the GTP-bound state of RAS. RMC-6236 is now undergoing clinical investigation for patients with advanced solid tumors harboring $KRAS^{G12A/D/V/R/S}$ mutations, including PDAC (NCT05379985)[129]. Although the current study is a phase I dose-escalation trial primarily aimed at identifying the maximum tolerated dose, early reports indicate that heavily pretreated patients are responding to RMC-6236 without significant toxicity. Furthermore, RMC-6236 is being tested in combination with RMC-6291 in clinical trials for advanced solid tumors with $KRAS^{G12C}$ mutations (NCT06128551).

Clinical benefits of targeting KRAS in PDAC

Current standard-of-care regimens against PDACs are often associated with side effects and toxicities, which limit clinical utility. For example, the PRODIGE trial highlighted a less favorable safety profile for FOLFIRINOX *vs.* gemcitabine alone with higher incidences of grade 3–4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and peripheral neuropathy and sometimes resulting in treatment-related deaths that affected nearly 50% of the patients[7]. Similarly, the MPACT phase III trial reported 38% grade 3 neutropenia and 17% grade 3 peripheral neuropathy in patients treated with gemcitabine plus nab-paclitaxel[9]. In addition, the NAPOLI-1 phase III trial observed treatment-related adverse events leading to dose modifications in 73% of patients receiving nal-IRI with 5-FU/LV[132]. In contrast, emerging clinical data has suggested that targeting KRAS in PDAC is associated with favorable outcomes and better safety and tolerability profiles (**Table 1**). For example, among 38 PDAC patients with $KRAS^{G12C}$ mutations enrolled in the CodeBreaK studies, a confirmed partial response was observed in 21% of patients following sotorasib treatment with an overall disease control rate of 84%. The median progression-free and overall survival were 4.0 and 6.9 months, respectively[133]. In addition, only 16% of patients experienced grade 3–4 treatment-related adverse events with gastrointestinal symptoms and fatigue the most common adverse events[133]. The KRYSTAL-1 trial involved adagrasib treatment in 21 patients with unresectable or metastatic PDAC carrying $KRAS^{G12C}$ mutations and reported a partial response rate of 33% and a disease control rate of 100% with median progression-free and overall survival of 5.4 and 8.0 months, respectively[134]. In addition, grade 3–4 treatment-related adverse events were only noted in 27% of patients and primarily involved fatigue and QT prolongation[134]. Moreover, a patient with stage IV PDAC and liver and peritoneal metastases has recently been reported to achieve a confirmed complete response after six cycles of RMC-6236 treatment following failure of conventional therapies[129]. In another clinical trial, among the clinically evaluable group, 20% achieved a partial response and the disease control rate was 87%[135]. The results from the same trial also suggested an even more favorable safety profile with 10% of lung and pancreatic cancer patients experiencing grade 3–4 treatment-related adverse events[135]. These findings are notable, especially considering earlier concerns about potential toxicity from inhibiting wild-type RAS isoforms. Compared to conventional second-line chemotherapies for advanced PDAC, all KRAS inhibitors tested thus far have shown markedly better response rates and considerably fewer severe treatment-related adverse events[136,137]. In summary, while larger datasets are required to definitively compare direct KRAS inhibitors with current standard-of-care regimens, the initial clinical outcomes are highly encouraging. The response rates, disease control, and toxicity profiles of these inhibitors appear superior to those of second-line chemotherapy for PDAC, potentially justifying advancing to at least second-line treatment, pending eventual FDA approval for PDAC patients.

Resistance against KRAS inhibition in PDAC

One of the foremost obstacles in treating cancer, both in general and PDAC specifically, is the emergence of drug resistance, which significantly diminishes the clinical effectiveness[138,139]. Resistance to KRAS inhibition can be broadly

Table 1 Clinical trials currently testing oncogenic KRAS-targeted therapies in PDAC

