Targeting RAS in Gastrointestinal Malignancies

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Abstract: Kirsten rat sarcoma virus (KRAS) is one of the prevalent oncogenic drivers in gastrointestinal (GI) cancers, including pancreatic ductal adenocarcinoma and colorectal cancer. The KRAS protein is a GTPase that activates several signaling pathways involved in cancer survival. Although *KRAS* mutations have long been considered difficult to target, recent advances have led to the development of small-molecule inhibitors targeting the mutations, particularly *KRAS* G12C. These inhibitors are showing promise in GI cancers. This review explores the molecular biology of *KRAS* mutations, their prevalence in GI malignancies, the current therapeutic approaches targeting KRAS, ongoing clinical trials, the challenges associated with resistance, and future directions for KRAS-targeted therapies in GI cancers.

Keywords
Combination therapies, gastrointestinal cancers, KRAS, RAS, resistance mechanisms, targeted therapies

Introduction

Rat sarcoma virus (RAS) proteins are small GTPases that are essential regulators of cell signaling pathways, particularly those controlling cell growth, differentiation, and survival. Mutations in *RAS* genes, which are among the most common oncogenic alterations,[1] are present in roughly 19% of all human cancers.[2] These mutations are frequently associated with poor clinical outcomes and resistance to standard therapies, positioning RAS as a critical focus for cancer research.[3]

The 3 primary RAS isoforms—KRAS, NRAS, and HRAS—are critical to cellular signaling, with *KRAS* mutations the most common and most frequently observed across the RAS family. *KRAS* mutations are particularly common in gastrointestinal (GI) malignancies, occurring in up to 40% to 50% of cases of colorectal cancer (CRC) and 90% of cases of pancreatic ductal adenocarcinoma (PDAC).[4-6] The prevalence of *KRAS* mutations in cancer has driven extensive research efforts over the past decades to develop targeted KRAS inhibitors. Historically, KRAS has been challenging to target because of its structural features, including a high affinity for guanosine-5'-triphosphate (GTP) and a paucity of accessible binding sites. As a result, developing small-molecule inhibitors of KRAS has

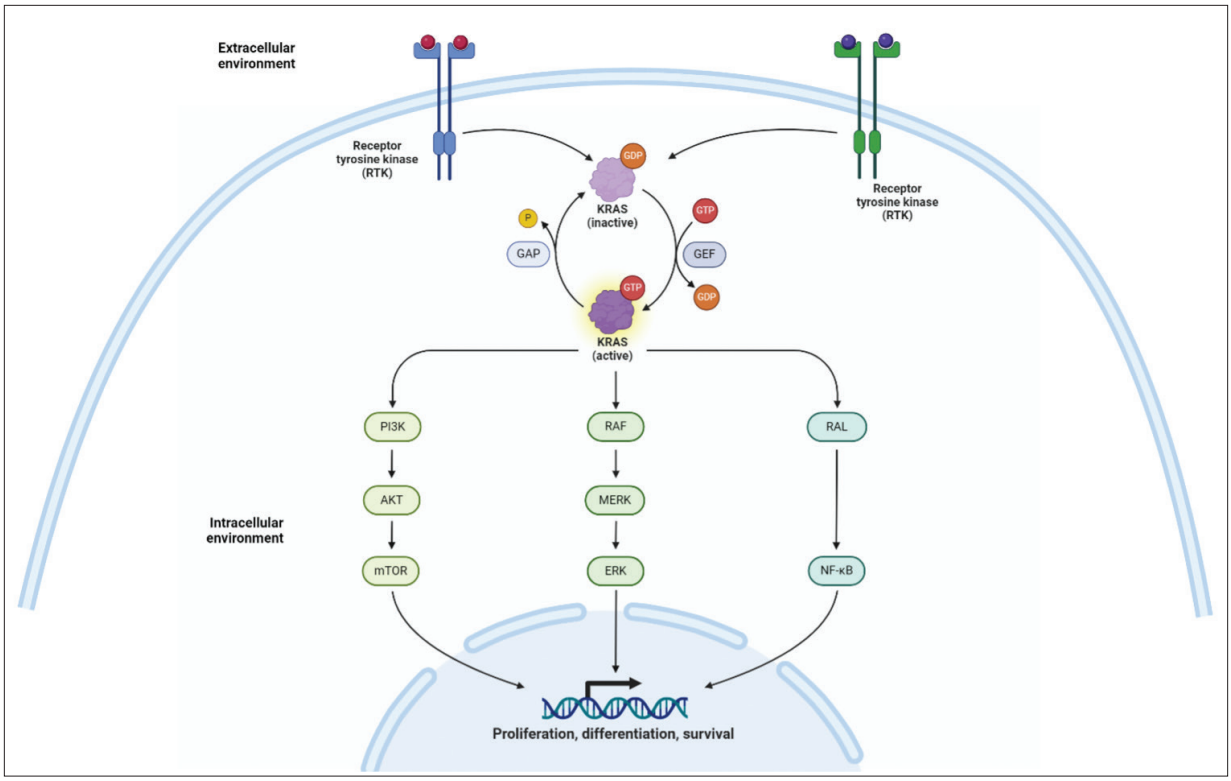

Figure. KRAS signaling pathways. Created in BioRender. Abidoye O (2024). https://BioRender.com/c66b459.
AKT, Ak strain transforming; ERK, extracellular signal–regulated kinase; GAP, GTPase-activating protein; GDP, guanosine-5′-diphosphate; GEF, guanine nucleotide exchange factor; GTP, guanosine-5′-triphosphate; KRAS, Kirsten rat sarcoma virus; MERK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; P, phosphate; PI3K, phosphoinositide 3-kinase complex; RAF, v-raf murine sarcoma viral oncogene homolog; RAL, RAS-like protein; RTK, receptor tyrosine kinase.

