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Review Article

Targeted therapy for KRAS G12C-mutated colorectal cancer: advances, challenges, and future directions

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Abstract: Colorectal cancer (CRC) is among the most prevalent malignancies worldwide, with approximately 40% of the patients carrying KRAS mutations. Among these, the KRAS G12C mutation accounts for approximately 4% of the cases. This mutation introduces a unique cysteine residue at codon 12, enabling covalent binding and rendering KRAS G12C a tractable therapeutic target. Recently, selective small-molecule inhibitors of KRAS G12C, including sotorasib and adagrasib, have shown encouraging activity in early clinical trials, indicating potential clinical benefits for this subset of patients. However, their translation into routine clinical practice has been challenged by intrinsic and acquired resistance, treatment-related toxicities, and the absence of reliable predictive biomarkers. The aim of this study is to construct a clear knowledge framework that could inform the design of future clinical trials and optimize clinical practice. Future studies should focus on developing more potent next-generation inhibitors, exploring and optimizing rational combination strategies with other targeted agents or immunotherapies, investigating innovative therapeutic methods, and systematically identifying and validating predictive biomarkers. Collectively, with these efforts, we aim to enhance the efficacy, overcome resistance, and advance precision therapy for patients with KRAS G12C-mutant CRC.

Keywords: Colorectal cancer, KRAS G12C mutation, combination therapy

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide, with over 1.9 million new cases and approximately 900,000 deaths annually, which accounts for 9.4% of all cancer-related mortality [1]. Approximately 20-25% of patients are diagnosed with distant metastases, a condition associated with poor prognosis and a 5-year relative survival rate of only approximately 15%. Targeted therapies and immunotherapies have improved the outcomes off some patients; nevertheless, those with RAS mutations are excluded from anti-EGFR targeted agents, including cetuximab and panitumumab. The treatment options for this population remain limited. The median overall survival (mOS) of these patients in the era of conventional chemotherapy or first-line treatment alone is typically only 12-15 months, highlighting a significant unmet clinical need.

KRAS mutation is observed in approximately 40-45% of metastatic CRC (mCRC) cases, with G12C mutations (glycine to cysteine at codon 12) accounting for 3-5% [2]. In absolute terms, this corresponds to 22,000-28,000 new cases worldwide annually. This mutation sustains constitutive RAS-GTP activation via the "switch-II" pocket, leading to aberrant activation of the RAF-MEK-ERK signaling cascade [3]. This directly promotes tumor cell proliferation, invasion, and metastasis and induces an immunosuppressive tumor microenvironment (TME) by upregulating neutrophil chemotactic factors, including CXCL1/8 and GM-CSF, thereby diminishing the efficacy of PD-1/PD-L1 inhibitors. Consequently, the G12C mutation serves as a marker of poor prognosis and a long-standing untargeted oncogenic driver.

Developing irreversible covalent inhibitors has overcome historical challenges associated with targeting KRAS. Sotorasib and adagrasib have

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received accelerated FDA approval for KRAS G12C-mutated non-small cell lung cancer (NSCLC), showing demonstrating objective response rates (ORR) of 40-50% [4, 5]. However, CRC monotherapy with these agents yields an ORR of only 19-22% and a median progression-free survival (mPFS) of less than 5.6 months, with most patients developing acquired resistance within 6 months. Mechanistically, a multifactorial escape network - comprising EGFR feedback reactivation, amplification of alternative receptor tyrosine kinases (RTKs), secondary KRAS mutations, and epithelial-mesenchymal transition (EMT) - undermines the effect of single-agent targeting [6, 7]. Thus, identifying combination strategies to overcome adaptive resistance, including the concurrent inhibition of EGFR, SHP2, SOS1, or immune checkpoints, is a major clinical challenge in CRC [8].

Given the limitations of KRAS G12C inhibitor monotherapy for CRC, combination regimens are necessary. Preliminary clinical evidence shows that combining adagrasib with the EGFR inhibitor cetuximab increases the ORR to 46% and extends the median PFS to 6.9 months, which outcomes superior to that achieved with monotherapy. Nevertheless, there are still many challenges, including determining the optimal combination regimens, identifying predictive biomarkers, and managing the toxicity associated with combination therapy. This review systematically synthesizes the existing literature to outline the development of KRAS G12C-targeted agents, elucidate complex resistance mechanisms [9], and evaluate preclinical and clinical data on various combination strategies. The aim of this study is to construct a clear knowledge framework that could inform the design of future clinical trials and optimize clinical practice.

Biological characteristics of the KRAS G12C mutation

Under physiological conditions, KRAS cycles between the GDP-bound (inactive) and GTP-bound (active) states under precise regulation by guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) [10]. In the KRAS G12C mutation, where glycine at codon 12 is substituted by cysteine, intrinsic GTPase activity is markedly reduced, and the protein resists GAP-mediated hydrolysis, resulting in persistent accumulation in the active, GTP-bound state. This aberrant activation drives the excessive stimulation of downstream signaling, notably the mitogen-activated protein kinase (MAPK) pathway, such as ERK and phosphoinositide-kinase/AKT/mechanistic target of rapamycin (PI3K/AKT/mTOR) cascades. KRAS G12C activates the RALGDS/RAL and TIAM1/RAC pathways, which regulate cell migration, invasion, and other malignant phenotypes. Complex feedback loops and pathway crosstalk sustain an abnormal signaling equilibrium, collectively promoting proliferation, metabolic reprogramming, and apoptosis evasion. Importantly, oncogenic KRAS G12C directly drives tumor growth, and establishes a profoundly immunosuppressive TME. Mechanistically, activating the AKT/GSK3β axis attenuates STAT3 phosphorylation, which downregulates the RNA helicase DDX60 (DEAD-box helicase 60), accelerates degradation of double-stranded RNA (dsRNA), and blocks the RIG-I - like receptor (RLR)/MAVS pathway. This disruption eliminates the pathway. This disruption promotes immune evasion, ultimately mediating resistance of CRC to immune checkpoint inhibitors (ICIs). Restoring DDX60 expression can reverse immunosuppression and enhances ICI efficacy [11]. Global multicenter studies have shown that the prevalence of KRAS G12C in CRC remains around 3%, with no significant sex bias [12]. The biological effects in CRC are further influenced by tissue context and concurrent mutations, including APC, TP53, and PIK3CA. Collectively, the intrinsic GTPase defect, constitutive activation, downstream signaling hyperactivation, and establishment of an immunosuppressive TME form the core biological basis through which KRAS G12C drives the malignant progression of CRC. **Figure 1** shows the sustained activation of the RTK-SOS-SHP2-RAS axis, which promotes tumor proliferation, survival, and metastasis through the MAPK and PI3K-AKT-mTOR pathways [13].

Advances in KRAS G12C-targeted therapy

KRAS has been regarded as an “undruggable” target because of its high affinity for GTP, the absence of prominent binding pockets, and complex regulatory mechanisms. The KRAS G12C mutation is difficult to target directly for a long time due to the dynamic concealment of the Switch II pocket of the KRAS protein [14,