Tumor type	Mutation	Therapy	Clinical trial	Phase	Status
PDAC	$KRAS^{G12C}$	Adagrasib	NCT05634525	I	Recruiting
PDAC	$KRAS^{G12C}$	Glecirasib	NCT06008288	II	Not yet recruiting
Advanced solid tumors	$KRAS^{G12C}$	Adagrasib	NCT05178888	I	Active, not recruiting
Advanced solid tumors	$KRAS^{G12C}$	Adagrasib	NCT05263986	I	Active, not recruiting
Advanced solid tumors	$KRAS^{G12C}$	Adagrasib	NCT06039384	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	Adagrasib	NCT03785249	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	Adagrasib	NCT06130254	Ib	Not yet recruiting
Advanced solid tumors	$KRAS^{G12C}$	BEBT-607	NCT06117371	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	BI-1823911	NCT04973163	I	Active, not recruiting
Advanced solid tumors	$KRAS^{G12C}$	BPI-421286	NCT05315180	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	D3S-001	NCT05410145	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	Divarasib	NCT04449874	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	Garsorasib	NCT04585035	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	Garsorasib	NCT05379946	I/II	Enrolling by invitation
Advanced solid tumors	$KRAS^{G12C}$	GEC255	NCT05768321	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	Glecirasib	NCT05002270	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	Glecirasib	NCT05009329	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	HBI-2438	NCT05485974	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	HS-10370	NCT05367778	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	IBI351	NCT05005234	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	JDQ443	NCT04699188	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	JDQ443	NCT05358249	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	Ly3537982	NCT04956640	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	MK-1084	NCT05067283	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	RMC-6291	NCT05462717	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	RMC-6291	NCT06128551	Ib	Not yet recruiting
Advanced solid tumors	$KRAS^{G12C}$	Sotorasib	NCT03600883	I/II	Active, not recruiting
Advanced solid tumors	$KRAS^{G12C}$	Sotorasib	NCT04185883	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	Sotorasib	NCT04892017	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	Sotorasib	NCT05638295	II	Not yet recruiting
Advanced solid tumors	$KRAS^{G12C}$	Sotorasib	NCT05993455	II	Active, not recruiting
Advanced solid tumors	$KRAS^{G12C}$	SY-5933	NCT06006793	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	YL-15293	NCT05173805	I/II	Enrolling by invitation
PDAC	$KRAS^{G12D}$	siRNA	NCT03608631	I	Active, not recruiting
Advanced solid tumors	$KRAS^{G12D}$	ASP3082	NCT05382559	I	Recruiting

Table 1 Continued

Tumor type	Mutation	Therapy	Clinical trial	Phase	Status
Advanced solid tumors	$KRAS^{G12D}$	HRS-4642	NCT05533463	I	Recruiting
Advanced solid tumors	$KRAS^{G12D}$	MRTX1133	NCT05737706	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12D}$	RMC-9805	NCT06040541	I/Ib	Recruiting
Advanced solid tumors	$KRAS^{G12}$	RMC-6236	NCT05379985	I	Recruiting
Advanced solid tumors	$KRAS^{G12}$	RSC-1255	NCT04678648	I	Recruiting
Advanced solid tumors	$KRAS^{ANY}$	YL-17231	NCT06096974	I	Not yet recruiting
Advanced solid tumors	$KRAS^{ANY}$	YL-17231	NCT06078800	II	Recruiting

PDAC, pancreatic ductal adenocarcinoma; siRNA, small interfering RNA.

classified into three main categories, all of which converge on heightened proliferative signaling. The first category involves alterations in upstream signaling pathways, such as mutational activation, amplification, or fusion of receptor tyrosine kinases[140]. These upstream changes not only reactivate RAS-MAPK signaling but also engage compensatory pathways, including PI3K/AKT and JAK/STAT, which illustrates the functional redundancy and pathway cross-activation that complicate targeted inhibition[141]. For example, RTK hyperactivation can induce EMT transcription factors, linking upstream signaling with cell state transitions that promote invasion and drug tolerance[142]. The second category pertains to mutations or amplifications at the RAS level and involves KRAS or NRAS[143]. Importantly, intra-tumoral heterogeneity often leads to subclones harboring distinct RAS mutations that cooperate to maintain signaling robustness. This RAS isoform switching and mutational diversification reinforce resistance by diversifying downstream effector engagement and metabolic rewiring[144]. The third category consists of downstream mutations that hyperactivate the PI3K and ERK MAPK pathways, including PTEN loss-of-function mutations, activating mutations in RAF, MEK and PI3K, and MYC amplification[145,146]. The PI3K and MAPK pathways engage in bidirectional crosstalk with MYC acting as a central integrator that regulates metabolic adaptation, proliferation, and EMT. MYC-driven nucleotide biosynthesis and glutaminolysis synergize with EMT programs to foster a drug-resistant mesenchymal phenotype characterized by metabolic plasticity and stem-like features[147,148]. Ultimately, most resistance pathways culminate in mechanisms that reinforce or reactivate ERK MAPK signaling (**Figure 3**)[149,150]. This centrality of ERK signaling underscores the difficulty of durable inhibition and the necessity for combination strategies that disrupt multiple nodes simultaneously.