proved extremely challenging.[3] These difficulties caused KRAS to be labeled as "difficult to target" for many years. However, recent breakthroughs in drug development, particularly the identification of covalent inhibitors that target the *KRAS* G12C mutation, have revolutionized the treatment landscape.[3,7,8] These advancements have paved the way for novel therapeutic approaches that hold significant potential to improve outcomes in *KRAS*-mutated GI cancers. In this review, we explore the rapidly advancing landscape of KRAS-targeted therapies in GI cancers.

Molecular Biology of *KRAS* Mutations

The RAS family, comprising KRAS, NRAS, and HRAS, is essential for regulating cell signaling through pivotal pathways, including the mitogen-activated protein kinase (MAPK) pathway, the phosphoinositide 3-kinase/mammalian target of rapamycin (PI3K/mTOR) axis, and the RAS-related protein/nuclear factor κB (RAL/NF-κB) pathway.[9-11] These small GTPases are key regulators of cell growth, differentiation, and survival. KRAS proteins function as molecular switches, toggling between an active (on) and inactive (off) state depending on whether they bind to guanosine diphosphate (GDP) or GTP. KRAS is bound to GDP in the inactive state, whereas it is bound to GTP in the active state. This transition between states is critical for controlling downstream signaling pathways involved in cellular processes.[9]

KRAS activation typically begins with the engagement of intramembrane tyrosine kinase receptors, such as fibroblast growth factor receptors (FGFRs), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and HER3.[12,13] Activation of cell surface receptors leads to the recruitment and activation of guanine nucleotide exchange factors (GEFs), such as son of sevenless 1 (SOS1) and SOS2. These GEFs facilitate the conversion of RAS-GDP to RAS-GTP, thereby activating KRAS. In its active state, KRAS proteins dimerize and initiate downstream signaling cascades that regulate key cellular processes such as growth, differentiation, and survival. The signaling pathways also engage a negative feedback mechanism through GTPase-activating proteins (GAPs) that promote the hydrolysis of KRAS-GTP back to KRAS-GDP, effectively switching off KRAS

signaling (Figure).

KRAS-activating mutations, particularly in codons 12, 13, and 61, lead to constitutive activation of the protein by switching KRAS-GDP to KRAS-GTP, bypassing normal regulatory mechanisms and maintaining downstream signaling independently of extracellular growth signals.[14,15] This persistent activation promotes uncontrolled cell proliferation, survival, and metastasis.

Specific *KRAS* mutations confer distinct biochemical properties that affect treatment response. For instance, *KRAS* G12C retains some GTPase activity, which enables selective inhibition by covalent inhibitors that bind to the cysteine residue unique to this mutation.[16] In contrast, mutations like *KRAS* G12D and *KRAS* G12V significantly reduce GTPase activity, so that they are more challenging to target with similar approaches.[16] Understanding these molecular differences is crucial for developing mutation-specific inhibitors and optimizing therapeutic strategies.

Prevalence and Effect of *KRAS* Mutations in GI Malignancies

KRAS mutations are heterogeneously distributed across GI cancers, with high rates observed in PDAC, CRC, and biliary tract cancer (BTC).[17] In PDAC, the most prevalent *KRAS* variants are G12D, G12V, and G12R.[17] In CRC, *KRAS* mutations are also common, with G12D, G12V, and G13D the most frequent. BTC, including cholangiocarcinoma, exhibits *KRAS* mutations in approximately 15% to 20% of cases, with G12D the most common.[17] However, *KRAS* G12C mutations are rare in GI cancers, occurring in approximately 1.5% of PDACs, 3.6% of CRCs, and 1% of BTCs. Even lower rates are observed in other GI malignancies, reflecting the overall infrequency of this specific mutation type in the GI cancer spectrum.[17]

KRAS mutations are key drivers of tumorigenesis and significantly influence prognosis and treatment response, with outcomes varying according to the specific biological variants involved.[18-22] In CRC, different *KRAS* G12 mutations have distinct prognostic implications. Specifically, *KRAS* G12C is associated with a poorer prognosis than other G12 mutations,[18,23] whereas *KRAS* G12R has shown an association with a more favorable prognosis. *KRAS* mutations are also associated with resistance to anti-EGFR therapies, limiting the effectiveness of targeted treatments for patients with *KRAS* mutations.[24] Similar adverse effects of *KRAS* mutations on prognosis and treatment response have been observed in other GI cancers.[25,26] Overall, *KRAS* mutations are frequently linked to aggressive disease and a poor outcome, underscoring the critical need for developing effective targeted therapies for patients with *KRAS* mutations.

