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REVIEW ARTICLE

Molecular landscape of KRAS G12C inhibitor resistance and rational combination strategies in cancer therapy

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Abstract

Background: Oncogenic alterations in *KRAS* are among the most frequent driver mutations in human cancers, particularly lung, colorectal, and pancreatic cancers. Mutant KRAS was historically considered an "undruggable" target because of its high affinity for guanosine triphosphate and guanosine diphosphate (GDP) and the absence of readily druggable binding pockets. However, the "undruggable" paradigm shifted following the discovery of mutation-selective covalent inhibitors that target the KRAS G12C mutant. These inhibitors selectively target the inactive GDP-bound form of KRAS G12C through covalent binding to the mutant cysteine residue at codon 12. Despite their clinical activity, intrinsic and acquired resistance limit the efficacy and durability of KRAS G12C inhibitors. Resistance mechanisms include secondary *KRAS* mutations, activation of bypass signaling pathways, reactivation of MAPK/PI3K signaling, feedback pathway activation, epithelial–mesenchymal transition, metabolic reprogramming, and tumor-microenvironment protection. Aim: This review provides a thorough investigation into the molecular mechanisms of resistance to KRAS G12C inhibitors through an examination of recent clinical and preclinical evidence. This review also discusses emerging therapeutic approaches, including next-generation KRAS inhibitors, rational combination strategies, and interventions targeting adaptive signaling. Conclusion: Understanding the evolutionary mechanisms by which *KRAS*-mutant cancers evade targeted therapies is important for developing durable treatment strategies. Relevance for patients: Advances in molecular diagnostics and KRAS-targeted therapies may improve patient selection and outcomes with personalized treatments.

Keywords: KRAS G12C; Resistance mechanisms; Covalent inhibitors; Targeted therapy; Combination therapy

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1. Introduction

The transformation of a proto-oncogene into an oncogene generally results in overexpression of the gene product or enhanced functional activity of the encoded protein, leading to dysregulation of signaling pathways involved in cell cycle progression and apoptosis.[1] Neoplasms arise due to acquired genetic and epigenetic alterations affecting proto-oncogenes,[2] tumor suppressor genes,[3] and DNA repair genes,[4] leading to disruption of normal cellular regulatory mechanisms. These changes may occur

through gene mutations, modifications in gene expression regulators, inactivation of tumor suppressor genes, protein alterations, and epigenetic modifications, all of which contribute to uncontrolled cell proliferation and tumor progression.[5]

Among the most important oncogenic signaling proteins are members of the RAS family. RAS proteins are composed of a conserved globular G-domain (amino acids 1–166) and a C-terminal hypervariable region of approximately 22–23 amino acids, which plays an important role in membrane localization and proper cellular function. RAS proteins are involved in multiple physiological signal transduction pathways regulating essential cellular processes such as cell growth, proliferation, differentiation, and survival. Functionally, RAS acts as a small GTPase enzyme that operates as a molecular switch by cycling between an inactive guanosine diphosphate (GDP)-bound state and an active guanosine triphosphate (GTP)-bound state. This conversion is regulated by guanine nucleotide exchange factors (GEFs), which promote the exchange of GDP for GTP, thereby activating downstream signaling pathways that control various cellular responses.[6]

The RAS family comprises three major members: Harvey-RAS (HRAS), neuroblastoma-RAS (NRAS), and Kirsten-RAS (KRAS), with KRAS expressed as two major splice isoforms, KRAS4A and KRAS4B. KRAS is a 188-amino-acid protein with a molecular weight of approximately 23.2 kDa and functions as an important regulator of intracellular signaling pathways.[7,8] GTP binding induces conformational changes primarily in two regions of KRAS, comprising amino acid residues 30–38 and 59–67, forming an effector loop responsible for interaction with downstream effector proteins. Structurally, RAS proteins contain a highly conserved G-domain (residues 1–166) with about 90% sequence homology among RAS isoforms, consisting of an effector lobe (residues 1–86) and an allosteric lobe (residues 87–166). The G-domain is composed of six β-strands surrounded by five α-helices, forming the structural framework required for its regulatory function.[9]

Among the RAS family members, *KRAS* is one of the most frequently mutated genes in human cancers, particularly in non-small cell lung cancer (NSCLC), colorectal cancer, and pancreatic ductal adenocarcinoma (PDAC). Despite its strong association with tumor initiation, progression, and metastasis, KRAS has remained a challenging therapeutic target for more than three decades and was historically considered an "undruggable" protein due to several limitations. One of the major obstacles in targeting KRAS is the absence of well-defined deep hydrophobic binding pockets on its surface, which are typically required for effective binding of small-molecule inhibitors.[10] Furthermore, KRAS binds its endogenous ligands, GTP and GDP, with extremely high affinity in the picomolar range, and the high intracellular concentration of GTP makes competitive inhibition particularly difficult using traditional drug design approaches. KRAS functions as a molecular switch cycling between an active GTP-bound state and an inactive GDP-bound state, thereby regulating multiple downstream signaling pathways including rapidly accelerated fibrosarcoma (RAF)–mitogen-activated protein kinase kinase (MEK)–extracellular signal-regulated kinase (ERK) and phosphatidylinositol 3-kinase (PI3K)–protein kinase B (AKT) pathways.[11] Structural flexibility within critical regions such as switch I and switch II further complicates inhibitor development, as conformational changes alter the accessibility of potential binding sites. Earlier therapeutic strategies, including inhibition of post-translational modifications such as farnesylation with farnesyltransferase inhibitors, demonstrated limited clinical efficacy due to compensatory signaling pathways, feedback activation, and lack of sustained efficacy. A significant breakthrough in KRAS drug discovery emerged with the identification of the KRAS G12C mutation, characterized by substitution of glycine with cysteine at codon 12. Advances in structure-based drug design and fragment screening enabled the discovery of a previously hidden allosteric binding region known as the switch-II pocket, located adjacent to the mutant cysteine residue and accessible in the inactive GDP-bound conformation of KRAS G12C.[12] This structural insight facilitated the development of mutation-specific covalent inhibitors capable of selectively binding to the cysteine residue and irreversibly locking KRAS in its inactive state, thereby preventing activation of downstream oncogenic signaling pathways. The development and regulatory approval of KRAS G12C inhibitors, including the first-in-class agent sotorasib (AMG 510) and the subsequently approved adagrasib (MRTX849), represented a major milestone in precision oncology, transforming KRAS from a historically undruggable target into a clinically actionable therapeutic target.[13] These inhibitors demonstrated promising clinical efficacy in patients with *KRAS* G12C-mutant cancers, particularly NSCLC. Figure 1 traces the evolving landscape of KRAS inhibitor development, marking pivotal breakthroughs from early challenges to targeted therapeutic success. Current data show that resistance does not arise through a single mechanism but instead reflects interactions among secondary mutations in the *KRAS* gene, activation of bypass signaling, feedback reactivation of mitogen-activated protein kinase (MAPK) and PI3K signaling, phenotypic plasticity, metabolic adaptation, and tumor microenvironment (TME) adaptation