Both intrinsic and acquired resistance are expected to hinder the efficacy of KRAS inhibitors in PDAC patients. To enhance therapeutic outcomes and prolong the frequent short-lived efficacy of existing KRAS inhibitors, a comprehensive understanding of both intrinsic and acquired resistance mechanisms is essential. For example, resistance to G12C inhibitors can emerge rapidly and may manifest in a dependent or independent manner[151]. Dependent adaptation occurs when cancer cells treated with G12C inhibitors enter a dormant state, while newly emerging G12C-mutant cells resume proliferation[149]. In contrast, independent adaptation involves multiple distinct pathways. Some KRAS-mutant cells acquire additional mutations in codons 12, 13, or 61, while others develop alterations in the switch II binding pocket, such as KRAS R68S, H95D/Q/R, and Y96C/D[149,152]. These mutations can interfere with the non-covalent binding of inhibitors at the pocket site, potentially reducing efficacy. Interestingly, certain mutations in the pocket site following adagrasib treatment have been shown to confer resistance to adagrasib while maintaining sensitivity to sotorasib[149]. This finding indicates that resistance to one inhibitor may be overcome using another $KRAS^{G12C}$ inhibitor with distinct properties[152]. The role of the tumor microenvironment and stromal components in resistance against KRAS inhibitors remains poorly understood and requires further exploration. The dense stroma in PDAC can limit drug delivery and create hypoxic niches that promote metabolic reprogramming and EMT induction, which in turn enhance therapeutic resistance[153]. Moreover, stromal cells secrete cytokines, such as TGF-β and IL-6, that drive EMT and reinforce cancer stem

cell phenotypes, synergizing with intrinsic tumor cell adaptations[154]. This microenvironmental crosstalk creates a feedback loop in which metabolic changes promote EMT and EMT, and in turn modulates metabolism and redox balance, collectively supporting resistance[155].

KRAS mutations contribute to metabolic adaptations, such as increased reliance on glycolysis and glutamine metabolism (**Figure 3**)[19,72]. This metabolic reprogramming contributes to hyperactivate the cell cycle progression, ultimately conferring therapy resistance in PDAC[156]. Notably, glutaminolysis-derived metabolites support epigenetic modifications that stabilize EMT transcription factors, thus linking metabolic shifts directly to cell state changes that promote resistance[157]. Furthermore, the MAPK/MYC/RPIA axis, which is involved in nucleotide synthesis, has been implicated in resistance to KRAS inhibitors[141]. MYC amplification not only drives anabolic metabolism but also promotes chromatin remodeling that facilitates transcriptional programs associated with drug tolerance and EMT[158]. Lastly, cell state transitions, such as the epithelial-to-mesenchymal transition, represent a notable resistance mechanism towards KRAS inhibitors, which contributes to both intrinsic and acquired resistance mechanisms (**Figure 3**)[149,159]. EMT promotes invasion, stemness, and metabolic plasticity, enabling tumor cells to evade apoptosis and tolerate metabolic stress induced by therapy[155]. Importantly, EMT-associated signaling activates antioxidant responses and autophagy, which intersect with KRAS-driven metabolic adaptations to sustain cell survival under therapeutic pressure[160,161]. This metabolic-EMT-autophagy nexus is a critical axis in maintaining drug-tolerant persister cells that fuel relapse.

The diverse array of resistance mechanisms associated with KRAS inhibition highlights the intricate challenges of targeting the RAS pathway. As research advances, particularly in the development of pan-RAS inhibitors, it is anticipated that additional resistance mechanisms will be identified. This mechanism underscores the necessity for rapid implementation of adaptive treatment strategies in clinical trials to address these evolving challenges. In this regard, a key strategy entailing the inhibition of downstream RAS-MAPK signaling pathway has led to the discovery of MEK inhibitors, including trametinib, cobimetinib, and binimetinib. However, PDAC tumors frequently develop adaptive resistance through mechanisms, such as epigenetic changes and oncogenic signaling aberrations, limiting the clinical effectiveness of these inhibitors[162]. MEK inhibitor treatment has also been linked to increased STAT3 activation, which is associated with advanced disease stages and poor survival outcomes in PDAC patients[163]. Chromatin-associated spermine/spermidine N1-acetyltransferase family protein 5 (STED5) has also been identified as a key regulator of adaptive resistance to MEK inhibitors. STED5 forms a complex with G9a/GLP, leading to the methylation of histone deacetylase 3 (HDAC3)[164]. Additionally, overexpression of the antigen peptide transporter 1 (TAP1), also known as ABCB2, has been implicated in trametinib resistance by hindering drug transport into PDAC cells. TAP1 is also associated with gemcitabine resistance[165] and has a role in tumor stemness, as evidenced by increased spheroid formation[166].

Overcoming therapy resistance against KRAS inhibition in PDAC

To address the challenges of resistance and improve the efficacy of KRAS inhibition, upstream pathway inhibition and use of combination therapies are the two primary strategies. These approaches are discussed in the following subsection in detail one-by-one.