Therapeutic Approaches Targeting KRAS

As highlighted earlier, targeting RAS has been a longstanding challenge owing to its strong affinity for GTP, the absence of suitable binding pockets for small molecules, and a low intrinsic rate of GTP hydrolysis.[27,28] Initial drug development strategies focused on inhibiting downstream or upstream components of RAS signaling, but these efforts were often ineffective because of the complexity of RAS pathways and the emergence of compensatory mechanisms. RAS was consequently labeled "undruggable," emphasizing the need for innovative approaches to target this critical oncogene.

A recent breakthrough in KRAS-targeted therapies was driven by the mechanistic discoveries of Dr Kevan Shokat and colleagues, which transformed the approach to treating *KRAS*-mutated cancers.[29,30] A novel mechanism identified a unique binding pocket in the switch II region of the *KRAS* G12C mutation, which contains a mutated cysteine residue.[29] This pocket allowed the irreversible covalent binding of small molecules with high affinity, specifically targeting the mutant KRAS protein. Once a covalent bond is formed, it locks KRAS in the GDP-bound (inactive) state, leading to sustained inactivation of the oncogenic *KRAS* mutation. This mechanistic effect is particularly effective in *KRAS* G12C because it has a minimal effect on GTPase activity and a greater intrinsic rate of GTP hydrolysis, features that distinguish it from other *KRAS* mutations and enhance its therapeutic potential.[16]

This discovery was pivotal in the creation of KRAS-targeted therapies, leading to the introduction of specific inhibitors for *KRAS* G12C mutations such as sotorasib (Lumakras, Amgen)[31,32] and adagrasib (Krazati, Mirati Therapeutics).[30,33,34] These inhibitors covalently bind to the unique cysteine at codon 12 of the *KRAS* G12C mutant, effectively locking it in the inactive GDP-bound state and blocking the aberrant signaling that drives cancer progression.

Sotorasib, the first KRAS G12C inhibitor approved by the US Food and Drug Administration (FDA) for non–small cell lung cancer (NSCLC), demonstrated clinical efficacy and paved the way for the direct targeting of mutant *RAS*.[35] In the phase 2 CodeBreaK 100 trial, 126 patients with previously treated *KRAS* G12C-mutated NSCLC were enrolled and received sotorasib. The trial demonstrated an objective response rate (ORR) of 37.1% (95% CI, 28.6%-46.2%) and a disease control rate (DCR) of 80.6% (95% CI, 72.6%-87.2%). The median progression-free survival (mPFS) was 6.8 months (95% CI, 5.1-8.2), and the median overall survival (mOS) was 12.5 months. On the basis of these landmark results, sotorasib received accelerated approval from the FDA in May 2021 for the treatment of patients with locally

Table 1. Emerging *KRAS* G12C Inhibitors

Agent	Manufacturer	Phase (Identifier)	Study Population
Olomorasib (LY3537982)	Lilly	1/2 (NCT04956640)	Advanced *KRAS* G12C-mutant tumors Tumor subtypes: non–small cell lung, colon, endometrial, pancreatic neoplasms; biliary tract neoplasms
ZG19018	Suzhou Zelgen Biopharmaceuticals	1/2 (NCT06237400)	Advanced *KRAS* G12C-mutant tumors Tumor subtypes: non–small cell lung cancer, colorectal cancer, and other advanced solid tumors
HBI-2438	HUYABIO International	1 (NCT05485974)	Advanced *KRAS* G12C-mutant tumors Tumor subtypes: non–small cell lung, colorectal, pancreatic cancers
Opnurasib (JDQ443)	Novartis	KontRASt-01 1/2 (NCT04699188)	Advanced *KRAS* G12C-mutant tumors Tumor subtypes: non–small cell lung, colorectal
HS-10370	Jiangsu Hansoh Pharmaceutical	1/2 (NCT05367778)	Advanced *KRAS* G12C-mutant tumors
BI-1823911	Boehringer Ingelheim	1 (NCT04973163)	Advanced *KRAS* G12C-mutant tumors
JNJ-74699157	Janssen Research & Development	1 (NCT04006301)	Advanced *KRAS* G12C-mutant tumors Tumor subtypes: non–small cell lung, colorectal
IBI351 (GFH925)	Innovent Biologics (Suzhou, China)	1/2 (NCT05005234)	Advanced *KRAS* G12C-mutant tumors
		1b/3 (NCT05497336)	Advanced *KRAS* G12C-mutant colorectal cancers
YL-15293	Shanghai Yingli Pharmaceutical	1 (NCT05173805)	Advanced *KRAS* G12C-mutant tumors
BPI-421286	Betta Pharmaceuticals	1 (NCT05315180)	Advanced *KRAS* G12C-mutant tumors
GH35	Suzhou Genhouse Bio	1 (NCT05010694)	Advanced *KRAS* G12C-mutant tumors
GEC255	GenEros Biopharma	1 (CTR20212486)	Advanced *KRAS* G12C-mutant tumors
MK-1084	MSD	1 (NCT05067283)	Advanced *KRAS* G12C-mutant tumors
D3S-001	D3 Bio	1 (NCT05410145)	Advanced *KRAS* G12C-mutant tumors
HBI-2438	HUYABIO International	1 (NCT05485974)	Advanced *KRAS* G12C-mutant tumors Tumor subtypes: non–small cell lung, colorectal, pancreatic cancers
SY-5933	Shouyao Holdings	1 (NCT06006793)	Advanced *KRAS* G12C-mutant tumors
JNJ-74699157	Janssen Research & Development	1 (NCT04006301)	Advanced *KRAS* G12C-mutant tumors