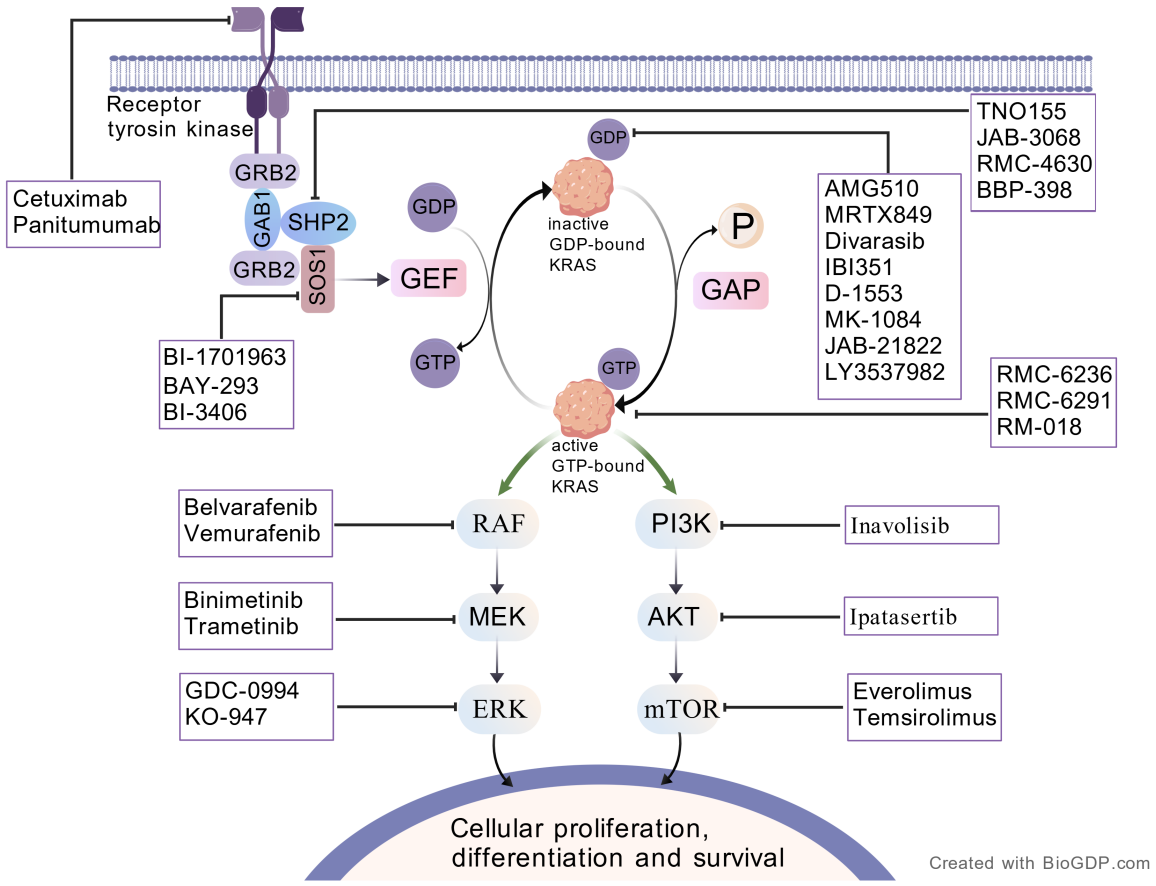

Figure 1. Illustrates sustained activation of the RTK-SOS-SHP2-RAS axis, which promotes tumor proliferation, survival, and metastasis through the MAPK and PI3K-AKT-mTOR pathways. Created with BioGDP.com.

15]. However, the discovery of this pocket has made it possible to design covalent inhibitors, promoting the marketing and clinical research of multiple KRAS G12C inhibitors [16]. Among them, sotorasib (AMG 510) and adagrasib (MRTX849) have shown meaningful clinical activity in NSCLC; however, their ORR remains at approximately 10% when used as monotherapy for CRC [17]. The KRAS G12C inhibitor IBI351, developed in China, reported an ORR of 45.8% with acceptable tolerability in a 600 mg BID cohort in a phase I study that involved patients with advanced CRC [18]. In addition to covalent G12C inhibitors, other novel strategies have emerged. For instance, daraxonrasib (RMC-6236), a pan-KRAS inhibitor from Revolution Medicines, indirectly reduces KRAS activity by engaging cyclophilin A (CYPA) to form a ternary complex, instead of occupying the GTP-binding pocket [19]. These findings underscore the progress and the remaining challenges. While the efficacy of KRAS G12C inhibitors in CRC is still limited, ongoing efforts in molecular innovation and drug design are expected to further improve therapeutic outcomes. The major milestones in developing KRAS inhibitors are shown in **Figure 2**.

Sotorasib

Sotorasib (AMG 510) is a first-class covalent inhibitor of KRAS G12C. It forms an irreversible bond with the mutant cysteine at codon 12 (Cys12) within the Switch II pocket, locking KRAS in the inactive GDP-bound state, and suppressing downstream RAS-MAPK signaling. Sotorasib has been approved for KRAS G12C-mutated NSCLC and is under clinical evaluation in CRC. In the phase II CodeBreaK 100 CRC cohort, 62 patients with KRAS G12C-mutant disease previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimens were enrolled. The ORR was 9.7% (all partial responses), mPFS was 4.0 months, and

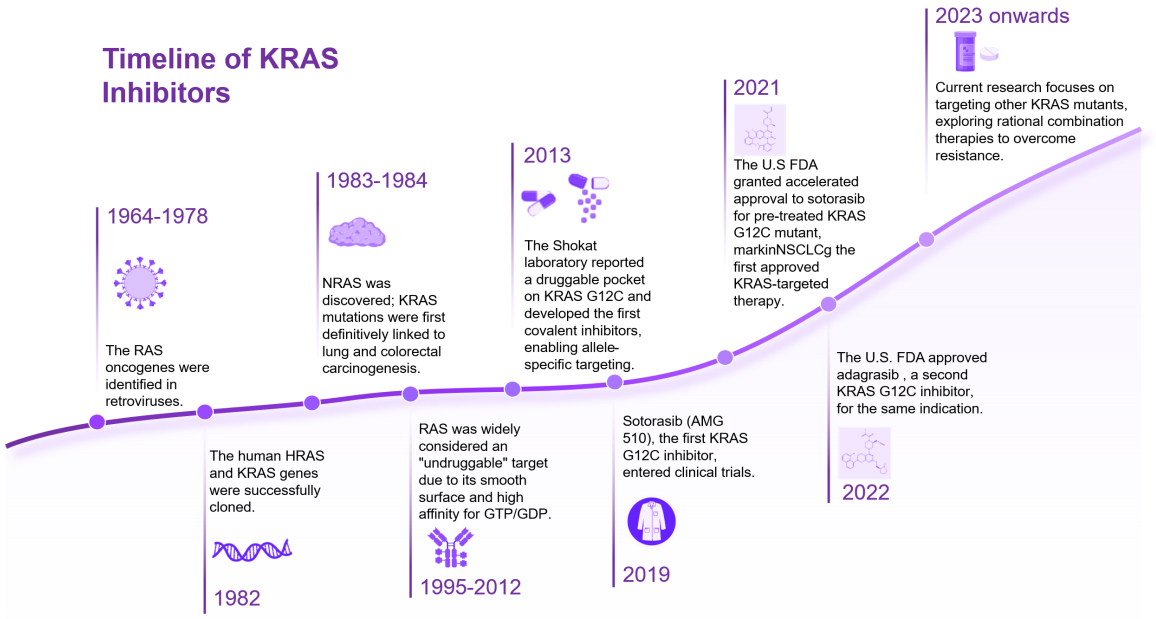

Figure 2. The RAS oncogene was discovered in retroviruses in the 1960s-70s. The human KRAS gene was cloned in 1982 and implicated in lung cancer in 1984. For nearly three decades thereafter, RAS was considered "undruggable". A pivotal breakthrough came in 2013 when the Shokat laboratory identified a druggable pocket on KRAS G12C. This led to the development of sotorasib (Lumakras), the first KRAS inhibitor, which received FDA accelerated approval in 2021 for KRAS G12C-mutated NSCLC. Adagrasib was approved in 2022. Current research focuses on inhibitors for other mutants (G12D), pan-KRAS inhibitors, and combination therapies.

mOS was 10.6 months. Treatment-related adverse events (TRAEs) were observed in 72.6% of the patients, with grade 3 events occurring in 10% (most common diarrhea), grade 4 events in 2% (elevated creatine kinase), and no treatment-related deaths [17]. Structural biology has implicated residue 95 in RAS isoforms, histidine in KRAS (H95) versus asparagine in NRAS (N95), as a determinant of inhibitor selectivity. Reportedly Sotorasib shows approximately inhibitory potency against NRAS G12C, fivefold greater than against KRAS G12C in preclinical assays [20], and a clinical case described regression of hepatic metastases and normalization of tumor markers in a patient with NRAS G12C-mutant CRC treated with sotorasib plus panitumumab [21]. In CRC, KRAS mutations occur in 40-50% of cases and KRAS G12C accounts for approximately 4%. Among the splice isoforms, KRAS4B is predominant in colorectal tissue and is deemed the principal isoform targeted by sotorasib. However contrast, the less abundant KRAS4A isoform was proposed to adopt a compact conformation through Q99 rotation and dimerization, potentially hindering inhibitor engagement, which may enhance suboptimal responses or resistance in a subset of patients. Furthermore, the unique features of KRAS H95 may affect their differential susceptibility to other inhibitors, including adagrasib.