Upstream pathway inhibition

Targeting upstream pathways is a promising approach because inhibiting GEFs, such as SHP2 or SOS1, can prevent the activation of KRAS signaling (**Table 2, Figure 4**)[167]. BI1701963, a molecule evolved from the BI-3406 scaffold, represents the inaugural SOS1 inhibitor to enter clinical evaluation. This compound disrupts KRAS activation but does not interfere with SOS2-dependent signaling pathways by selectively binding to the catalytic region of SOS1[168]. Early-phase clinical data from patients with KRAS-mutant solid tumors has revealed that BI1701963 exhibits an acceptable safety profile with disease stabilization observed in 23% of participants over an 18-month period[169]. Despite these encouraging findings, safety concerns, including dose-limiting toxicities, have prompted early discontinuation of several SOS1 inhibitor trials (NCT04835714 and NCT0462714)[170]. Notably, PROTACs targeting SOS1 are under development with promise to alleviate the toxicity issues associated with pharmacologic inhibition[171]. Parallel efforts in SHP2 inhibitor development are also advancing with multiple agents now in first-in-human trials. Among these inhibitors, RMC-4630, a tri-complex SHP2 inhibitor, has

Table 2 Clinical trials currently testing SOS1 and SHP2 inhibitors in KRAS-mutated PDAC

Tumor type	Mutation	Primary therapy	Combination therapy	Clinical trial identifier	Phase	Status
PDAC/Colorectal cancer/NSCLC	$KRAS^{G12C}$	RMC-4630	LY3214996	NCT04916236	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	BBP-398	Sotorasib	NCT05480865	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	BMS-986466	Adagrasib, Cetuximab	NCT06024174	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	JAB-3312	Glecirasib	NCT05288205	I/II	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	RMC-4630	Pembrolizumab. Adagrasib	NCT04418661	I/II	Active, not recruiting
Advanced solid tumors	$KRAS^{G12C}$	TNO155	Adagrasib	NCT04330664	I/II	Active, not recruiting
Advanced solid tumors	$KRAS^{G12C}$	GH35	-	NCT05010694	I	Recruiting
Advanced solid tumors	$KRAS^{G12C}$	HBI-2376	-	NCT05163028	I	Recruiting
Advanced solid tumors	$KRAS^{ANY}$	BI-1701963	Trametinib	NCT04111458	I	Active, not recruiting
Advanced solid tumors	$KRAS^{ANY}$	BI-1701963	BI-1823911	NCT04973163	I	Active, not recruiting
Advanced solid tumors	$KRAS^{ANY}$	MRTX0902	Adagrasib	NCT05578092	I/II	Recruiting

PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer.

demonstrated notable activity in a subset of $KRAS^{G12C}$-driven NSCLC patients. Disease control was achieved in 71% (5/7) of cases, accompanied by tumor volume reductions in 43% of cases (3/7)[172]. Circulating tumor DNA (ctDNA) analysis further revealed that 59% (5/9) of baseline-positive patients experienced a decline in $KRAS^{G12C}$ variant allele frequency, which is in alignment with clinical responses. However, no similar reductions were observed in tumors harboring $KRAS^{G12D}$ or $KRAS^{G12V}$ mutations, which cast doubt on the standalone efficacy in pancreatic cancer[173]. TNO155, an allosteric SHP2 inhibitor leveraging a pyrazine-based mechanism, has shown modest clinical benefit in a phase I dose-escalation study (n = 118), in which 20% of participants achieved stable disease[174]. In contrast, early results from the FLAGSHP-1 trial evaluating ERAS-601 revealed limited activity with only a single partial response among 27 treated patients[175]. Emerging evidence also highlights intrinsic resistance patterns. Specifically, $KRAS^{G12R}$ and $KRAS^{Q61}$ mutations demonstrate reduced susceptibility to both SOS1 and SHP2 inhibition, suggesting mutation-specific limitations in targeting these pathways[176]. These disparities underscore the potential need for combination therapies to optimize the efficacy of SOS1 and SHP2 inhibitors. In this regard, simultaneous inhibition of $KRAS^{G12C}$ and SHP2 has been shown to significantly suppress RAS signaling and improve therapeutic outcomes in laboratory and animal models[177]. In addition, several preclinical studies have indicated that resistance to $KRAS^{G12C}$ inhibition can be mitigated by co-administering SHP2 inhibitors along with $KRAS^{G12C}$ inhibitors[178,179]. A phase I/IIa study evaluated the combination of JAB-3312, an SHP2 inhibitor, with the $KRAS^{G12C}$ inhibitor, glecirasib, in patients with $KRAS^{G12C}$-mutated solid tumors. Among 28 treatment-naïve NSCLC patients, the overall response rate was 50% with a disease control rate of 100%. The overall response rate was 14.3% in patients who had previously received $KRAS^{G12C}$ inhibitors, suggesting that this combination could benefit even those with prior resistance[180].