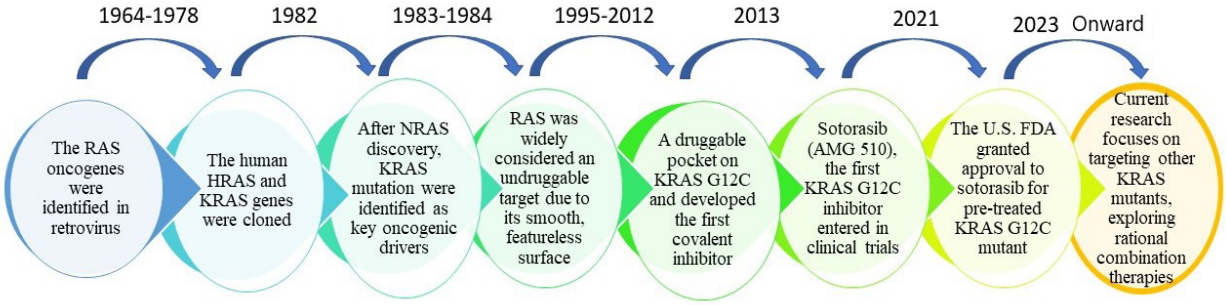


Figure 1. Timeline of KRAS inhibitors
Abbreviations: U.S. FDA: United States Food and Drug Administration; HRAS: HRAS proto-oncogene, GTPase; KRAS: KRAS proto-oncogene, GTPase; NRAS: NRAS proto-oncogene, GTPase; RAS: Rat sarcoma.

mechanisms. Importantly, the strength of evidence varies substantially across proposed resistance mechanisms, ranging from preclinical observations to mechanisms supported by clinical samples, making it important to distinguish clinically established resistance mechanisms from emerging hypotheses. Additionally, the awareness of heterogeneity of tumors and adaptation through evolution implies that monotherapy targeting KRAS would be ineffective. As a result, future treatment approaches should focus on combination therapy guided by mechanisms, biomarker-based patient selection, molecular monitoring with liquid biopsy, and generation of new-generation KRAS inhibitors that can bypass multiple mechanisms of resistance. This review focuses on a critical evaluation of the existing literature on resistance to KRAS G12C inhibitors, integration of information from preclinical and clinical research, identification of open issues, and consideration of potential treatment strategies.

2. Structural and functional biology of KRAS G12C mutation

2.1. Structure of KRAS protein

As shown in Figure 2, RAS proteins typically cycle between GTP-bound and GDP-bound states, with the GTP-bound state representing the "on" state and the GDP-bound state representing the "off" state. RAS proteins in the GTP-bound "on" state undergo marked structural changes in two regions called switch I and switch II, which then coalesce to form an interaction surface. These conformational changes create an interaction surface for downstream effectors, including RAF kinases and PI3K.[14] RAS binds GDP and GTP with very high affinity, with dissociation constants in the picomolar range. Consequently, cellular RAS is essentially always nucleotide-bound. Moreover, the RAS proteins have low dissociation rates for GDP and low intrinsic enzymatic GTPase activity. Conversion of GDP-bound RAS to the active GTP-bound state therefore requires GEF-mediated nucleotide exchange, whereas conversion back to the GDP-bound inactive form requires GTPase-activating proteins (GAPs), which stimulate the intrinsic hydrolytic activity of the RAS proteins.[15] The fact that RAS and other GTPases depend on GEFs and GAPs for switching them on and off allows both of these processes to be tightly controlled and to be rapidly responsive to diverse signals. By contrast, mutant forms of RAS that are constitutively active generally function by preventing GTP hydrolysis, thereby generating active GTP-bound RAS (RAS-GTP) molecules that cannot be turned off. Sustained RAS signaling can have severe consequences for the cell, including dysregulated proliferation and malignant transformation. The picomolar affinity of RAS for GTP, the high GTP levels in cells (>500 μM), and the inability of oncogenic RAS to hydrolyze GTP create significant challenges for traditional drug discovery approaches.[16,17]

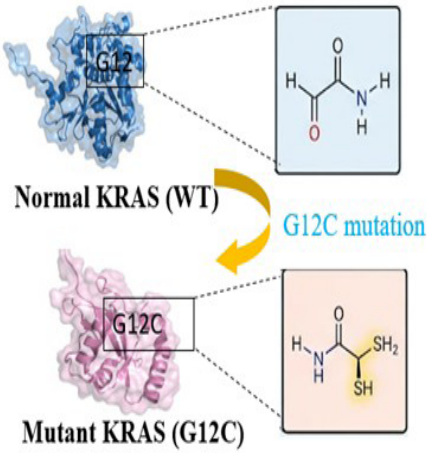


Figure 2. Structural organization of KRAS protein and oncogenic mutation sites
Abbreviations: KRAS: Kirsten; WT: Wild type.