Adagrasib

Adagrasib (MRTX849) is an orally available, potent, and irreversible small-molecule inhibitor that targets KRAS G12C mutations, especially in NSCLC and CRC [22]. It selectively traps KRAS G12C in its inactive state by covalently binding to the mutant cysteine, thereby suppressing downstream signaling while sparing the wild-type protein. Pharmacokinetic analyses indicated a high oral bioavailability, pronounced steady-state accumulation (~6-fold), and a terminal half-life of approximately 23 h. Importantly, adagrasib penetrates the blood-brain barrier [23] and has shown therapeutic activity against brain metastases. In the phase I/II KRYSTAL-1 trial on CRC, adagrasib monotherapy produced an ORR of 19% and a disease control rate (DCR) of 86%. The median duration of response (mDOR) was 4.3 months, mPFS was 5.6 months, and OS was 19.8 months [24]. Tumor reduction was observed in

79% of the patients, and the most frequent TRAEs included diarrhea, nausea, vomiting, fatigue, elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and increased serum creatinine. Most cases were grade 1-2 in severity and were managed using dose adjustment or temporary interruption. Notably, adagrasib showed minimal activity against HRAS G12C and NRAS G12C mutations, confirming its high specificity for KRAS G12C. Currently, pivotal phase III studies (KRYSTAL-10 and KRYSTAL-14) are ongoing to define its clinical benefits as a monotherapy and in combination strategies, including cetuximab, with the aim of optimizing therapeutic approaches for KRAS G12C-mutant malignancies.

Divarasib

Divarasib (GDC-6036) is a highly selective covalent inhibitor of KRAS G12C, which blocks tumor-associated signaling by irreversibly targeting cysteine in codon 12 of KRAS. In the phase 1 dose-expansion cohort of the NCT-04449874 study, results presented at the 2022 ASCO meeting showed that among 137 patients with advanced solid tumors treated with divarasib monotherapy, the ORR was 53.4% with a mPFS of 13.1 months in NSCLC, and 29.1% with a median PFS of 5.6 months in CRC [25]. The New England Journal of Medicine reported updated findings from the same trial in 2023, emphasizing on a CRC cohort (n=64). With longer follow-up, centralized imaging review using standardized criteria, and exclusion of early unconfirmed responses, the confirmed ORR reached 35.9%, and the mPFS increased to 6.9 months, indicating durable activity and reinforcing the efficacy signal. Regarding safety, the most common toxicities were grade 1-2 gastrointestinal events, including nausea and diarrhea; 12% of patients experienced grade ≥3 adverse events, and no dose-limiting toxicities or treatment-related deaths were reported [26]. In vitro, divarasib showed inhibitory potency against KRAS G12C approximately 5-20 fold higher than that of other agents, including sotorasib and adagrasib, which may, in part, underlie the higher clinical response rates observed.

Garsorasib

Garsorasib (D-1553) is the first KRAS G12C inhibitor in China to be part of human clinical trials [27]. A phase II study (NCT04585035) showed the therapeutic potential in patients with KRAS G12C-mutant mCRC who had received multiple prior lines of therapy. In the cohort with the highest proportion of Asian patients, 26 patients received garsorasib monotherapy (600 mg twice daily). The treatment achieved a confirmed ORR of 19.2% and DCR of 92.3%. The mPFS was 5.5 months, and the mOS was 13.1 months. Importantly, the regimen showed enhance efficacy in 42 patients who received garsorasib combined with cetuximab. The confirmed ORR increased to 45.2%, whereas the DCR was maintained at 92.9%. The mPFS was prolonged to 7.5 months, and the mOS was not yet reached at the time of analysis. This indicated a potential survival benefit. Regarding safety, the incidence of grade ≥3 treatment-related adverse events remained low in both cohorts, at 19.2% with monotherapy and 14.3% with combination therapy. The most common adverse events were manageable increases in liver enzyme levels and dermatological reactions. Collectively, these findings support garsorasib, either as monotherapy or combined with cetuximab, as a promising later-line precision therapy for patients with KRAS G12C-mutated mCRC, especially in Asian populations.

IBI351

IBI351 is the first KRAS G12C inhibitor to be approved for marketing in China [28]. It showed notable antitumor activity with a manageable safety profile in a phase I study conducted in Chinese patients with advanced solid tumors. In the CRC cohort (n=56), the confirmed ORR was 44.6% (95% CI, 31.3-58.5), the DCR was 87.5%, the mPFS was 8.1 months, and the mOS was 17.0 months. The ORR in the subgroup treated with the recommended phase II dose (RP2D; 600 mg twice daily [BID]) (n=48) was 45.8%, whereas the ORR in patients who received two or more prior lines of therapy (n=27) increased to 63.0% [18]. In the NSCLC cohort (n=166), at the RP2D, the ORR was 45.5%, the DCR was 92.1%, and the median PFS was 9.6 months; per independent review, the confirmed ORR reached 49.1% with a median PFS of 9.7 months. The agent also showed intracranial activity in patients with brain metastases (intracranial response rate, 22.6%) [18]. Regarding safety, TRAEs occurred in over 94% of patients, with grade ≥3 TRAEs in

Table 1. Key clinical trials targeting KRAS G12C in mCRC, completed or with already published data

Clinical trials	Phases	Drug	Cancer Type	Results
CodeBreaK 100 NCT03600883	I	Sotorasib (AMG510)	advanced KRAS G12C mutant mCRC (42)	ORR: 7.1% (3/42) DCR: 73.8% (31/42) mPFS: 4 mo
CodeBreaK 100 NCT03600883	II	Sotorasib (AMG510) 960 mg qd	advanced KRAS G12C mutant mCRC (62)	ORR: 9.7% (6/62) DCR: 82.3% (51/62) mPFS: 4.0 mo
KRYSTAL-1 NCT03785249	I/Ib	Adagrasib (MRTX849)	advanced KRAS G12C mutant solid tumors (4 mCRC)	mCRC treated with 600 mg bid ORR: 50% (1/2) DOR: 4.2 mo
KRYSTAL-1 NCT03785249	I/II	Adagrasib (MRTX849) 600 mg bid	advanced KRAS G12C mutant mCRC (44)	ORR: 19% (8/43) DCR: 86% (37/43) mPFS: 5.6 mo
NCT04449874	Ib	Divarasib (GDC-6036)	advanced KRAS G12C mutant solid tumors (55 mCRC)	ORR: 29.1% (20/55) mPFS: 5.6 mo mCRC treated with 400 mg qd ORR: 35.9% (14/39) mPFS: 6.9 mo
NCT05005234 NCT05497336	I	Fulzerasib (IBI351)	advanced KRAS G12C mutant mCRC	mCRC treated with 600 mg bid ORR: 45.8% (22/48) DCR: 89.6% (43/48) mPFS: 8.2 mo
NCT04585035	II	D-1553 (Garsorasib)	advanced KRAS G12C mutant mCRC	ORR: 19.2% (5/26) DCR: 92.3% (24/26) mPFS: 5.5 mo
NCT05067283	I	MK-1084	advanced KRAS G12C mutant mCRC (58)	ORR: 38% (22/58) DCR: 83% (48/58) DOR: 7.1 mo
NCT05002270	I/II	JAB-21822 (Glecirasib)	advanced KRAS G12C mutant mCRC (33)	ORR: 33.3% (11/33) DCR: 90.9% (30/33)
NCT04956640	I/II	LY3537982	advanced KRAS G12C mutant mCRC (32)	ORR: 9.4% (3/32) DCR: 84.4% (27/32) mPFS: 3.7 mo

ORR: objective response rate; DCR: disease control rate; mPFS: progression-free survival; Mo: months; DOR: duration of response.

25.0%-36.4%. The most common TRAEs were anemia (6.8%-7.1%) and elevation in gamma-glutamyl transferase (5.4%-10.2%). Gastrointestinal toxicities were less frequent than those with other KRAS G12C inhibitors (7.1%), potentially due to the compound's low lipophilicity (cLogP <4.4) and the cyclized piperazine moiety that confers enhanced stability. These findings show that IBI351, as a monotherapy or combined with anti-EGFR strategies, warrants further evaluation as a potential new standard of care for KRAS G12C-mutated mCRC in later and possibly first line settings. **Table 1** shows the clinical trials that have evaluated KRAS G12C inhibition in patients with KRAS G12C-mutated CRC.