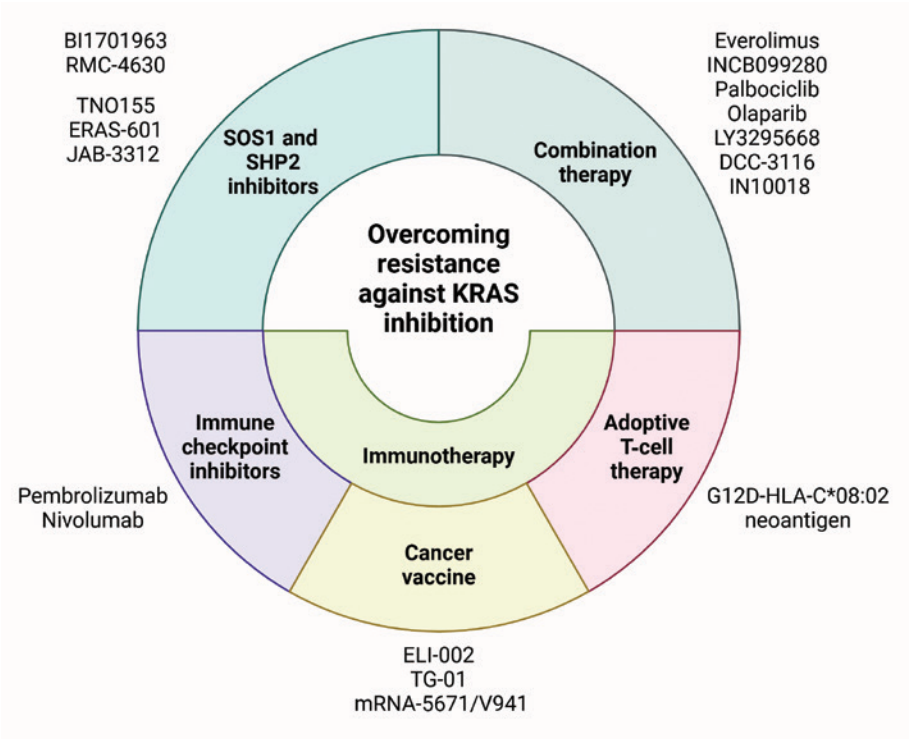


Figure 4 Overcoming therapy resistance against KRAS inhibition in PDAC. Targeting SOS1 and SHP2 upstream of KRAS has shown promise in overcoming therapy resistance against KRAS inhibitors. Representative inhibitors include BI1701963 and RMC-4630 (SHP2 inhibitors), as well as TNO155, ERAS-601, and JAB-3312 (SOS1 inhibitors). In addition, different combination therapies are being tested to enhance efficacy of KRAS inhibitors in PDAC. Key combination agents include everolimus (mTOR inhibitor), INCB099280 (PI3K inhibitor), palbociclib (CDK4/6 inhibitor), olaparib (PARP inhibitor), LY3295668 (Aurora kinase A inhibitor), DCC-3116 (autophagy inhibitor), and IN10018 (FAK inhibitor). Immunotherapy using immune checkpoint inhibitors (pembrolizumab and nivolumab), cancer vaccines (ELI-002, TG-01, and mRNA-5671/V941), and adoptive T cell therapy (G12D-HLA-C*08:02 neoantigen) represents another promising option to promote efficacy of KRAS inhibitors in PDAC.

However, toxicity remains a concern because 36.7% of patients experienced grade 3 and 4 treatment-related adverse events.

Combination therapy

Currently, efforts to enhance the efficacy of $KRAS^{G12C}$ inhibitors and limit therapeutic resistance against these therapies include combination strategies with other targeted therapies (**Figure 4**). For example, combining $KRAS^{G12D}$ inhibition with chemotherapy enhances tumor control, supporting combination therapies to overcome resistance[146]. The addition of epidermal growth factor receptor (EGFR) inhibitors to $KRAS^{G12C}$ inhibitors in chemotherapy-refractory $KRAS^{G12C}$-mutant metastatic colorectal cancer has led to a significant improvement in response rates[181-183]. Preclinical findings also suggest that combining MRTX1133 with a pan-ErbB inhibitor may be a promising therapeutic approach for $KRAS^{G12D}$-mutant PDAC[184]. More compelling data support combining $KRAS^{G12C}$ inhibitors with inhibitors of parallel pathways, such as the PI3K/Akt/mTOR axis. For example, co-treatment with an mTORC inhibitor and a $KRAS^{G12C}$ inhibitor synergistically induced cell death in preclinical models[185]. Several clinical trials are investigating these combinations. For example, sotorasib, a $KRAS^{G12C}$ inhibitor, is being tested with the mTOR inhibitor, everolimus, while adagrasib, another $KRAS^{G12C}$ inhibitor, is being paired with the PI3KCA inhibitor, INCB099280. Another approach focuses on co-occurring mutations in the tumor suppressor, CDKN2A, which leads to the loss of the cell cycle inhibitor, p16INK4a. CDK4/6 inhibitors, which restore p16INK4a function, have been considered for combination therapy. However, clinical results with CDK4/6 inhibitors in PDAC have been disappointing. Emerging evidence suggests that combining CDK4/6 inhibitors with MAPK pathway inhibitors, such as MEK inhibitors, may yield better outcomes. For