advanced or metastatic *KRAS* G12C-mutated NSCLC that had progressed on at least one prior systemic therapy.[36] Similar outcomes were observed in a comparable patient population with adagrasib monotherapy, leading to its approval by the FDA in December 2022.[37] These approvals represent significant advancements in targeted therapy for *KRAS* G12C-mutated NSCLC, offering new treatment options for patients with this challenging mutation.

Given the prevalence of *KRAS* mutations in GI cancers,

the efficacy of sotorasib and adagrasib were evaluated in the GI space. Sotorasib and adagrasib have provided encouraging, although varied, results in GI cancers. In PDAC, sotorasib and adagrasib showed modest activity as monotherapy, with an ORR of approximately 20% to 33%. In the CodeBreaK 100 trial, 38 patients with *KRAS* G12C-mutated PDAC who received sotorasib monotherapy had an mPFS of 4.0 months and an mOS of 6.9 months, with an ORR of 21% and a DCR of 84%.[38] Similarly, the phase 1/2 KRYSTAL-1 trial evaluated adagrasib monotherapy in patients with metastatic PDAC, showing an mPFS of 5.4 months (95% CI, 3.9-8.2) and an mOS of 8 months (95% CI, 5.2-11.8).[39] In this group, the ORR was 33% and the DCR was 49%, demonstrating efficacy comparable with that of sotorasib. Similar results were observed in patients with BTC in the KRYSTAL-1 study, in which 12 patients demonstrated an ORR of 41.7%, a DCR of 91.7%, an mPFS of 8.6 months, and an mOS of 15.1 months.[39] These findings have established sotorasib and adagrasib as options for PDAC and BTC with *KRAS* G12C mutations. Owing to the promising results from clinical studies and the limited treatment options for patients with these aggressive cancers, both sotorasib and adagrasib are available as treatment options for *KRAS* G12C-mutated PDAC and BTC. Both drugs are now included as single-agent therapies in the National Comprehensive Cancer Network guidelines for advanced *KRAS* G12C-mutated PDAC, with adagrasib also specifically recommended for BTC.[40,41]

Although KRAS G12C inhibitors have shown potential in various GI cancers, their efficacy in CRC is notably relatively low. As monotherapy, sotorasib and adagrasib exhibit modest activity in CRC, with response rates ranging between 10% and 20%. However, their effectiveness significantly improves when they are combined with anti-EGFR antibodies like cetuximab (Erbitux, Lilly), with response rates nearly doubled. This combination strategy helps to counteract adaptive resistance mechanisms such as the reactivation of upstream signaling pathways, which often reduce the effectiveness of KRAS G12C inhibitors in GI cancers. The CodeBreaK 101 phase 1b study evaluated sotorasib alone or in combination with EGFR inhibitors in chemorefractory *KRAS* G12C-mutated CRC.[42] The ORR with the combination of sotorasib and panitumumab (Vectibix, Amgen) was 30%, whereas it was 9.7% with sotorasib monotherapy. Similarly, the KRYSTAL-1 trial assessed adagrasib combined with an anti-EGFR therapy in the metastatic setting, showing an ORR of 34% (95% CI, 24.6%-44.5%) for the combination vs an ORR of 21.4% (95% CI, 10.3%-36.8%) for adagrasib alone, with similar DCRs (85.1% vs 86.2%).[43,44] The combination demonstrated superiority in all other efficacy endpoints, with an mPFS of 6.9 months (95% CI, 5.7–7.4) vs 4.1 months (95% CI, 2.8-6.5) for monotherapy and an mOS of 15.0 months (95% CI, 11.8-18.8) vs 12.2 months (95% CI, 8.1-15.2) for monotherapy. Notably, combination therapy was well tolerated, with grades 3 and 4 treatment-related adverse events (TRAEs) occurring in 27% of patients.

Combining EGFR and KRAS inhibitors has emerged as a key strategy to overcome resistance in *KRAS*-mutant cancers, particularly CRC. EGFR inhibitors alone, such as cetuximab and panitumumab, are ineffective in *KRAS*-mutant tumors owing to persistent downstream signaling.[45-47] Recent studies demonstrate that inhibition of KRAS with an agent like sotorasib or adagrasib plus inhibition of EGFR effectively blocks the RAS/mitogen-activated protein kinase (MAPK) pathway, enhancing antitumor efficacy. The CodeBreaK 101 and KRYSTAL-1 trials highlight the potential of this approach, showing improved response rates and survival outcomes in *KRAS* G12C-mutant CRC vs monotherapy.[48] Early evidence also suggests that adding chemotherapy to this regimen may still further improve outcomes.[49] Building on this strategy, several clinical trials are investigating the combination of KRAS G12C inhibitors with chemotherapy to optimize treatment efficacy. The phase 3 CodeBreaK 301 trial (NCT06252649) is assessing the efficacy of sotorasib, panitumumab, and FOLFIRI (leucovorin, 5-fluorouracil, and irinotecan) vs FOLFIRI with or without bevacizumab in treatment-naive patients who have metastatic CRC harboring the *KRAS* G12C mutation. Additionally, the ongoing INTRINSIC trial (NCT04929223) is a phase 1 study evaluating the combination of divarasib and cetuximab with either FOLFOX (leucovorin, 5-fluorouracil, and oxaliplatin) or FOLFIRI in CRC. Although this study is still in progress, its results are anticipated to provide further insights into the efficacy of these novel combination therapies.