Pan-RAS inhibitors

Targeted therapy for KRAS G12C-mutated CRC is shifting from inhibitors that selectively target the inactive, GDP-bound state to strategies that primarily reduce the active, GTP-bound state. Conventional agents (BI-2865/BI-2493) bind KRAS in its GDP-bound conformation, thereby reducing the activation and downstream signaling of multiple mutants, including G12C. Their selectivity depends on the KRAS-specific residues (H95, P121, and S122), with relatively weak inhibition by HRAS and NRAS [29]. Conversely, next-generation reversible tri-complex inhibitors (RMC-7977) constitute a novel approach. These inhibitors directly engage active RAS proteins by forming a CYPA-compound - RAS ternary complex with the molecular chaperone CYPA, including oncogenic and wild-type KRAS, NRAS, and HRAS [30]. This interaction prevents RAS-effector binding, blocks downstream signaling, and counteracts adaptive feedback such as RTK-driven resistance. This mechanism confers broad-spec-

Table 2. Key clinical trials of pan-RAS inhibitors in mCRC

Clinical trials	Phases	Drug	Cancer Type	Results
NCT05379985	I/Ib	RMC-6236	Metastatic Colorectal Cancer	ORR: 78% (18/23) DCR: 100% (23/23)
NCT06445062	II	RMC-6236 + Cetuximab + mFOLFOX6	Metastatic Colorectal Cancer	ORR: 37.5% (12/32) DCR: 81.3% (26/32) mPFS: 7.1 mo
NCT06445062	II	RMC-9805 + RMC-6236 + Cetuximab ± mFOLFOX6	Metastatic Colorectal Cancer	ORR: 34.4% (11/32) DCR: 78.1% (25/32) mPFS: 6.8 mo

trum activity, with in vitro studies showing specific vulnerability of in KRAS G12X-mutant cancer cell lines [31]. RMC-7977 has also shown preclinical efficacy in overcoming the resistance to current KRAS inhibitors. It remains active in adagrasib-resistant models associated with RTK overexpression (EGFR/HER2) or gene fusions (EML4-ALK), and in sotorasib-resistant patient-derived xenograft models with KRAS amplification, where it significantly reduces tumor growth [32]. Building on the same principle, the first-in-class RAS(ON) multi-selective inhibitor RMC-6236 identified KRAS G12X mutations as the strongest predictors of sensitivity in large-scale cell line screening [19]. RMC-6236 has entered phase I clinical testing (NCT05379985), and early findings have reported objective responses in patients with advanced KRAS G12X-mutated cancers, including lung and pancreatic tumors. These findings highlight the potential use of pan-RAS inhibitors in KRAS G12C-mutated CRC and their potential to overcome drug resistance; however, further clinical validation is required. **Table 2** shows ongoing clinical trials of pan-RAS inhibitors in mCRC.

Despite the groundbreaking advent of KRAS G12C inhibitors as a targeted therapy, accumulating clinical and preclinical evidence has revealed some limitations. First, the sample size and population representativeness were insufficient. Except for the IBI351 Phase I study, early trials of other G12C inhibitors for CRC included fewer than 70 evaluable cases, over 70% of which were of European descent. Data on Asian populations, microsatellite instability-high (MSI-H) subtypes, and right-sided colon cancer remain largely unavailable, resulting in potential ethnic and anatomical biases when extrapolating efficacy outcomes. Second, the definition of efficacy endpoints has been lenient, potentially overestimating the clinical benefits. Early studies, including CodeBreaK 100 and KRYSTAL-1, allowed local radiological assessment and included unconfirmed partial responses in ORR calculations. Consequently, the initially reported ORRs were 30% initially reported ORRs were 30% included unconfined an independent review. For instance, the ORR for divarasib reported in the 2022 ASCO abstract was 29.1%, which decreased to 19% after a central reassessment published in the NEJM in 2023, indicating an inflation of historical efficacy data. Third, current resistance monitoring strategies are limited, and mechanistic insights remain fragmented. Most studies have focused solely on baseline RAS status without incorporating dynamic liquid biopsies or multi-region tissue sequencing. Acquired resistance is frequently due to well-established mechanisms, including KRAS amplification or RTK bypass activation, while the roles of epigenetic alterations, TME, and microbiota-immune interactions remain systematically underexplored [33].

To address these limitations, we propose the following perspectives based on previous findings. First, we suggest implementing a propose the following perspectives based on alterations, TME, and microbiota-immune electron microscopy, we identified a propose the following perspectives based on alterations, TME, and microbiota-immune indeed 42°C, the protein showed increased sensitivity to covalent inhibitors [34]. Tumors may thus be classified into “rigid” and “flexible” subtypes, with the former responding to G12C inhibitors alone, while the latter may require combination with SOS1 or SHP2 inhibitors to stabilize the pocket conformation [35]. In vitro models indicated that this approach could reduce the IC50 values by 5- to 8-fold. Second, we propose an “immune-

tumor synchronous activation" sequential regimen. Single-cell RNA sequencing revealed an early expansion of IFN-γ^{+}CD8^{+} T cells within 7 days of G12C inhibitor treatment, accompanied by downregulation of MHC-I expression on tumor cells [36]. This supports a strategy in which a low dose of a G12C inhibitor (20% of the MTD) is initially administered to release tumor antigens, then adding a PD-L1 antibody and an HDAC inhibitor from day 8 onward to sustain antigen presentation.

Combination therapy

The efficacy of KRAS G12C inhibitors as monotherapy in CRC remains limited, with an ORR of only 7.1%-19.0% for agents, including sotorasib and adagrasib. These results were notably lower than those observed in NSCLC, where the ORRs ranged from 41.0% to 53.4%. Conversely, adding anti-EGFR antibodies (cetuximab or panitumumab) to KRAS G12C inhibitors has significantly improved efficacy, achieving ORR of 46.0%-62.5% and DCR of 86.0%-100% [37, 38]. These findings redirect research efforts toward combination strategies. Despite improvements in ORR and PFS, resistance remains a major clinical barrier. Therefore, developing novel combinatorial approaches is currently prioritized for the further enhancement of clinical benefits.

Combination with EGFR inhibitors

An important mechanism underlying resistance to KRAS G12C inhibitors is the activation of bypass signaling, especially through the EGFR pathway. Therefore, combining KRAS G12C inhibitors with anti-EGFR monoclonal antibodies (cetuximab or panitumumab) [39] achieves a more effective blockade of mitogenic pathways, maintains prolonged suppression of MAPK signaling, and induces tumor regression in patient-derived xenograft (PDX) models for up to 7 days [40]. Notably, KRAS G12C-mutated and BRAF V600E-mutated CRC differ in their molecular characteristics (MSS versus MSI); nevertheless, both display primary resistance to anti-EGFR antibody monotherapy. Consequently, dual targeting with KRAS G12C inhibitors and anti-EGFR antibodies is a promising therapeutic strategy for patients with KRAS-mutant CRC, for whom effective targeted options are currently lacking. The clinical evidence from completed or published trials evaluating EGFR-directed combinations with KRAS G12C inhibitors in mCRC is shown in **Table 3**.