2.2. Molecular basis of G12C mutation

The KRAS G12C mutation is characterized by a missense substitution of glycine with cysteine at codon 12 within the phosphate-binding loop (P-loop) of the KRAS GTPase domain. This substitution introduces a nucleophilic thiol (–SH) group, inducing local conformational perturbations that impair the intrinsic GTP hydrolysis activity and diminish the catalytic efficiency of KRAS.[18] Furthermore, the mutation disrupts the interaction with GAPs, thereby reducing GAP-mediated acceleration of GTP hydrolysis and favoring retention of the active GTP-bound state. As a consequence, KRAS G12C exhibits prolonged occupancy of the active GTP-bound state, resulting in persistent activation of downstream signaling cascades, primarily the RAF/MEK/ERK (MAPK) and PI3K/AKT/mechanistic target of rapamycin (mTOR) pathways.[19] Persistent signaling through these pathways promotes aberrant cellular proliferation, enhanced survival, metabolic reprogramming, and resistance to apoptosis, collectively contributing to oncogenic transformation and tumor progression. Importantly, the presence of a reactive cysteine residue at position 12 generates a structurally accessible and chemically tractable binding site proximal to the switch-II pocket. This unique feature enables selective covalent targeting by small-molecule inhibitors that irreversibly bind to the mutant cysteine via electrophilic warheads, thereby stabilizing the inactive GDP-bound conformation of KRAS and suppressing downstream oncogenic signaling.[20] Consequently, KRAS G12C represents a highly druggable oncogenic driver and a critical target in precision oncology. Table 1 and Figure 3 collectively highlight the key factors influencing RAS-driven tumor development and the molecular impact of the KRAS G12C mutation, emphasizing its role in aberrant signaling pathways and illustrating the mechanism of action of targeted inhibitors that selectively suppress oncogenic activity.

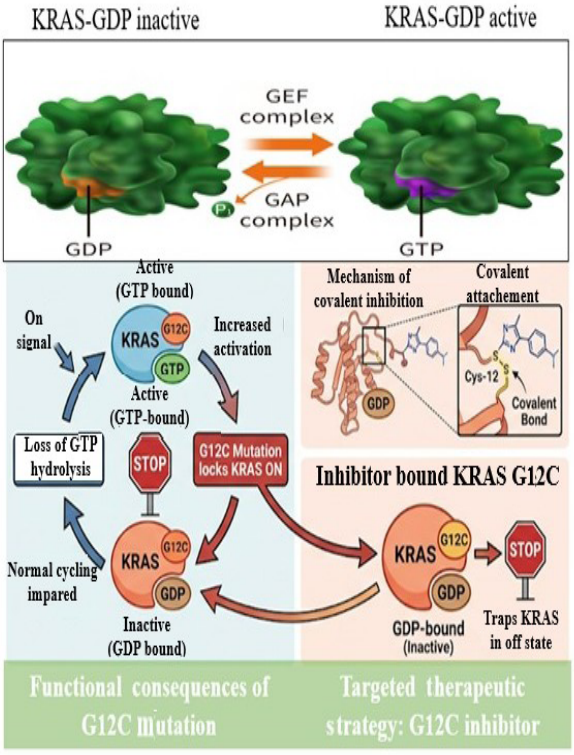


Figure 3. Molecular consequences of the KRAS G12C mutation and the mechanism of KRAS G12C inhibitor action
Abbreviations: Cys: Cysteine; GAP: GTPase-activating protein; GDP: Guanosine diphosphate; GEF: Guanine nucleotide exchange factor; GTP: Guanosine triphosphate; KRAS: Kirsten-RAS; Pi: Inorganic phosphate.

Table 1. Factors influencing KRAS-driven tumor development

Factor	Description	Effect on tumorigenesis
KRAS protein level & GTP-bound proportion	Active KRAS (30%–90%) varies with mutation type, isoform, and tissue; excessive signaling may induce senescence or cell death	Determines strength of oncogenic signaling and therapy response[21]
Stability of GTP-bound state	Stability or fast cycling of GTP-bound RAS influences signaling duration	Stable activation increases oncogenic potential[21]
Isoform-specific signaling	KRAS, HRAS, NRAS differ in intracellular localization and downstream effector interactions (e.g., BRAF, CRAF)	Produces selective pathway activation and tumor variability[22]
Tissue and cell type context	Genetic and proteomic environment influences Ras interaction with cellular drivers	Creates tissue-specific susceptibility to RAS-driven tumors[22]
Biological outcome	Combined Ras signaling regulates proliferation, differentiation, and apoptosis	Controls tumor initiation and progression[22]

Abbreviations: BRAF: B-Raf proto-oncogene, serine/threonine kinase; CRAF: RAF1 proto-oncogene, serine/threonine kinase; GTP: Guanosine triphosphate; HRAS: Harvey-RAS; KRAS: Kirsten-RAS; NRAS: Neuroblastoma-RAS.