The CodeBreaK 300 trial also demonstrated that the combination of sotorasib and panitumumab significantly improved outcomes in refractory *KRAS* G12C-mutated metastatic CRC vs physician's choice of therapy—regorafenib (Stivarga, Bayer HealthCare) or trifluridine/tipiracil (Lonsurf, Taiho Oncology)—with an ORR of 26.4% and an mPFS of 5.6 months vs an ORR of 0% and an mPFS of 2.2 months in the control group. These results support the use of this combination in chemotherapy-refractory cases.[50] The ORR was 26.4% and the mPFS was 5.6 months, vs an ORR of 0% and an mPFS of 2.2 months in the physician's choice group. These findings advocate for the use of sotorasib combined with panitumumab in chemotherapy-refractory *KRAS* G12C-mutated CRC. Meanwhile, the KRYSTAL-10 trial (NCT04793958) is investigating adagrasib with cetuximab vs chemotherapy, with results yet to be released.

Although these advancements demonstrate the potential of EGFR and KRAS inhibitor combinations to improve outcomes in *KRAS* G12C-mutant CRC, challenges remain. Increased toxicity, optimal dosing strategies, and integration into earlier treatment lines require further investigation. Continued research will be critical to refine these therapies and maximize their clinical application.

Several novel KRAS G12C-targeted therapies, including glecirasib,[51-53] garsorsib,[54-56] divarasib,[57] and olomorasib,[58] are being integrated into clinical practice. These agents have a mechanism of action similar to that of adagrasib and sotorasib, covalently binding to KRAS G12C in its inactive state. They have demonstrated clinical benefits in GI cancers.

Glecirasib has shown promising results in CRC, with an ORR of 33.3% as monotherapy. Its efficacy improved significantly when it was combined with cetuximab, achieving an ORR of 62.8%.[51] Ongoing phase 1/2 trials (NCT05009329 and NCT05002270) are evaluating its effects in various solid tumors harboring *KRAS* G12C mutations.[52] For patients with PDAC in the trial, the ORR was 46.4% and the DCR was 96.4%. The median duration of response (DOR) was 4.1 months, and the mPFS was 5.5 months. Common TRAEs included anemia, elevated bilirubin levels, and decreased white blood cell counts, with 25% of patients experiencing grade 3 or higher TRAEs. These preliminary results indicate that glecirasib is well tolerated and shows promising antitumor activity in *KRAS* G12C-mutated PDAC and other solid tumors. Additional studies are ongoing to further evaluate the clinical efficacy of glecirasib (NCT06008288).

Garsorsib has also demonstrated potential in CRC, with an ORR of 21% as monotherapy.[59] Improved outcomes have been observed with combination therapies, similar to those of adagrasib and sotorasib when paired with anti-EGFR agents. In a phase 2 trial (NCT04585035), garsorsib combined with cetuximab showed an ORR of 45% and a DCR of 95% in refractory metastatic CRC.[55] In PDAC, garsorsib monotherapy achieved an ORR of 50%, a DCR of 80%, and an mPFS of 8.5 months.[54]

Divarasib, another KRAS G12C inhibitor, is noted for its higher potency and selectivity for KRAS G12C compared with adagrasib and sotorasib.[57] It has shown promising results in both CRC and PDAC.[57,60] In a phase 1 trial involving 137 patients, including 55 with mCRC, divarasib monotherapy showed an ORR of 29% with an mPFS of 5.6 months at a daily dose of 400 mg. More recently, in a phase 1b trial (NCT04449874), the combination of divarasib and cetuximab yielded an ORR of 62.5% and an mPFS of 8.1 months in patients with mCRC.[60] In smaller cohorts, divarasib demonstrated encouraging results in PDAC and BTC, with further investigation warranted to confirm these findings in larger, randomized trials.[57]