Sotorasib panitumumab

The initial clinical evidence for sotorasib combined with panitumumab was derived from the phase Ib CodeBreaK 101 trial, including both dose escalation and expansion cohorts, and enrolled 48 patients with KRAS G12C-mutated mCRC. The patients received 960 mg of sotorasib once daily, combined with panitumumab 6 mg/kg every 2 weeks. TRAEs occurred in 94% of patients (any grade) and in 27% of patients at grade ≥3. The ORR in the expansion cohort was 30.0% [41], with mPFS and OS of 5.7 and 15.2 months, respectively. Frequently detected co-alterations included APC (84%), TP53 (74%), SMAD4 (33%), PIK3CA (28%), and EGFR (26%) [42]. Adding FOLFIRI to this doublet regimen increased the ORR to 58% and achieved a DCR of 93.5% in CodeBreaK 101. The phase III CodeBreaK 300 trial (n=219) compared sotorasib (960 mg or 240 mg) plus panitumumab with the standard of care (SOC; trifluridine/tipiracil or regorafenib) [43]. An interim analysis published in the New England Journal of Medicine in 2023 [44] revealed that the 960 mg group achieved a mPFS of 5.6 months and an ORR of 26.4%, significantly superior to SOC (mPFS, 2.2 months; ORR, 0%) with a hazard ratio (HR) of 0.49 (P=0.006). The 240 mg group (mPFS, 3.9 months; ORR, 5.7%) also outperformed the SOC group. Finally, updated in the Journal of Clinical Oncology in April 2025 [45], confirmed these findings. The 960 mg group showed a mPFS of 5.7 months and an ORR of 30.2%, while the 240 mg group (mPFS, 4.0 months; ORR, 7.5%) and SOC (mPFS, 2.0 months; ORR, 1.9%) showed only modest activity. Both analyses consistently substantiated the superiority of the 960 mg dose plus panitumumab over the lower dose and SOC. Concerns were raised regarding potential efficacy inflation owing to censored data in 11 patients with SOC; however, sensitivity analyses conducted by Fakih et al. reaffirmed the significant PFS benefit of the 960 mg regimen (HR=0.55) [46]. Preclinical investigations further showed that a triple regimen of sotorasib, trametinib (an MEK inhibitor), and cetuximab significantly suppressed colorectal tumor growth by through blocking MAPK pathway reactivation and EGFR upregulation [47].

Table 3. Key clinical trials EGFR-directed combinations with KRAS G12C inhibitors in mCRC

Clinical trials	Phases	Drug	Cancer Type	Results
CodeBreak 101 NCT04185883	Ib	Sotorasib (AMG510) 960 mg qd + panitumumab	advanced KRAS G12C mutant mCRC (54)	ORR: 33% (18/54) DCR: 85% (46/54) mPFS: 7.9 mo
CodeBreak 101 NCT04185883	Ib	Sotorasib (AMG510) 960 mg qd + panitumumab + FOLFIRI	advanced KRAS G12C mCRC previously treated ≥1 prior treatment (33)	ORR: 58.1% (95% CI, 39.1-75.5%) DCR: 93.5% (95% CI, 78.6-99.2%) mPFS: 5.7 mo (95% CI, 4.2 to 7.6 mo)
CodeBreak300 NCT05198934	III	Sotorasib 960 mg + panitumumab Sotorasib 240 mg + panitumumab SOC (trifluridine-tipiracil/regorafenib)	advanced KRAS G12C mutant mCRC (160)	Sotorasib 960 mg + pantumumab ORR: 30.2% (95% CI, 18.3-44.3%) DCR: 69.8% (95% CI, 55.7-81.7%) mPFS: 5.6 mo (95% CI, 4.2 to 6.3 mo) Sotorasib 240 mg + pantumumab ORR: 7.5% (95% CI, 2.1-18.2%) DCR: 67.9% (95% CI, 53.7-80.1%) mPFS: 3.9 mo (95% CI, 3.7 to 5.9 mo) SOC ORR: 1.9% (95% CI, 0.0-9.9%) DCR: 46.3% (95% CI, 32.6-60.4) mPFS: 2.2 mo (95% CI, 1.9 to 3.9 mo)
KRYSTAL-1 NCT03785249	I/II	Adagrasib (MRTX849) + cetuximab	advanced KRAS G12C mutant mCRC (32)	ORR: 46% (13/28) DCR: 100% (28/28) mPFS: 6.9 mo mOS: 13.4 mo
NCT06412198	Ib/II	Adagrasib + Cetuximab + Cemiplimab	Metastatic Colorectal Cancer Harboring KRAS G12C Mutations	No data
NCT04449874	Ib	Divarasib (GDC-6036) + cetuximab	advanced KRAS G12C mutant mCRC (29)	limited to KRAS G12C inhibitor naive population ORR: 62.5% (14/24) mPFS: 8 mo
NCT04585035	II	D-1553 (Garsorasib) + Cetuximab	advanced KRAS G12C mutant mCRC (42)	ORR: 45.2% (95% CI, 29.8-61.3%) DCR: 92.9% (95% CI, 80.5-98.5) mPFS: 7.5 mo (95% CI, 5.5 to 8.1 mo)
NCT05067283	I	MK-1084 + Cetuximab	advanced KRAS G12C mutant mCRC (41)	ORR: 46% (95% CI, 30-63%) DCR: 92% (95% CI, 79-98%) DOR: 10.8 mo (95% CI, 2.7-11.1 + mo)
NCT05067283	I	MK-1084 + Cetuximab + mFOLFOX6	advanced KRAS G12C mutant mCRC (33)	ORR: 38% (95% CI, 21-58%) DCR: 93% (95% CI, 77-99%)
NCT05002270	II	JAB-21822 (Glecirasib) + Cetuximab	advanced KRAS G12C mutant mCRC (42)	ORR: 42.5% (95% CI, 30-61.1%) DCR: 92.9% (95% CI, 80.5-98.5%) mPFS: 7.5 mo (95% CI, 5.5 to 8.1 mo)
NCT04956640	I/II	LY3537982 + Cetuximab	advanced KRAS G12C mutant mCRC (11)	ORR: 45% (5/11) DCR: 100% (11/11)

Collectively, these findings support the establishment of targeted combination therapy as a new treatment paradigm for KRAS G12C-mutated mCRC, leading to accelerated FDA approval.

Adagrasib cetuximab

Preclinical evidence showed that activating EGFR feedback may compromise the therapeutic efficacy of KRAS inhibitors [48]. The KRYSTAL-1 trial was the first to validate the strategy of combining adagrasib with cetuximab in humans [49]. In phase 1/2 cohorts of patients with KRAS G12C-mutated mCRC, adagrasib monotherapy (n=44) resulted in an ORR of 19%, a mDOR of 4.3 months, a mPFS of 5.6 months, and a mOS of 19.8 months. Conversely, combination therapy (n=32) produced a significantly higher ORR of 46%, with an mDOR, PFS, and OS of 7.6, 6.9, and 13.4 months, respectively. The safety profile also improved, with grade 3-4 TRAEs observed in 16% versus 34% of the monotherapy cohort, and no grade 5 events reported. The long half-life of adagrasib (~23 h), notably exceeding that of sotorasib (~5 h), enables sustained KRAS G12C inhibition [50]. In a subsequent phase 2 expansion, including 94 patients previously treated for with KRAS G12C-mutated mCRC, results remained consistent. In the combination subgroup, the ORR was again 46% and the mPFS 6.9 months, superior to that of monotherapy (ORR, 19%, mPFS 5.6 months). While the mOS in the combination arm (13.4 months) was numerically shorter than that in the monotherapy (19.8 months), this difference was likely attributable to baseline imbalances or post-progression treatments. Nevertheless, improvements in ORR and PFS substantiate the clinical benefits of this combination strategy [51]. In the NSCLC cohort, adagrasib monotherapy showed exhibited robust antitumor activity, with central nervous system (CNS) penetration providing therapeutic opportunities for patients with brain metastases [5]. Furthermore, in a cohort of 57 patients with advanced non-NSCLC/non-mCRC solid tumors, including pancreatic, biliary tract, and ovarian cancers, adagrasib had an ORR of 35.1% with a mPFS and OS of 7.4 and 14.0 months, respectively, thereby confirming its activity across multiple KRAS G12C-mutated tumor types [52].

Divarasib cetuximab

The effect of KRAS G12C inhibitor, divarasib (400 mg once daily), combined with cetuximab in patients with mCRC (n=29) was evaluated in a phase Ib study [53]. Among KRAS inhibitor-naïve patients (n=24), the regimen produced an ORR of 62.5% (1 complete and 15 partial responses), with a mDOR of 6.9 months and a mPFS of 8.1 months, surpassing outcomes observed with divarasib monotherapy (ORR 35.9%). The regimen showed a manageable safety profile; the most frequent adverse events were grade 1-2 rash (96.6%) and diarrhea (82.8%), and 13.8% of patients required dose adjustments. These findings support the therapeutic rationale that concomitant EGFR inhibition suppresses feedback reactivation after KRAS blockade, providing an effective targeted combination approach for KRAS G12C-mutated mCRC.