example, the combination of the MEK inhibitor, trametinib, and the CDK4/6 inhibitor, palbociclib, induced tumor senescence, improved vascularization, and increased CD8+ T cell infiltration in preclinical PDAC models[186]. Notably, combining MEK and STAT3 inhibitors has shown synergistic effects, resulting in sustained suppression of ERK, EGFR, and STAT3 signaling. This combination also reduces cancer stem cell populations (CD44+CD133+) and fibrosis[163]. Other studies have demonstrated reduced fibrosis with combinations, such as MEK inhibitors, with Src and EGFR[187] or PDGFR/STAT3 inhibitors[188]. Additionally, combining MEK and STAT3 inhibitors enhance CD8+ T cell infiltration and promote stromal plasticity, shifting pro-inflammatory myofibroblast phenotypes toward mesenchymal-like phenotypes through macrophage polarization[189]. In contrast, simultaneous inhibition of CDK2, a cyclin-dependent kinase involved in cell cycle progression, with CDK4/6 inhibition has demonstrated enhanced anti-tumor effects in laboratory and animal studies[190,191]. Another promising strategy involves co-inhibition of CDK4/6 and ERK, which has been shown to induce apoptosis in PDAC models[192]. Other combination strategies under investigation include pairing KRAS inhibitors with poly (ADP-ribose) polymerase (PARP) inhibitors (e.g., olaparib), aurora kinase inhibitors (e.g., LY3295668), autophagy inhibitors (e.g., DCC-3116), and focal adhesion kinase (FAK) inhibitors (e.g., IN10018). Overall, combination therapies targeting KRAS and other related pathways represent a promising strategy to overcome resistance, enhance therapeutic efficacy, and potentially provide durable responses in patients with KRAS-driven cancers, particularly in PDAC.

Tackling KRAS-driven PDAC with immunotherapy

Because PDAC is generally classified as an immunologically "cold" tumor, immunotherapy is gaining attention to heat-up and tackle KRAS-driven tumors[193]. Specifically, KRAS mutations have been associated with enhanced responses to immune checkpoint inhibitors (**Table 3**). Patients with KRAS-mutated tumors have shown better responses to anti-programmed death 1 (PD-1) therapies (pembrolizumab and nivolumab) compared to patients with wild-type KRAS in trials, such as KEYNOTE-042 and CA209-057[194,195]. However, this effect appears more pronounced in $KRAS^{G12C}$ mutations than other KRAS variants[196]. $KRAS^{G12D}$ inhibition using MRTX1133 has been shown to modulate the tumor microenvironment in syngeneic subcutaneous models of PDAC by shifting cytokine and chemokine secretion from an immunosuppressive state dominated by MDSCs to a more immunostimulatory state characterized by an increased presence of CD4- and CD8-positive T cells[197]. Combining KRAS-directed therapies with immune checkpoint inhibitors has shown synergistic effects. For example, the anti-tumor response was significantly improved when $KRAS^{G12D}$-mutant PDAC models were treated with a combination of an immune checkpoint inhibitor and RMC-9805[117]. In agreement with this finding, the addition of pembrolizumab to adagrasib in the KRYSTAL-07 trial resulted in a response rate of 49% with a manageable toxicity profile[198]. Conversely, combining sotorasib with pembrolizumab or atezolizumab was shown to cause hepatotoxicity[199], underscoring the need for careful evaluation of toxicity in such combinations. Another promising approach involves combining SHP2 inhibitors with PD-1 inhibitors because SHP2 modulates T cell function through PD-1 signaling[200].