Olomorasib, an oral, potent, and highly selective second-generation KRAS G12C inhibitor, has demonstrated encouraging results in treating *KRAS* G12C-mutant advanced solid tumors.[58,61] Updated data from the phase 1/2 LOXO-RAS-20001 trial demonstrated its efficacy and safety in 184 patients, including 83 with NSCLC, 32 with CRC, 24 with PDAC, and 45 with other solid tumors. Olomorasib monotherapy achieved consistent efficacy across tumor types; the ORR was 35% and the mPFS was 7.1 months in patients with KRAS G12C inhibitor–naive non-CRC solid tumors, and the mPFS was 7.9 months (95% CI, 4.1 to not estimable) in patients with KRAS G12C inhibitor–naive NSCLC. Efficacy varied by tumor type, with an ORR of 40% (30 partial responses, 5 pending/ongoing responses) and a DCR of 90% in 88 patients with non-CRC tumors across 13 tumor types. In contrast, the patients with CRC had a lower ORR of 9% (3 partial responses) but a high DCR of 84%. Median PFS ranged from 4 months in CRC (95% CI, 3-7) to 9 months in NSCLC (95% CI, 3 to not estimable). Safety data revealed that TRAEs were predominantly mild, with diarrhea (23%), nausea (11%), and fatigue (10%) the most common.[62] Discontinuation due to TRAEs occurred in only 1% of patients, and the safety profile was favorable even in those who had discontinued prior KRAS G12C inhibitors because of toxicity. These findings establish olomorasib as a highly promising treatment option for patients with *KRAS* G12C-mutant cancers, offering both efficacy and tolerability, including in patients with prior exposure to targeted therapy.

It is essential to consider the side effect profiles of KRAS G12C inhibitors. Common adverse effects include GI symptoms such as nausea, vomiting, and diarrhea.[3,32,35,37,39,57,59,63] Most trials have reported that the majority of TRAEs are mild to moderate and nonfatal. Other notable side effects include elevated liver enzymes and cytopenias. A particular concern with adagrasib is the risk of QT interval prolongation. Although rare, this can be clinically significant, especially as many patients may be taking other QT-prolonging medications. Additionally, pneumonitis is another important side effect to monitor. In NSCLC trials, 2.6% of patients receiving adagrasib and 1% of patients treated with sotorasib experienced grade 3 or higher pneumonitis.[35,37] Although uncommon, these findings highlight the need for careful monitoring for potential respiratory complications in patients taking these agents.

Several novel agents, including opnurasib,[64,65] IBI351,[66] and MK-1084,[67] are currently under clinical evaluation. Table 1 provides an overview of these emerging KRAS G12C inhibitors, which function similarly to

Table 2. Next-Generation KRAS Agents

Drug Class	Agent	Phase (Identifier)	Study Population
KRAS G12C "ON" inhibitors	BBO-8520[98]	Preclinical	
	RMC-6291	1 (NCT05462717)	Advanced *KRAS* G12C-mutant tumors
	FMC-376	1/2 (NCT06244771)	Advanced *KRAS* G12C-mutant tumors
	D3S-001	1 (NCT05410145)	Advanced *KRAS* G12C-mutant solid tumors
KRAS G12D inhibitors	MTRX1133	1/2 (NCT05737706)	Advanced *KRAS* G12D-mutant tumors
	RMC-9805	1 (NCT06040541)	Advanced *KRAS* G12D-mutant tumors
	HRS-4642	1 (NCT05533463)	Advanced *KRAS* G12D-mutant tumors
	ASP3082	1 (NCT05383559)	Advanced *KRAS* G12D-mutant tumors
	QTX3046	1 (NCT06428500)	Advanced *KRAS* G12D-mutant solid tumors
	LY3962673	1 (NCT06586515)	Advanced *KRAS* G12D-mutant solid tumors
	BI-2852[99]	Preclinical	
	ERAS-4001[100]	Preclinical	
	JAB-22000[100]	Preclinical	
KRAS G12V inhibitor	RMC-5127[71]	Preclinical	
KRAS G13C inhibitor	RMC8839[72]	Preclinical	
KRAS Q61H inhibitor	RMC-0708[72]	Preclinical	
Multi-/pan-RAS inhibitors	RMC-6236	1 (NCT05379985)	Advanced *KRAS*-mutant lung cancer and PDAC
	BI-3706674	1 (NCT06056024)	Advanced *KRAS* wild-type amplified gastric, esophageal, and gastroesophageal junction adenocarcinomas
	QTX3034	1 (NCT06227377)	Advanced *KRAS* G12D-mutant solid tumors
	BBP-454[101]	Preclinical	
	RM-042[102]	Preclinical	
Vaccine-based agents	ELI-002 7P (AMPLIFY-7P)	1/2 (NCT05726864)	*KRAS*-mutant localized PDAC and CRC
	KRAS peptide vaccine	1 (NCT05013216)	*KRAS*-mutant localized PDAC

CRC, colorectal cancer; PDAC, pancreatic ductal adenocarcinoma.

existing KRAS G12C inhibitors, and the details of ongoing clinical trials.

Next-Generation KRAS Inhibitors

Emerging therapies targeting *KRAS* mutations are showing promise in addressing a broader range of KRAS-driven cancers, particularly PDAC and other GI malignancies. Agents such as RMC-6291[68] and FMC-376,[69] designed to target KRAS G12C in its active state, are undergoing clinical evaluation. Beyond KRAS G12C, novel inhibitors are being developed to target other *KRAS* mutations, including G12D, G12V, and Q61H.[70-72] These inhibitors employ diverse mechanisms, such as targeting the active GTP-bound state or promoting the degradation of mutant KRAS proteins.[70-72]