Garsorasib cetuximab

A study involving patients with KRAS G12C-mutated mCRC who had progressed after ≥1 prior line of therapy showed that the KRAS G12C inhibitor garsorasib (D-1553) was evaluated as monotherapy or combined with cetuximab, with outcomes reported in 68 predominantly heavily pretreated patients [27]. Monotherapy (n=26) produced an ORR of 19.2% and mPFS of 5.5 months, whereas the combination regimen (n=42) achieved a higher ORR of 45.2% and mPFS of 7.5 months. The safety profile was acceptable, with grade ≥3 TRAEs observed in up to 19.2% of patients. Importantly, the combination arm had a high proportion of Asian patients (85.7%), providing the first supportive evidence for using a KRAS G12C inhibitor plus an anti-EGFR antibody in this population and justifying the initiation of a phase III confirmatory trial.

Other combinations therapy

Therapeutic strategies for KRAS G12C-mutant tumors have evolved from single-agent targeted therapies to combination regimens to enhance efficacy and overcome resistance. In the immunotherapy setting [54], KRAS G12C inhibitors combined with PD-1/PD-L1 antibodies can remodel the immune microenvironment, activate $CD8^+$ T cells, and improve an-

Table 4. Key ongoing clinical trials evaluating KRAS G12C inhibitors, alone or in combination with other compounds in CRC

Clinical trials	Phases	Drug	Cancer Type
NCT05480865	I	Sotorasib (AMG510) + BBP-398 (SHP2 inhibitor)	advanced KRAS G12C mutant solid tumors
NCT04892017	I	DCC-3116 (ULK inhibitor) ± trametinib, binimetinib, or sotorasib (AMG510)	advanced solid tumors harboring any mutation in RAS/MAPK pathway
CodeBreak 101 NCT04185883	I/Ib	Sotorasib + BI 1701963 (anti-SOS1)	advanced KRAS G12C mutant solid tumors
CodeBreak 101 NCT04185883	I/Ib	Sotorasib + RMC-4630	anecdotal advanced KRAS G12C mCRC previously treated ≥1 prior treatment
NCT06039384	I	Adagrasib + INCB099280 (oral anti-PD-L1)	advanced KRAS G12C mutant solid tumors
NCT06024174	I/II	Adagrasib (MRTX849) + BMS-986466 (SHP2 inhibitor) ± Cetuximab	advanced KRAS G12C mutant NSCLC, PDCA, BTC and CRC
NCT05578092	I/II	Adagrasib (MRTX849) + MRTX0902 (SOS1 inhibitor)	advanced solid tumors KRAS G12C mutant or harboring any mutations in MAPK pathway effectors
NCT06764771	I/Ib	BMS-986488 + adagrasib + cetuximab	Metastatic Colorectal Cancer Harboring KRAS G12C Mutations
NCT06026410	I	KO-2806 + adagrasib	advanced KRAS G12C mutant solid tumors
NCT04418661	I/II	Adagrasib (MRTX849) + Vociprotafib (SHP2 inhibitor)	advanced KRAS G12C mutant solid tumors
NCT05840510	I	Adagrasib (MRTX849) + nab-sirolimus	advanced KRAS G12C mutant solid tumors
NCT06130254	I	Adagrasib (MRTX849) + Olaparib	advanced KRAS G12C mutant solid tumors
NCT04330664	I/II	Adagrasib (MRTX849) + TNO155 (SHP2 inhibitor)	advanced KRAS G12C mutant solid tumors
NCT05722327	I	Adagrasib (MRTX849) + Cetuximab + Irinotecan	Metastatic Colorectal Cancer Harboring KRAS G12C Mutations
NCT05178888	I/Ib	Adagrasib (MRTX849) + palbociclib (CDK4/6 Inhibitor)	advanced KRAS G12C mutant solid tumors
NCT04793958	III	Adagrasib (MRTX849) + cetuximab vs chemotherapy (FOLFIRI or mFOLFOX6)	Metastatic Colorectal Cancer Harboring KRAS G12C Mutations
NCT04975256	I/Ib	Adagrasib (MRTX849) + BI 1701963 (SOS1 inhibitor)	advanced KRAS G12C mutant solid tumors
NCT05848843	I	Adagrasib (MRTX849) + Durvalumab (PD-L1)	Advanced Non-small Cell Lung Cancers and Gastrointestinal Cancers Harboring KRAS G12C Mutations
NCT04929223	I/Ib	Divarasib (GDC-6036) + Cetuximab ± FOLFOX or FOLFIRI (in KRAS G12C)	Metastatic Colorectal Cancer Harboring KRAS G12C Mutations
NCT05497336	I	Fulzerasib (IBI351) + Cetuximab	Metastatic Colorectal Cancer Harboring KRAS G12C Mutations
NCT06166836	Ib/II	Garsorasib (D-1553) + ifebemtinib (IN10018) (FAK inhibitor)	advanced KRAS G12C mutant solid tumors
NCT06435455	Ib/II	Garsorasib (D-1553) + GH21 (SHP2 inhibitor)	
NCT06997497	III	MK-1084 + Cetuximab + mFOLFOX6	Metastatic Colorectal Cancer Harboring KRAS G12C Mutations
NCT05853367	I/Ib	MK-1084 + MK-0472 (SHP2 inhibitor)	advanced solid tumors
NCT05462717	I	RMC-6291	advanced KRAS G12C mutant solid tumors
NCT06128551	Ib	RMC-6291 + RMC-6236 (pan-RAS inhibitor)	advanced KRAS G12C mutant solid tumors
NCT04699188	I/II	Opnurasib (JDQ443) ± TNO155 (SHP2 inhibitor) + tislelizumab	KRAS-G12C-mutant advanced solid cancers
NCT05358249	I/II	Opnurasib (JDQ443) + cetuximab	KRAS-G12C-mutant advanced solid cancers
NCT05288205	I/IIa	JAB-21822 (Glecirasib) + JAB-3312 (SHP2 inhibitor)	KRAS-G12C-mutant advanced solid cancers
NCT05485974	I	HBI-2438	KRAS-G12C-mutant advanced solid cancers
NCT05726864	I/II	ELI-002	KRAS/NRAS-mutated solid cancers

NCT04853017	I	ELI-002	KRAS/NRAS-mutated solid cancers
NCT04006301	I	JNJ-74699157	KRAS-G12C-mutant advanced solid cancers
NCT06117371	I/Ib	BEBT-607	KRAS-G12C-mutant advanced solid cancers
NCT06006793	I	SY-5933	KRAS-G12C-mutant advanced solid cancers
NCT05315180	I	BPI-421286	KRAS-G12C-mutant advanced solid cancers
NCT04973163	Ia/Ib	BI 1823911	KRAS-G12C-mutant advanced solid cancers
NCT05410145	I	D3S-001	KRAS-G12C-mutant advanced solid cancers
NCT05768321	I	GEC255	KRAS-G12C-mutant advanced solid cancers
NCT06244771	I/II	FMC-376	KRAS-G12C-mutant advanced solid cancers

FAK: focal adhesion kinase; SHP: Src homology region 2-containing protein tyrosine phosphatase 2; SOS1: Son of Sevenless homolog 1.

titumor activity. This approach has shown potential as a first-line treatment for NSCLC. CRC is predominantly microsatellite stable (MSS) and shows limited response to immunotherapy monotherapy; nevertheless, this strategy has been actively investigated owing to its capacity to modulate the TME. Regarding targeted combinations, SHP2 inhibitors (TNO155) administered with adagrasib suppress feedback reactivation of the RAS-MAPK pathway. Clinical data indicate an ORR of up to 58% with sustained responses in some patients, highlighting a role in maintaining immune memory. Proapoptotic approaches have also progressed. Sotorasib stabilizes the proapoptotic protein BIM, whereas co-administration with the BCL-XL degrader DT2216 disrupts the BCL-XL/BIM interaction, significantly enhancing apoptosis and antitumor efficacy in vivo [55]. Similarly, SOS1 inhibitors (BI-3406) combined with adagrasib significantly inhibited proliferation, promoted tumor regression, and downregulated downstream mediators, including DUSP6 and EGR1 [56]. Furthermore, agents with alternative mechanisms of action are currently under investigation. The PLK1 inhibitor onvansertib shows activity against multiple KRAS mutations (G12D and G12V) [57]. It achieved an ORR of 77% in KRAS-mutant mCRC when combined with chemotherapy and anti-angiogenic agents [58] through the inhibition of hypoxia pathways and synergy with angiogenesis blockade. These strategies are advancing to first-line clinical applications. **Table 4** shows the pivotal clinical studies on KRAS G12C inhibitor-based combinations in CRC.