Cancer vaccines targeting mutant KRAS are gaining traction as a potential treatment for PDAC (**Table 3, Figure 4**). One example is the ELI-002 peptide vaccine, which incorporates amphiphile-modified KRAS mutant peptides (G12D and G12R) and a Toll-like receptor (TLR) 9 agonist, CPG-7909 DNA. Patients who had completed surgery or adjuvant therapy in the AMPLIFY-201 study and exhibited elevated serum biomarkers or detectable ctDNA were treated with ELI-002. Among the 25 participants, 84% showed a KRAS-specific T cell response, 77% had reduced ctDNA levels, and 33% achieved ctDNA clearance[201] Another promising vaccine, TG01, consists of seven synthetic KRAS peptides designed to target KRAS mutations. In a phase I/II trial, 32 patients with resected stage I or II PDAC received TG01/GM-CSF with adjuvant gemcitabine. Greater than 90% of patients exhibited an immune response, as measured by delayed-type hypersensitivity or T cell proliferation assays. The median overall survival was 33.1 months (95% CI, 16.8–45.8 months)[202]. A phase II trial is currently underway (NCT 05638698). Additionally, a long peptide vaccine targeting pooled mutant KRAS peptides is being tested in a phase I trial in combination with nivolumab and ipilimumab in patients with resected, microsatellite stable (mismatch repair-proficient) colorectal and pancreatic cancers (NCT04117087). An mRNA vaccine, mRNA-5671/V941, targeting multiple KRAS mutations (G12D, G12V, G13D, and G12C) and encapsulated in a lipid nanoparticle has shown

Table 3 Clinical trials currently testing immunotherapies in KRAS-mutated PDAC

Tumor type	Primary therapy	Secondary therapy	Clinical trial	Phase	Status
PDAC	Dendritic cell vaccine	-	NCT03592888	I	Active, not recruiting
PDAC	ELI-002	-	NCT04853017	I	Active, not recruiting
PDAC	Mutant KRAS-targeted vaccine	-	NCT05013216	I	Recruiting
PDAC	TCR-based therapy	-	NCT05438667	I	Recruiting
PDAC	ATP1450/ATP152	VSV-GP154, Ezabenlimab	NCT05846516	I	Recruiting
PDAC	TG01	QS-21, Balstilimab	NCT05638698	II	Recruiting
PDAC	$KRAS^{G12V}$-specific TCR-based therapy	PD-1 inhibitor	NCT04146298	I/II	Recruiting
PDAC/Colorectal cancer	Mutant KRAS-targeted vaccine	Ipilimumab, Nivolumab	NCT04117087	I	Recruiting
PDAC/Gastric cancer/Colorectal cancer	Peripheral blood lymphocytes with murine $KRAS^{G12D}$-specific TCR-based therapy	Cyclophosphamide, Fludarabine, Aldesleuki	NCT03745326	I/II	Recruiting
PDAC/Gastric cancer/Colorectal cancer	Peripheral blood lymphocytes with murine $KRAS^{G12V}$-specific TCR-based therapy	Cyclophosphamide, Fludarabine, Aldesleuki	NCT03190941	I/II	Recruiting
PDAC/NSCLC	Anti-CD38 antibody with KRAS vaccine	Anti-PD1 antibody	NCT06015724	II	Recruiting
Advanced solid tumors	ELI-002-7P	-	NCT05726864	I/II	Recruiting
Advanced solid tumors	YK0901; $KRAS^{G12V}$-specific TCR-based therapy	-	NCT05933668	I	Not yet recruiting
Advanced solid tumors	RMC-4630	Pembrolizumab. Adagrasib	NCT04418661	I/II	Active, not recruiting
Advanced solid tumors ($KRAS^{G12V}$)	CD8+/CD4+ TCR-based therapy	-	NCT06105021	I/II	Not yet recruiting
Advanced solid tumors ($KRAS^{G12V}$)	investigational new drug	Chemotherapy Immunotherapy	NCT05389514	I	Available

PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer; TCR, T cell receptor; VSV-GP 154, vesicular stomatitis virus glycoprotein 154.

robust T-cell responses in preclinical models[203]. A phase I clinical trial evaluating this vaccine, either alone or in combination with pembrolizumab, is currently underway (NCT03948763).

Recently, adoptive T cell therapy is gaining attention as a promising immunotherapeutic strategy for targeting KRAS mutations (**Table 3, Figure 4**). A colorectal cancer patient with $KRAS^{G12D}$ mutations was treated with T cells engineered to recognize the G12D-HLA-C*08:02 neoantigen and exhibited regression of all seven metastases[204]. Similarly, another $KRAS^{G12D}$-mutated metastatic pancreatic cancer patient has been treated with autologous CD8+ and CD4+ T cells engineered to express a T cell receptor targeting $KRAS^{G12D}$. The patient showed a sustained response at the 6-month follow-up evaluation[205].