3. Mechanism of action of KRAS G12C inhibitors

3.1. Covalent targeting strategy

3.1.1. Stabilization of inactive GDP-bound conformation

KRAS G12C retains the ability to undergo nucleotide cycling in cancer cells, dynamically interconverting between the active GTP-bound and inactive GDP-bound states.[23] Secondary mutations that markedly impair intrinsic GTP hydrolysis, such as A59G or Q61L, significantly increase basal KRAS G12C activation and reduce responsiveness to KRAS G12C inhibitors.[24] Experimental studies using quantitative mass spectrometry and highly potent inhibitors indicate that preserved intrinsic GTPase activity is essential for effective inhibition by inactive state-selective compounds. Binding of KRAS G12C inhibitors to the mutant cysteine residue restricts nucleotide exchange, thereby preventing reactivation of KRAS G12C and stabilizing the protein in its inactive GDP-bound conformation.[25] Evidence suggests that inhibitor-bound KRAS G12C is unable to undergo nucleotide exchange mediated by son of sevenless homolog 1 (SOS1) or chelating agents, indicating that these inhibitors primarily interfere with nucleotide exchange rather than directly altering nucleotide binding affinity.[26] Furthermore, mutations that enhance nucleotide exchange kinetics diminish inhibitor efficacy, whereas suppression of SOS1 activity enhances KRAS G12C inhibition. Although KRAS G12C demonstrates relatively higher intrinsic GTP hydrolysis compared with other oncogenic KRAS variants, it remains uncertain whether this intrinsic hydrolytic activity alone is sufficient to support efficient drug trapping under physiological cellular conditions.[27]

3.1.2. Binding to switch-II pocket

A series of KRAS small-molecule inhibitors were compared for their binding affinity against a panel of *KRAS* mutant alleles.[28] These inhibitors either covalently target the G12C mutant or reversibly target other mutants by binding in a transient pocket known as the switch-II pocket. Covalent inhibitors bound KRAS-GDP with KD values ranging from 10−9 to 10−3 M, whereas reversible inhibitors bound in the low nM range.[29] A loss of affinity was observed for KRAS–GppNHp, due in part to rearrangements in switch II, where the hydrogen bond between G60 and the γ-phosphate needs to break to form the switch-II pocket. Interestingly, these inhibitors had reduced affinity for KRAS Q61R–GppNHp, but not for wild-type KRAS or other KRAS mutants. A reported crystal structure of KRAS Q61R–GppNHp showed that access to the switch-II pocket was restricted due to R61 forming an additional hydrogen bond with the backbone carbonyl of T35 in switch I.[30] The restricted access to the switch-II pocket caused a decrease in the association rate of inhibitor binding and resulted in a loss of affinity. These findings across KRAS mutants provide valuable insights into the conformational adaptability of the switch-II pocket and may prove useful in developing the next generation of allele-specific and pan-KRAS small-molecule inhibitors.[31]

3.1.3. Electrophilic warheads targeting cysteine thiol groups

Fragment-sized molecules incorporating a common structural scaffold but functionalized with diverse electrophilic warheads play a crucial role in covalent drug discovery, enabling both initial covalent fragment screening and subsequent optimization of reversible lead compounds into targeted covalent inhibitors.[32] Covalent inhibition strategies rely on selective interaction between electrophilic warheads and nucleophilic amino acid residues present at functionally important sites of proteins. Although amino acids such as serine, lysine, tyrosine, and threonine can serve as nucleophilic targets in certain United States Food and Drug Administration (FDA)-approved covalent drugs, cysteine remains the most widely exploited residue due to the strong nucleophilicity of its thiol group, favorable reactivity under physiological conditions, and its frequent localization within catalytic or allosteric pockets of disease-relevant proteins. Additionally, cysteine residues often exhibit lower abundance across the proteome, allowing improved selectivity and reduced off-target toxicity. Various electrophilic warheads, including acrylamides, chloroacetamides, vinyl sulfonamides, cyanoacrylamides, boronic acids, epoxides, and sulfonyl fluorides, have been developed to modulate reactivity, selectivity, and pharmacokinetic properties of covalent inhibitors.[33] Advances in covalent ligand discovery have been facilitated by fragment-based approaches, where small electrophile-containing fragments are screened to identify reactive hotspots within protein binding pockets. Ligand-based chemoproteomic strategies have enabled systematic mapping of cysteine reactivity and accessibility by screening a chemically diverse library of covalent probes with varied intrinsic electrophilicity.[34] This approach incorporated structurally diverse cysteine-reactive fragments derived from previously reported covalent inhibitors, allowing identification of optimal warhead reactivity profiles while minimizing nonspecific protein modification. Such strategies have significantly accelerated the rational design of targeted covalent inhibitors, particularly for challenging drug targets such as KRAS G12C, kinases, and proteases, by balancing reactivity with selectivity to achieve improved therapeutic efficacy and safety profiles.

4. Molecular mechanisms of resistance to KRAS G12C inhibitors

Resistance to KRAS G12C inhibitors is a dynamic and multifactorial process driven by overlapping genetic, adaptive, and microenvironmental mechanisms. A primary challenge arises from on-target secondary mutations within *KRAS* (e.g., G13, R68, H95, and Y96 substitutions), which alter the switch-II pocket and impair inhibitor binding, often in an inhibitor-specific manner, thereby reducing the clinical durability of agents such as sotorasib and adagrasib. In parallel, gene amplification events, including amplification of *KRAS* (e.g., the G12C allele) or *MET*, increase oncogenic protein abundance, allowing sustained downstream signaling despite partial target inhibition and reflecting strong evolutionary selection under therapeutic pressure.[35] Resistance is further reinforced through activation of bypass signaling pathways, where alterations in *BRAF*, *NRAS*, *MAP2K1*, and receptor tyrosine kinases (RTKs), along with oncogenic fusions involving *ALK*, *RET*, or *FGFR3*, restore MAPK and PI3K/AKT signaling independently of KRAS. Additionally, TME factors, including cancer-associated fibroblast (CAF)-derived growth factors, immune suppression, and microbiome interactions, create a permissive niche for resistant clones, particularly in colorectal cancer, which often exhibits an immunologically "cold" phenotype.[36]