Despite the improved ORR achieved with combining KRAS G12C inhibitors and EGFR antibodies in mCRC, critical evaluation of existing clinical data and research paradigms has revealed persistent limitations that hinder further therapeutic break-throughs. First, there is an efficacy Plateau and Insufficient Survival Benefit. The observed improvements in ORR and PFS with current combination therapies are largely measured against the historically low efficacy of prior standard treatments (regorafenib or trifluridine/tipiracil). Even the most effective combination regimens generally yield a median PFS of only 6-8 months, with mOS rarely exceeding 20 months [27]. These outcomes indicate that these strategies temporarily suppress, rather than eradicate, the disease as most patients eventually develop resistance. Moreover, the current clinical development paradigm focuses excessively on short-term end-points such as ORR and PFS, while strategies to overcome resistance and achieve meaningful OS extension remain inadequately defined. Second, Lack of Predictive Biomarkers and "One-Size-Fits-All" Patient Selection [59]. Currently, all patients with mCRC harboring KRAS G12C mutations are considered potential candidates for combination therapy. However, whole-exome sequencing has failed to identify molecular features beyond KRAS G12C that reliably predict treatment response. This raises the concern that all patients with this mutation will continue to be managed under a homogeneous treatment approach without distinguishing between potential long-term responders and those with intrinsic resistance.

To overcome these limitations, the following perspectives and directions that extend beyond the current therapeutic framework have been proposed. First, from Static Targeting to Dynamic Monitoring and Preemptive Intervention: A Closed-Loop Precision Medicine Framework. Future combination therapies should not be fixed regimens but dynamically adjustable strategies guided by real-time molecular monitoring. We propose implementing circulating tumor DNA sequencing at baseline [60], during

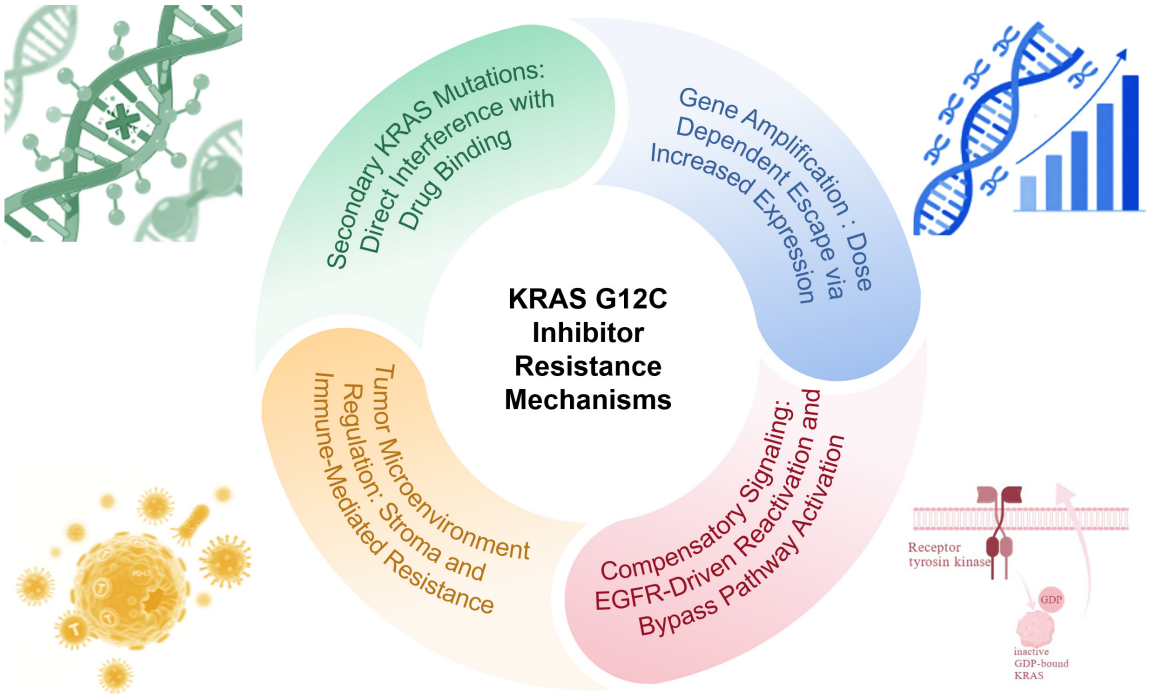

Figure 3. A variety of drug resistance mechanisms that may be produced by tumor cells after treatment with KRAS G12C inhibitors, including secondary KRAS mutations that directly hinder drug binding, EGFR feedback reactivation leading to upstream signal rebound, gene amplification-induced dependent pathway escape, compensatory activation of bypass pathways such as MAPK and PI3K, regulation of drug resistance by stromal cells in TME, and immune-mediated drug resistance pathways.

early treatment, and after radiologic progression to track fluctuations in KRAS G12C mutant allele frequency (MAF) as a predictor of response and to detect emerging resistance mechanisms (NRG1 fusions and MET amplifications). This approach may provide actionable insights into subsequent therapies. Second, moving beyond MAPK Pathway Inhibition: Novel Combinations Based on Synthetic Lethality and Metabolic Intervention. KRAS-mutant tumor cells show high levels of replication stress. Combining KRAS G12C inhibitors with agents targeting DNA damage repair pathways, including ATR, CHK1, or WEE1 inhibitors, may induce synthetic lethality, enabling selective tumor cell killing [61-63]. Furthermore, KRAS G12C mutations show a unique metabolic dependence. Co-targeting of glutamine metabolism, serine biosynthesis, or mitochondrial oxidative phosphorylation can disrupt the energy and biosynthetic supply to tumor cells, producing synergistic effects with direct KRAS inhibition. Given the profound effect of the gut microbiota on local immunity, future studies could explore combining KRAS-targeted therapy with specific probiotics or engineered microbial communities to remodel the tumor immune microenvironment and improve antitumor immunity.

Challenges

Anticancer drug resistance is a multifaceted process that involves multiple concurrent mechanisms. These include on-target secondary mutations (substitutions arising after KRAS G12C inhibition at G13, R68, or H95), gene copy-number gains (including KRAS G12C amplification and MET amplification), activation of bypass or compensatory signaling (including BRAF, NRAS, RET, or MAP2K1 [MEK1] mutations, and ALK, RET, BRAF, or FGFR3 fusions) [64], along with influences from the TME, epigenetic regulation, and intratumoral heterogeneity [65]. AI enabled integration of large-scale genomic, epigenomic, and clinical datasets is required to address these challenges to guide the rational development of combination strategies. Promising avenues include the co-administration of allosteric and orthosteric inhibitors as well as combinations of targeted and epigenetic therapies, ultimately advancing precision oncology [66]. **Figure 3** shows the prima-

ry resistance mechanisms against of KRAS G12C inhibitors.

Secondary KRAS mutations

This resistance mechanism arises from secondary point mutations in KRAS G12C that hinder the binding of the inhibitor to the target protein [67]. The clinical benefit of KRAS G12C inhibitors, such as sotorasib is frequently compromised by subclonal acquired mutations that serve as key drivers. In one clinical study, 63% (27/43) of patients receiving sotorasib developed resistance-associated mutations, including low-frequency variants of KRAS (G12V and G13D), NRAS, and BRAF [68]. Single-cell sequencing revealed that secondary RAS/BRAF mutations co-exist with the primary KRAS G12C allele within the same cell, thereby restoring ERK signaling and promoting bypass resistance. Notably, 87% of the resistant clones (124/142) were associated with specific KRAS substitutions, including Y96D, H95R, and R68S, which directly disrupted the binding pocket [38]. The Y96D mutation interferes with hydrogen bonding in inhibitors such as MRTX849 and induces high-level resistance to sotorasib and adagrasib (RI>100) [69]. Resistance can show inhibitor specificity: adagrasib interacts with H95 via hydrogen-bond and cation-π contacts, such that H95 mutations cause adagrasib resistance but preserve sotorasib sensitivity. Sotorasib primarily binds Y96 through π-π and hydrophobic interactions, and mutations such as Y96C or R68S drive cross-resistance to both agents [70]. Structural studies further showed that Y96D stabilizes the D96-R68 salt bridge, reducing the switch-II pocket (SII-P) volume by ~33% and disabling the binding of both inhibitors, whereas R68M selectively impairs sotorasib engagement. Comprehensive mutagenesis screening identified key resistance residues, including R68L/S and H95D/R, indicating that S17E enhances inhibitor sensitivity by suppressing the PI3K/AKT/mTOR pathway. However, this finding, derived from the NCI-H358 cell line, requires further validation across additional tumor types and new inhibitors such as JDQ443 [71]. To overcome resistance, strategies, including BI-3406 plus trametinib and the next-generation inhibitor RM-018, have shown promise for targeting Y96D and related resistance variants [72].