RAS(ON) mutant-selective inhibitors for other *KRAS* mutations are being developed, such as RMC-5127 (G12V),[71] RMC-0708 (Q61H),[72] and RMC-8839 (G13C),[72] that have demonstrated promising antitumor activity in preclinical studies. Among these, MRTX1133,[73] HRS-4642,[74] RMC-9805,[70] and ASP3082[75] specifically target KRAS G12D (the *KRAS* G12D mutation is commonly seen in pancreatic and biliary cancers). RMC-9805, an oral covalent RAS(ON) KRAS G12D–selective inhibitor, showed an ORR of 30% and a DCR of 80% in patients with PDAC in an ongoing phase 1 trial, with tolerable side effects such as GI symptoms and rash.[76] Similarly, ASP3082, a KRAS G12D-targeting protein degrader, displayed dose-dependent efficacy in a phase 1 trial involving 98 patients with advanced *KRAS* G12D-mutated cancers, including PDAC, CRC, and NSCLC.[77] At a 300-mg

dose, the ORR was 33.3% and the DCR was 75%, with especially encouraging responses in patients with pancreatic cancer or NSCLC. TRAEs included fatigue and infusion-related reactions and were manageable. Further investigation at higher doses is warranted.

Additionally, pan- or multi-RAS inhibitors, such as RMC-6236[78] and BI-3706674,[79] have been developed to target multiple *KRAS* mutations. RMC-6236, an oral RAS(ON) multi-selective noncovalent inhibitor, targets *KRAS* mutations including G12X, G13X, and Q61X. RMC-6236 demonstrated an mPFS of 8.5 months in patients with *KRAS* G12X mutations and of 7.6 months in those with other *RAS* mutations in a phase 1/2 trial (NCT05379985).[80] The mOS was 14.5 months, with an ORR of 22% to 29% and a DCR of 89% to 91%. The treatment was well tolerated, with mild adverse effects such as rash, diarrhea, and stomatitis, and no patients discontinued treatment because of toxicity. These promising results have led to the initiation of a global phase 3 trial, RASolute 302, comparing RMC-6236 with standard chemotherapy in patients undergoing second-line treatment for metastatic PDAC with *KRAS* G12X mutations.

Beyond small molecules, novel KRAS-targeted immunotherapies, such as peptide vaccines (eg, ELI-002), are also under investigation, potentially expanding therapeutic options for patients with KRAS-driven cancers.[81-83] These advancements could potentially expand treatment options for patients with various KRAS-driven cancers. Table 2 lists the next-generation KRAS inhibitors.

Mechanisms of Resistance to KRAS Inhibitors

Resistance to KRAS inhibitors remains a significant challenge in the treatment of patients with *KRAS*-mutant cancers, with both intrinsic and acquired mechanisms contributing to therapeutic failure. Understanding these resistance pathways is crucial for optimizing treatment strategies and improving patient outcomes. Resistance to KRAS inhibitors can occur through intrinsic/adaptive resistance mechanisms or acquired resistance mechanisms.

Intrinsic/Adaptive Resistance Mechanisms

Adaptive resistance refers to pre-existing factors within a tumor that diminish initial sensitivity to KRAS inhibitors. Adaptive resistance often involves the reactivation of alternative signaling pathways such as PI3K/AKT/mTOR or the increased activity of receptor tyrosine kinases (RTKs) like EGFR, HER2, and FGFR, which support cell growth and survival despite KRAS inhibition, thereby reducing the effectiveness of KRAS G12C-targeted therapies.[84 85] Normally, mutant *KRAS* G12C exerts negative feedback on RTK activity and the activity of other wild-type RAS proteins through ERK-mediated inhibition. However, KRAS G12C inhibitors that stabilize the protein in its inactive state can attenuate this suppression, leading to increased RTK activity and the reactivation of wild-type RAS molecular variants. In response to KRAS inhibition, tumors may activate compensatory feedback mechanisms, such as upregulation of RTKs, SHP2, or SOS1, which can also reactivate the MAPK pathway. These rapid adaptive responses often limit the efficacy of KRAS inhibitors when used as monotherapy. This feedback loop was demonstrated in studies by Ryan and colleagues, in which treatment with KRAS G12C inhibitors led to a rapid resurgence of MAPK signaling owing to the increased expression of multiple upstream RTKs, including EGFR, HER2, and FGFR.[84,85] Additionally, the responsiveness of tumors harboring concurrent mutations, such as those in *TP53*, *STK11*, or *KEAP1*, may be reduced as a consequence of altered cellular dependencies and increased tumor plasticity.[17,86]

Acquired Resistance Mechanisms

Acquired resistance typically emerges after an initial positive response to KRAS inhibitors as a result of evolutionary pressures that select for resistant cell populations.[3,87-89] In the trials involving adagrasib and divarasib in patients with CRC, 45% of the patients had detectable genetic acquired alterations and 60% had detectable genetic resistance alterations that affected treatment response.[57,87] Resistance mutations that were commonly reported were new activating *KRAS* amplifications or alterations, new alterations in upstream RTKs (eg, EGFR, FGFRs), and mutations in downstream signaling components (eg, PIK3CA, RAF, MEK). These mutations affected both downstream signaling proteins (eg, MAPK, PI3K) and upstream RTKs, compromising the effectiveness of the treatment.

Overcoming Resistance: Combination Strategies

To combat resistance mechanisms, ongoing research is exploring various combination strategies aimed at simultaneously targeting multiple pathways or vulnerabilities within the tumor.