4.1. Primary (intrinsic) resistance mechanisms

Intrinsic resistance to KRAS-targeted therapies may arise from reduced cellular dependence on KRAS-mediated signaling, which contributes to heterogeneous therapeutic responses observed in preclinical models and patients. RAS proteins regulate multiple downstream signaling cascades, primarily the MAPK/ERK and PI3K/AKT/mTORC1 pathways; however, activation of the PI3K pathway is not exclusively dependent on RAS and can occur through alternative upstream mechanisms.[37] Experimental studies have demonstrated that *KRAS*-mutant lung cancer and PDAC cell lines exhibit variable reliance on RAS signaling for survival and proliferation. Notably, even after complete pharmacological inhibition of KRAS, a subset of *KRAS*-mutant PDAC cells remains viable, with many of these cells maintaining PI3K-dependent survival signaling and exhibiting sensitivity to MAPK-pathway inhibition.[38] Additionally, compensatory mechanisms such as amplification of *YAP1* or activation of the Yes-associated protein 1 (YAP1) transcriptional coactivator have been identified as alternative pathways that enable cancer cells to bypass KRAS inhibition. YAP1 is also a major downstream effector of the Hippo pathway, which regulates cell proliferation, apoptosis, tissue homeostasis, organ size, and stem cell maintenance.[39]

4.2. Resistance induced following inhibition of mutant KRAS

Acquired resistance to KRAS-targeted therapies occurs through three major mechanisms: (i) secondary mutations in the target protein, (ii) activation of alternative signaling pathways, and (iii) phenotypic or cellular reprogramming. The first mechanism is primarily genetic, whereas the latter two may involve both genetic and nongenetic processes.[40] Tumor cells can also develop adaptive resistance, an intermediate state between intrinsic and acquired resistance, which involves rewiring of signaling, transcriptomic, epigenetic, metabolic, and protein localization networks, often influenced by the TME. Although KRAS G12C inhibitors have shown promising results in clinical trials, sustained responses remain challenging because of both tumor-cell-intrinsic and TME-mediated resistance mechanisms. The TME includes CAFs, immune cells, endothelial cells, extracellular matrix (ECM), cytokines, and growth factors that interact with tumor cells to sustain pro-survival signaling during KRAS inhibition.[41] In KRAS G12C-mutant tumors, CAFs may contribute to resistance by secreting hepatocyte growth factor (HGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), interleukin-6, C-X-C motif chemokine ligand 12 (CXCL12), and neuregulins. The efficacy of KRAS G12C inhibitors is therefore influenced substantially by the TME. Tumors with an inflamed immune microenvironment and abundant $CD8^+$ T-cell infiltration may exhibit better responses, whereas fibrosis, hypoxia, and immune exclusion can promote therapeutic resistance.[42] In addition, subpopulations of drug-tolerant persister cells can survive treatment and serve as a reservoir from which stably resistant populations may subsequently emerge.

(a) Metabolic reprogramming

KRAS inhibition alters metabolic pathways, including branched-chain amino acid metabolism, glycolysis, gluconeogenesis, and the tricarboxylic acid cycle, and can shift surviving cells toward greater reliance on oxidative phosphorylation. ZBTB11, a transcriptional regulator of mitochondrial genes, has been identified as a potential target to overcome KRAS inhibitor-induced metabolic adaptation.[43]

(b) Protein localization and signaling rewiring

KRAS inhibition induces relocalization of E-cadherin and Scribble, a polarity protein, from the membrane to the cytosol, downregulating Hippo signaling and activating YAP/transcriptional coactivator with PDZ-binding motif (TAZ)-mediated transcription.[44] YAP activation upregulates MRAS, which forms a ternary complex with SHOC2 and protein phosphatase 1 (PP1), leading to dephosphorylation of RAF1 proto-oncogene,

serine/threonine kinase (CRAF) S259 and reactivation of MAPK signaling. Inhibitors targeting RTKs, SOS1, or Src homology 2 domain-containing protein tyrosine phosphatase 2 (SHP2) reduce MRAS activity and can suppress this feedback loop. Combining KRAS inhibitors with TEA domain transcription factor inhibitors or targeting the MRAS/SHOC2 axis offers potential strategies to overcome adaptive resistance.[45]

(c) Genetic mechanisms of resistance to KRAS inhibitors

Genetic resistance can arise when tumor evolution restores oncogenic signaling despite effective inhibition of the original KRAS G12C proteins. Resistance to inhibition of KRAS is achieved through mutations in the target protein, such as mutations in the switch-II pocket or mutations that affect the binding of the G12C inhibitor to the protein. Off-target resistance involves activation of other signaling pathways through the mutation or amplification of other genes such as *NRAS*, *HRAS*, *BRAF*, *MAP2K1* (MEK1), *PIK3CA*, and *AKT1*.[46]