KRAS G12C gene amplification

In some patients, therapeutic intervention promotes KRAS gene amplification, resulting in elevated KRAS protein levels. While inhibitors can reduce part of the mutant KRAS fraction, the overall protein surplus is sufficient to maintain downstream signaling and drive drug resistance. This event has been reported in approximately 23.5% (4/17) of resistant cases [70]. Notably, this resistant phenotype shows dynamic evolution; under treatment pressure, clones carrying amplification are selectively enriched, whereas these clones may regress upon drug discontinuation, owing to oncogene induced senescence. A study published in Cancer Discovery in 2022 further showed that KRAS G12C - amplified resistant cells enter senescence once therapy is withdrawn; at this stage, re-challenge fails to restore efficacy because the cells establish alternative survival programs through mTOR pathway upregulation [73]. These observations underscore the adaptive plasticity of resistance and provide key insights for the design of durable therapeutic strategies.

Bypass signaling activation

The aberrant stimulation of downstream KRAS effectors or parallel pathways can bypass KRAS G12C inhibition and sustain tumor progression. KRAS G12C CRC models display higher basal RTK activity and remain highly responsive to growth factors compared with NSCLC cell lines. In CRC, treatment with KRAS G12C inhibitors triggers a more pronounced rebound in phospho-ERK than in NSCLC, largely due to enhanced RTK input; among these, EGFR signaling has emerged as a predominant driver of resistance [74]. Through ligand independent dimerization, EGFR persistently activates signaling and shifts wild type RAS isoforms, notably NRAS and HRAS, to a GTP bound active state, thus providing an alternative oncogenic source [50]. Additional bypass alterations include BRAF V600E, activating MAP2K1 (MEK1) mutations, and oncogenic fusions involving BRAF, RAF1, RET, or ALK, which directly stimulate the MAPK effectors downstream of KRAS. For instance, an AGK-BRAF fusion detected in a resistant patient was shown to constitutively activate MEK-ERK signaling [70]. Moreover, PI3K/AKT reactivation enhances resistance,

and PTEN loss activation of PIK3CA mutations enables KRAS independent survival [75]. Given this compensatory adaptation, the combination of KRAS G12C inhibitors with a PI3K or AKT blockade is a rational strategy for attenuating the development of development.

Impact of the TME

The anatomical context of CRC leads to a distinct TME. Gut microbiota, stromal elements, and local immune landscape form a dynamic ecosystem that affect therapeutic outcomes. Cancer-associated fibroblasts release growth factors such as EGF and HGF, which activate RTKs on tumor cells, thereby driving bypass signaling that engages the RAS-MAPK pathway and diminishes the effect of KRAS G12C inhibition. KRAS G12C-mutant CRC frequently displays an immunologically "cold" phenotype with limited T-cell infiltration [76]. This immunosuppressive microenvironment attenuates the therapeutic responses and facilitates the selection of resistant clones.

Future research prospects

Advanced development of novel targeted agents and optimization of combination strategies

Current KRAS G12C inhibitors, including sotorasib and adagrasib, exert their anti-tumor effects by covalently binding to the mutant cysteine residue and trapping KRAS in its inactive GDP-bound state within the switch-II pocket [77]. Future drug development should focus on two key strategies: first, creating allosteric inhibitors capable of directly targeting the active GTP-bound conformation to achieve more profound pathway suppression [78], and second, the design of agents targeting other prevalent KRAS mutations [79], including G12D. In the realm of combination therapies, research is moving beyond the established "KRAS G12Ci + anti-EGFR" paradigm, which showed an 80% ORR in the first-line KROCUS study. Investigations are now exploring vertical inhibition strategies, combining KRAS G12C inhibitors with upstream nodal inhibitors (SHP2 and SOS1) or downstream effector inhibitors (MEK and ERK), with preclinical models confirming that SHP2 inhibition effectively blocks upstream RAS signaling [80]. Furthermore, applying Proteolysis-Targeting Chimeras to develop KRAS G12C degraders provides a novel pathway to overcome resistance mediated by mutant protein accumulation or conformational changes aimed at directly eliminating oncogenic drivers through the ubiquitin-proteasome system.

Building the framework for precision medicine and biomarker identification

KRAS G12C-mutant colorectal carcinoma shows significant intertumoral and intratumoral heterogeneity, presenting a significant obstacle to precision therapy [81]. Future research should integrate genomic, transcriptomic, and proteomic data to systematically decipher the molecular basis of this heterogeneity and identify predictive biomarkers. A critical focus is to elucidate the collective impact of key comutations and establish transcriptional subtypes on therapeutic response and resistance emergence [77]. Prospectively incorporating dynamic circulating tumor DNA monitoring into all clinical trial designs is essential, as this technology has proven sensitive for predicting efficacy, enabling early detection of resistant clones, and facilitating real-time guidance of treatment [82]. Ultimately, high-throughput functional drug screening platforms using patient-derived organoids and xenografts will provide the most robust preclinical evidence for crafting individualized, "one-to-one" precision combination regimens [83].

Overcoming adaptive resistance and targeting the TME

Conquering adaptive resistance to targeted therapy requires a comprehensive unveiling of the underlying complex networks, NRF2 [84-86]. Beyond EGFR feedback reactivation, future studies should use multiomics and spatial transcriptomics to systematically map the "multifaceted escape network", including RTK bypass activation, secondary KRAS mutations, epigenetic remodeling, and EMT. Combining therapies with epigenetic modulators is a viable strategy for targeting this network [87]. For instance, preclinical models indicate that resistant cell lines retain sensitivity to epigenetic drugs, supporting the potential to reverse tumor cell phenotypic plasticity and stemlike properties to overcome resistance. Conversely, the interplay between targeted therapy and the tumor immune microenvironment is essential.

Research shows that oncogenic signaling pathways can shape an immunologically "cold" microenvironment [88], while targeted agents may increase this landscape. This insight has motivated the exploration of synergies between KRAS G12C inhibitors [89] and ICIs [90] or novel immunomodulatory agents, aiming to convert the immunosuppressive milieu into an immune-supportive one and ultimately improve the typically poor response of patients with G12C-mutant CRC to immunotherapy.

Conclusion

Recently, targeted therapies against KRAS G12C-mutant CRC have achieved meaningful breakthroughs. Covalent small molecule inhibitors, typified by sotorasib and adagrasib, together with combinations involving EGFR monoclonal antibodies (cetuximab and panitumumab), have significantly improved the ORR by 46-62.5%, providing therapeutic options for patients previously lacking effective treatments [91]. Nevertheless, primary and acquired resistance remain major obstacles, mediated by diverse and often overlapping mechanisms, including secondary KRAS mutations (Y96D and H95R), bypass activation (EGFR feedback and RTK/MAPK reactivation), and remodeling of the TME. Looking forward, three priorities have emerged. First, we developed next generation inhibitors, including the pan-RAS (ON) inhibitor RMC-6236, which targets active KRAS; allosteric pocket degraders designed to circumvent resistance; and brain-penetrant agents to address CNS metastases. Second, the systematic dissection of resistance biology, specifically in individuals with unexplained resistance, is paired with dynamic monitoring and predictive modeling technologies [92]. Third, the rational design of combinatorial regimens, including intensified EGFR blockade and synergistic partners, including ICIs or SHP2/MEK inhibitors, integrated within precision-oncology frameworks guided by ctDNA dynamics, clonal evolution, and multiomics biomarkers (KRAS allele fraction and immune contexture). Multifaceted innovations across these directions are anticipated to provide a foundation for long-trem survival benefits in patients with KRAS G12C-mutant CRC.

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Disclosure of conflict of interest

None.

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