Combining KRAS Inhibitors With SHP2 or SOS1 Inhibitors

SHP2 and SOS1 are key mediators of RTK signaling involved in RAS protein activation. These agents function by promoting the conversion of GDP-bound KRAS to its active GTP-bound state. By inhibiting these proteins, it is possible to prevent adaptive feedback reactivation of the KRAS pathway. Preclinical studies and early clinical trials have shown that this approach can enhance the efficacy

of KRAS inhibitors and delay the onset of resistance. For example, JAB-3312, an SHP2 inhibitor, in combination with glecirasib demonstrated an ORR of 50% and a DCR of 100% in patients with NSCLC who had not previously been treated with KRAS G12C inhibitors.[90] Another SHP2 inhibitor, RMC-4630, is being evaluated in combination with sotorasib.[91] In a small cohort of 6 patients with CRC, the DCR was 83%. One patient showed a tumor burden reduction of approximately 26%, although no objective responses have been observed to date.[91]

Combining KRAS Inhibitors With MEK or ERK Inhibitors

Combining a KRAS inhibitor with a downstream MAPK pathway inhibitor, such as a MEK or ERK inhibitor, can effectively suppress pathway reactivation—a common adaptive mechanism of resistance to KRAS inhibitors. This approach aims to achieve a more comprehensive blockade of MAPK signaling, thereby reducing the chances of tumor cells escaping through alternative mutations. The combination of sotorasib and the MEK inhibitor trametinib (Mekinist, Novartis) is being evaluated as part of the CodeBreaK 101 study.[92] In this trial, 36 patients, including 18 with *KRAS* G12C-mutant CRC, were treated with the combination, resulting in a notable DCR of 86%. Importantly, even in patients previously exposed to KRAS G12C inhibitors, the maximum tolerated dose (2 mg of trametinib and 960 mg of sotorasib) resulted in stable disease across the cohort. Despite promising efficacy, the study reported a 34% incidence of grade 3 or higher toxicities, leading to therapy discontinuation in 24% of patients. Other trials (NCT05074810, NCT05375994) are currently looking at the combination of MEK inhibitors with anti-KRAS therapy.

Combination With PI3K or mTOR Inhibitors

The PI3K/AKT/mTOR pathway serves as a common escape mechanism in *KRAS*-mutant cancers. Combining KRAS inhibitors with PI3K or mTOR inhibitors can block this alternative survival pathway and is being evaluated in clinical trials to assess its effect on the antitumor response. For instance, mTOR inhibitors like everolimus are being explored in combination with sotorasib in NSCLC.[3] Phase 1 basket trials are also evaluating other combinations, such as adagrasib with nab-sirolimus (Fyarro, Aadi Bioscience; NCT05840510) and divarasib with the PI3K inhibitor inavolisib (Itovebi, Genentech; NCT04449874) in patients with advanced solid tumors.[3]

Combination With Immune Checkpoint Inhibitors

Combining immune checkpoint inhibitors (ICIs) with KRAS inhibitors is an emerging strategy to enhance antitumor immune responses by altering the tumor microenvironment (TME) and making tumors more susceptible to immune attack. *KRAS* mutations have been shown to promote both anti-inflammatory and pro-inflammatory effects within the TME.[31,93] Interestingly, adagrasib and sotorasib have been observed to promote a pro-inflammatory microenvironment, recruiting macrophages, dendritic cells, and CD8+ T cells and thereby enhancing antitumor immune responses in NSCLC.[3,94,95] These findings indicate a potential synergistic effect when KRAS inhibitors are combined with ICIs. However, the efficacy and safety of these combinations have been variable. In the CodeBreaK 101 study, sotorasib combined with pembrolizumab (Keytruda, Merck) or atezolizumab (Tecentriq, Genentech) showed an ORR of 29% and a DCR of 83%, but with an increased incidence of liver toxicity.[96] In contrast, the KRYSTAL-7 study reported a higher ORR of 63% and a DCR of 84% for adagrasib combined with pembrolizumab in patients with a high level of programmed death ligand 1 expression, along with lower rates of severe toxicity.[97]

Future Directions and Clinical Implications

The advent of KRAS-targeted therapies has introduced new opportunities for treating GI malignancies, particularly in patients with limited therapeutic options. As research advances, the focus will increasingly be on precision medicine strategies that optimize treatment on the basis of specific *KRAS* mutations and associated resistance mechanisms. Future clinical trials will be crucial in evaluating the use of KRAS inhibitors in earlier lines of therapy and in combination regimens, and their potential application in adjuvant and neoadjuvant settings. The overarching aim is to enhance the efficacy and durability of these treatments, improve survival outcomes, and alleviate the burden of KRAS-driven GI cancers.

Conclusion

KRAS mutations are a pivotal therapeutic target in GI malignancies, and the development of small-molecule inhibitors has significantly reshaped treatment options. Although challenges like resistance persist, the ongoing refinement of KRAS-targeted therapies, particularly in combination with other relevant agents, holds promise for improving outcomes in patients with *KRAS*-mutated GI cancers. A deeper understanding of KRAS biology and resistance mechanisms will be key to fully harnessing the potential of these innovative treatments as the field continues to evolve.

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