4.2.1. Secondary KRAS mutations

Secondary mutations in *KRAS* G12C are among the most prevalent examples of on-target resistance to KRAS G12C inhibitors. Cis mutations arise on the same *KRAS* allele as G12C. These secondary mutations (for example, R68S, H95D/Q/R, Y96C/D, Q99L, or V8L) lead to direct changes in the pocket where the inhibitor binds or influence the conformational dynamics of KRAS, resulting in reduced binding of the covalent inhibitors and maintenance of oncogenic signaling. In cis resistance mutants, G12C and the secondary mutation occur on the same allele, producing a double-mutant KRAS protein with reduced inhibitor sensitivity. Therefore, cis mutations are drug-resistant mutations, and pan-KRAS inhibitors, KRAS degraders, and downstream pathway inhibitors may be necessary.[47] On the other hand, trans mutations may arise on the wild-type *KRAS* allele or in a distinct subclone of the tumor. In this case, mutations lead to the formation of another constitutively active mutant form of the KRAS protein (such as G12D, G12V, G13D, Q61H, or A146T) that is insensitive to G12C-specific drugs. While inactivating mutations do not affect drug interaction, the trans mutations lead to the re-establishment of the signaling pathway by forming another group of active KRAS mutants, which can stimulate cell proliferation even in the case of complete blocking of the initial G12C allele.[48] Patients with acquired resistance often harbor additional *KRAS* mutations, either in trans on a separate allele or in cis on the G12C allele. Cis mutations can result in a mutational switch, replacing G12C with an alternative *KRAS* mutation, while trans mutations coexist with G12C. Frequently, these occur in the switch-II pocket, which is critical for inhibitor binding. Experimental studies introducing double-mutant *KRAS* alleles (G12C plus switch-II mutations) revealed that R68S, H95D, H95Q, and Y96C mutations confer resistance to adagrasib, with R68S and Y96C also reducing sotorasib sensitivity.[49] Some H95 variants remain sensitive to sotorasib, highlighting the residue-specific effect on switch-II pocket binding. Alterations such as Y96C increase hydrophilicity of the pocket, weakening drug-target interactions. While mutations in the drug-binding pocket often cause high-level resistance, activating mutations at codons 12, 13, 59, 61, 117, and 146 increase the proportion of GTP-bound KRAS, which is not targeted by GDP-specific inhibitors.[50] Drugs capable of binding both GDP- and GTP-bound KRAS may overcome this resistance. Novel tri-complex inhibitors such as RMC-6291 interact with KRAS residues in both switch I (E31, D33, E37) and switch II (Y64).[51] Mutations at these sites disrupt tri-complex formation, emphasizing their role in drug efficacy and potential treatment strategy considerations.

4.2.2. Alterations in upstream and downstream signaling

Resistance can also arise through mutations or amplifications outside *KRAS*, which activate bypass signaling pathways. Clinical analyses of resistant tumors have identified alterations in *NRAS*, *BRAF*, *EGFR*, *FGFR2*, *NF1*, *MAP2*, and gene fusions such as *CCDC6::RET*, *EML4::ALK*, *AGAP3::RAF1*, *AGK::BRAF*, and *TACC3::FGFR3*, as well as amplifications of *MET*, *KRAS*, *FGFR2*, and *MYC*.[52] CRISPR-based functional screens further highlighted the contribution of upstream regulators such as SHP2 and SHOC2, and downstream effectors including aurora kinase A (AURKA) and cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B), in mediating resistance to KRAS inhibitors such as adagrasib and MRTX1133.[53] SHP2 (PTPN11) functions downstream of activated RTKs such as epidermal growth factor receptor (EGFR) and MET proto-oncogene, receptor tyrosine kinase (MET) to promote RAS-GTP loading and reactivation of MAPK/ERK signaling during KRAS inhibition. Likewise, SHOC2, a scaffold protein that makes up the MRAS–SHOC2–PP1 complex, acts by dephosphorylating the inhibitory RAF residues and causing dimerization of RAF.[54] The AURKA pathway is predominantly responsible for the acquisition of resistance through maintaining mitotic functions, suppressing apoptosis, promoting chromosomal instability, and facilitating persister-cell survival in response to sustained inhibition of KRAS signaling via MYC- and FOXM1-dependent mechanisms. Moreover, loss or dysfunction of *CDKN2A/B*, which encode the tumor suppressor proteins $p16^{INK4A}$, $p14^{ARF}$, and $p15^{INK4B}$, disrupts the CDK4/6-RB

checkpoint and may enable proliferation with reduced dependence on KRAS signaling.[55] Figure 4 depicts the molecular mechanisms underlying therapeutic resistance and highlights corresponding targeted strategies designed to overcome these challenges and improve treatment efficacy.

4.2.3. Phenotypic plasticity and tumor evolution

(a) Lineage plasticity

Lineage plasticity, the ability of cells to switch between developmental programs, is increasingly recognized as a mechanism by which tumors adapt to targeted therapies. Epithelial–mesenchymal transition (EMT) is a prominent example, contributing to KRAS independence and both intrinsic and acquired resistance in lung and pancreatic cancers. EMT is a reversible form of cellular reprogramming whereby epithelial cancer cells lose their ability to adhere to other cells and epithelial properties like E-cadherin but gain mesenchymal features like N-cadherin and vimentin, and also become more motile and invasive as well as take on stem-like cell properties.[56] EMT enhances tumor progression, metastasis, immune escape, and tolerance to drugs through the formation of persister cells. EMT makes cancers resistant to KRAS inhibitors since it decreases tumor dependence on mutant KRAS signaling and enables alternative activation of downstream signaling. This form of adaptive resistance is due to the activation of various pathways such as TGF-β/SMAD, PI3K/AKT/mTOR, Wnt/β-catenin, JAK/STAT3, YAP/TAZ, NF-κB, and RTK. In preclinical models and patient samples, the mesenchymal phenotype has been associated with resistance to KRAS G12C inhibitors such as sotorasib. Other forms of plasticity also play a role in resistance. Adenosquamous transformation (AST) has been observed in *KRAS*-mutant lung adenocarcinomas treated with adagrasib. During AST, the transcription factor E74-like ETS transcription factor 5 (ELF5) induces NK2 homeobox 1 (NKX2-1), essential for lung development, while suppressing the N-terminally truncated p63 isoform (ΔNp63) through inhibition of VEZF1. Reduced ELF5 expression during AST increases ΔNp63 levels, promoting squamous gene expression.[57] While ΔNp63 overexpression alone is insufficient to trigger AST, the loss of LKB1 facilitates this process, highlighting the complex regulation of lineage switching. Changes in cell identity can also contribute to drug-tolerant persister states. In the alveoli, alveolar type 2 cells, which maintain and repair lung tissue, can transition to a quiescent alveolar type 1-like state after KRAS inhibition (e.g., MRTX1133 in KRAS G12D mouse models).[58] These alveolar type 1-like cells are drug-tolerant