Despite encouraging advances in KRAS-targeted vaccines and adoptive T cell therapies, several formidable challenges limit efficacy in PDAC. Antigen presentation variability remains a primary hurdle. PDAC tumors frequently exhibit heterogeneous and downregulated expression of major histocompatibility complex (MHC) class I molecules that is driven by epigenetic silencing and mutations in antigen processing machinery components, which reduce neoantigen visibility and impair effective T cell recognition[206,207]. This finding leads to immune evasion and reduced responsiveness to antigen-specific immunotherapies. Moreover, the PDAC microenvironment is characterized by a dense desmoplastic stroma that not only physically restricts T cell infiltration but also actively fosters immunosuppression. CAFs and myeloid-derived suppressor cells (MDSCs) secrete factors, such as TGF-β, CXCL12, and adenosine, that promote immune exclusion and suppress effector T cell function[208,209]. This stromal barrier limits the homing and persistence of both endogenous and adoptively transferred T cells. T cell exhaustion and dysfunction represent additional major obstacles. Chronic antigen exposure and metabolic stress within the tumor induce expression of inhibitory immune checkpoints (PD-1, CTLA-4, LAG-3, and TIM-3) and metabolic regulators that impair cytokine production, proliferation, and cytotoxicity[210,211]. Furthermore, nutrient competition within the tumor microenvironment, especially glucose and amino acids, constrains T cell metabolism and effector functions, compounding exhaustion and reducing immunotherapy efficacy[212]. Lastly, intra-tumoral heterogeneity and neoantigen loss variants arise dynamically under immune pressure, enabling tumors to escape recognition even by engineered T cells and vaccine-elicited immunity[213].

Overall, diverse immunotherapy strategies offer a multifaceted approach to overcoming the challenges of treating KRAS-driven cancers. Continued research and clinical trials are crucial to identify and validate the most effective strategies and to address the associated challenges, particularly for PDAC, for which therapeutic options remain limited.

Conclusion and future prospect

Targeting KRAS in PDAC represents a transformative shift in precision oncology, yet significant challenges persist. While KRAS inhibitors outperform current second-line therapies[28,149], limited durability and the emergence of resistance underscore the need for innovative strategies. The biochemical diversity among KRAS mutations, such as differential effector engagement (e.g., impaired PI3Kα binding of $KRAS^{G12R}$)[67], GTPase activity (e.g., fast-cycling $KRAS^{G12C}$)[28], and mutation-specific dependencies (e.g., the critical role of $KRAS^{G12D}$ in PDAC), demands tailored therapeutic approaches. Furthermore, resistance mechanisms vary between inhibitor classes. Specifically, inactive-state inhibitors (e.g., sotorasib) face NF1 loss-driven resistance, while active-state inhibitors (e.g., RMC-6291) may evade such adaptation[149]. Advances in multi-selective RAS inhibitors (e.g., RMC-7977) and pan-KRAS inhibitors (e.g., BI-2865) offer promise in overcoming mutation-specific and compensatory resistance[113,214]. Future efforts must prioritize mutation-specific combinations, such as pairing $KRAS^{G12D}$ inhibitors with PI3Kα-targeting agents[67] or integrating active-state inhibitors with therapies blocking receptor tyrosine kinase-driven ERK reactivation[128,177]. Mechanistic studies should dissect intrinsic/acquired resistance, leveraging biomarkers to stratify patients by KRAS variant biology, metabolic dependencies, and tumor microenvironment profiles. At the pre-clinical level, multi-selective inhibitors, such as RMC-7977, which delay ERK rebound and target secondary resistance mutations[128], warrant clinical validation. In parallel, emerging strategies, such as mutation-specific PROTACs that induce degradation of $KRAS^{G12D}$ or $KRAS^{G12C}$, offer promise for irreversible target ablation and may overcome limitations of conventional inhibitors[215]. Furthermore, biomarker-guided clinical trials stratified by co-mutations (e.g., TP53 and SMAD4) and immune/metabolic profiles are critical for personalizing regimens and maximizing therapeutic windows[216]. Stromal-targeted combinations, including CXCL12–CXCR4 antagonists and CAF-modulating agents (e.g., FAP or hyaluronan inhibitors), aim to disrupt the PDAC immune-excluded

microenvironment and improve immune and drug access[217]. In like manner, metabolic co-targeting strategies, such as combining KRAS inhibitors with glutaminase inhibitors or autophagy blockers, may exploit the metabolic vulnerabilities unique to some KRAS alleles[218]. To further enhance immune responsiveness, future work must also address T-cell exhaustion, neoantigen loss, and MHC-I downregulation, which are barriers that currently limit the success of vaccines and adoptive cell therapies in PDAC[206]. Finally, combining mutation-selective inhibitors (e.g., MRTX1133) with pan-KRAS agents may broaden efficacy, while mitigating adaptive resistance[214]. Researchers are building on encouraging preclinical findings to develop more effective treatment regimens by integrating KRAS inhibitors with upstream and downstream pathway inhibitors, immunotherapies, and other targeted agents. Ongoing clinical trials will be critical in identifying the most effective combinations and optimizing therapeutic strategies to improve outcomes for patients with KRAS-mutant cancers. Eventually, by harmonizing these insights, the field can advance toward durable responses and redefine standards of care for KRAS-mutant PDAC.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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