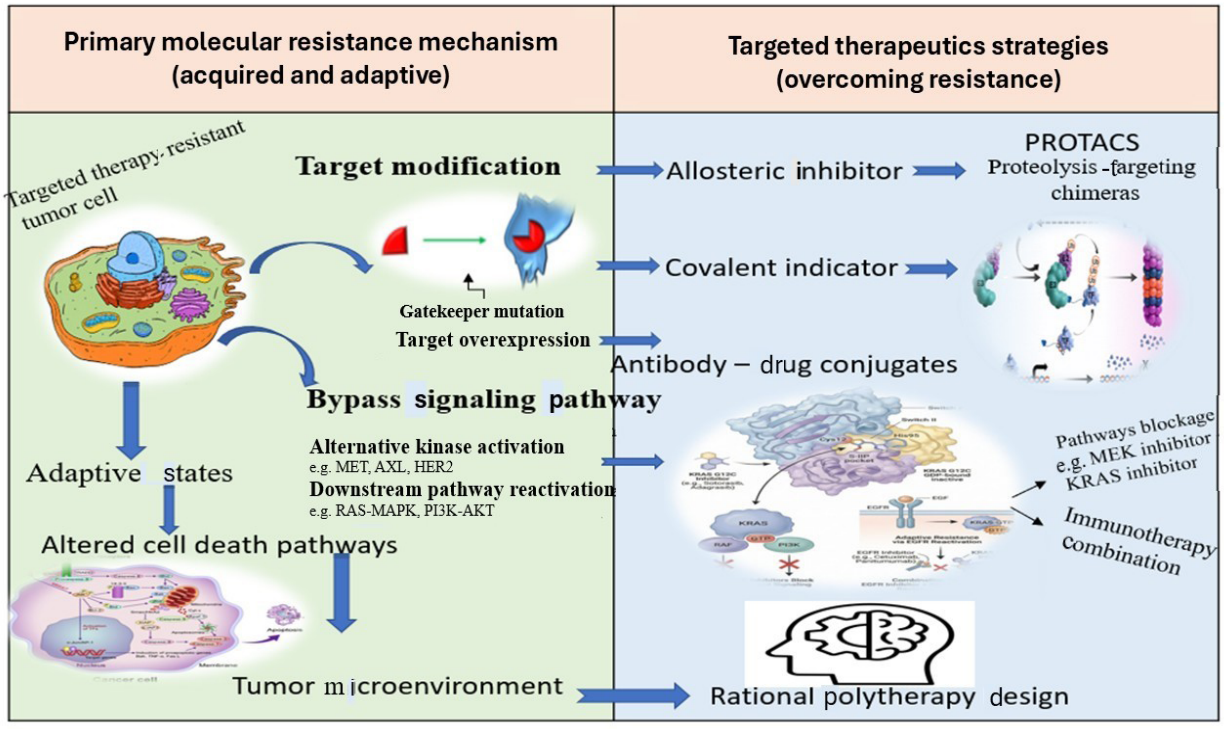


Figure 4. Molecular resistance mechanisms and targeted therapeutic strategies

and may serve as a reservoir for subsequent resistance through secondary mutations. Mucinous differentiation is another adaptive program associated with RAS inhibitor tolerance. In murine KRAS G12C tumor models, treatment with the tri-complex inhibitor RMC-7977 induces genes involved in gastrointestinal homeostasis, including trefoil factor family (TFF) peptides, gastrokines, and mucins. This transcriptional program is also seen with sotorasib treatment. Baseline mucinous features in tumors correlate with poorer progression-free survival in patients with KRAS G12C-mutant tumors, potentially linked to derepression of latent gastric differentiation pathways due to reduced NKX2-1 expression.[59] Experimental evidence indicates that AST can represent an acquired, nongenetic resistance mechanism in *KRAS*-mutant lung adenocarcinoma, with tumor cells retaining the original KRAS mutation while acquiring squamous characteristics.[60] Rather, AST arises by lineage plasticity as a result of the development of resistance, where the *KRAS*-mutant adenocarcinoma cells retain their original *KRAS* mutation and develop squamous features.

(b) Cellular plasticity

Cellular plasticity is further amplified in pre-EMT states during tissue regeneration or macrometastasis formation. KRAS inhibition can induce similar conditions, suggesting that plasticity-driven adaptation is a common mechanism of resistance in oncogene-addicted lung cancers.[61] In *KRAS*-mutant pancreatic cancer, resistance mechanisms are more complex. Although EMT has been associated with KRAS independence, resistance to MRTX1133 can also emerge in the classical epithelial-like subtype, which is generally more sensitive to KRAS inhibition. The TFF comprises three small secreted peptides: TFF1, TFF2, and TFF3, which play an important role in protecting and repairing epithelial tissues. However, in cancer, aberrant TFF expression, particularly TFF3, has been implicated in cancer progression by promoting proliferation, migration, invasion, EMT, angiogenesis, and resistance to apoptosis.[62] TFF proteins can trigger a number of oncogenic signal transduction pathways such as EGFR, PI3K/AKT, MAPK/ERK, STAT3, and Wnt/β-catenin. Increased TFF3 levels in *KRAS*-mutant tumors have been linked to MAPK pathway signaling and drug tolerance. Thus, TFF-triggered signaling may play a role in resistance to KRAS-directed drugs.[63] Marker genes of this subtype, including TFFs and mucins, are associated with endodermal or gastric lineages, suggesting that lineage programs beyond EMT may contribute to KRAS inhibitor resistance. Differences in resistance mechanisms across tumor types highlight the need for further investigation into tissue- and lineage-specific adaptive responses.[64]

5. Emerging therapeutic strategies to overcome resistance

5.1. Rational combination therapy

Rational combination therapy involves the strategic use of two or more therapeutic agents based on a clear understanding of disease biology, signaling pathways, and mechanisms of drug resistance. In the context of targeted cancer therapy, it aims to simultaneously inhibit primary oncogenic drivers and compensatory pathways, thereby enhancing treatment efficacy, delaying resistance, and achieving more durable clinical responses. Table 2 summarizes combination strategies involving KRAS G12C inhibitors with SHP2, MEK, and EGFR inhibitors, highlighting their potential to overcome adaptive resistance and improve therapeutic efficacy.

The following sections discuss the rationale, advantages, limitations, and clinical evidence for combining KRAS G12C inhibitors with SHP2, MEK, and EGFR inhibitors.

5.2. KRAS inhibitor + SHP2 inhibitor

KRAS G12C inhibitors block signaling by mutant KRAS, but resistance can arise via RTK-induced feedback stimulation and restoration of RAS-MAPK pathway activation.[65] As SHP2 is a major effector of RTK-driven RAS activation, its inhibition may suppress upstream signaling and increase the efficacy of KRAS G12C inhibitors.[66]

Advantages:

- Provides stronger and more sustained MAPK pathway inhibition.
- Reduces adaptive resistance caused by RTK activation.
- May improve response in tumors with high RTK signaling activity. Disadvantages and
- Limitations:
- Increased toxicity due to SHP2 involvement in normal cellular signaling.
- Alternative pathways such as PI3K/AKT/mTOR may still promote survival.
- Variable efficacy due to tumor heterogeneity and differences in KRAS dependency.[67]

Example 1: The KontRASt-01 phase Ib trial evaluated the combination of TNO155 and JDQ443 in patients with advanced *KRAS* G12C-mutant solid tumors. This combination demonstrated manageable safety, with common adverse events including edema and neutropenia. Importantly, an objective response rate (ORR) of ~33% was observed in NSCLC patients, irrespective of prior exposure to KRAS G12C inhibitors, indicating potential benefit even in pretreated populations.[68]

Example 2: In the CodeBreaK 101 study, the combination of RMC4630 and sotorasib was investigated in patients with previously treated *KRAS* G12C-mutant cancers. The safety profile included adverse events such as diarrhea, edema, and fatigue, with some grade 3–4 toxicities reported. Notably, while no significant responses were seen in patients previously treated with KRAS inhibitors, treatment-naïve NSCLC patients exhibited improved outcomes, with an ORR of around 50%.[69-70]

5.3. KRAS inhibitor + MEK inhibition

KRAS G12C inhibitors inhibit the mutant form of KRAS, although there are feedback mechanisms that may reinitiate the MAPK pathway. MEK inhibitors inhibit the downstream effectors of the RAF/MEK/ERK pathway to ensure vertical MAPK inhibition.[71]

Advantages:

- Enhances and prolongs MAPK pathway suppression.
- Reduces adaptive resistance.
- May improve antitumor efficacy in MAPK-dependent tumors.

Disadvantages:

- Alternative pathways (e.g., PI3K/AKT) may still drive resistance.
- Tumor heterogeneity can reduce treatment response.[72]

Example 1: In a sub-cohort of the CodeBreaK 101 trial, trametinib was combined with sotorasib in patients with previously treated advanced *KRAS* G12C-mutant solid tumors. The combination showed a manageable safety profile, with diarrhea, rash, and nausea as the most common adverse events, although ~34% of patients experienced grade 3–4 toxicities. Efficacy was modest, with limited responses in previously treated patients, while KRAS inhibitor–naïve patients showed slightly improved outcomes, particularly in NSCLC.[73]

Example 2: The RAMP203 study evaluated avutometinib in combination with sotorasib in advanced NSCLC patients. The treatment was generally well tolerated, with most adverse events being grade 1–2, including nausea, diarrhea, and fatigue. Higher-grade toxicities such as alkaline phosphatase elevation and diarrhea were less frequent. Notably, response rates were higher in KRAS inhibitor–naïve patients (~40%) compared to those previously treated (~14%), suggesting greater benefit in earlier treatment settings.[74]

5.4. KRAS inhibitor +EGFR inhibitor

KRAS G12C inhibition can induce EGFR-mediated feedback activation, particularly in colorectal cancer, thereby restoring MAPK signaling. EGFR inhibition can suppress this adaptive feedback and enhance pathway blockade.[75]

Advantages:

- Overcomes EGFR-driven adaptive resistance.
- Improves the depth and duration of MAPK pathway inhibition.
- Demonstrates greater efficacy, especially in *KRAS* G12C-mutant colorectal cancer.

Disadvantages:

- Resistance can still develop through alternative RTKs or PI3K/AKT pathway activation.
- Tumor heterogeneity and acquired secondary mutations may reduce long-term efficacy.[76]

Example 1: In the KRYSTAL-1 (NCT03785249) study, cetuximab combined with adagrasib showed promising efficacy in metastatic CRC, with an ORR of ~46% and manageable toxicity, mainly nausea and diarrhea.[77]

Example 2: A phase Ib trial (NCT04449874) evaluated divarasib + cetuximab, demonstrating higher efficacy (ORR ~62.5%) in KRAS inhibitor–naïve patients, although grade 3–4 toxicities such as rash and diarrhea were relatively frequent.[78]

Example 3: In a phase II study (NCT04585035), D1553 combined with cetuximab showed an ORR of ~45% with a tolerable safety profile.[79]

Example 4: The phase III CodeBreaK 300 trial evaluated sotorasib + panitumumab, demonstrating improved progression-free survival compared to standard care, with ORR up to ~26% at higher sotorasib dose.[80]

Example 5: In the CodeBreaK 101 trial, panitumumab + sotorasib ± chemotherapy (FOLFIRI) showed enhanced efficacy (ORR up to ~55% with FOLFIRI), though with increased toxicity.[81]

Example 6: Another sub-cohort of CodeBreaK 101 investigated afatinib + sotorasib in NSCLC, showing moderate activity (ORR ~33–35%) but higher discontinuation rates due to gastrointestinal toxicity.[82]

5.5. Combination with immunotherapy

The combination of KRAS G12C inhibitors with immunotherapy, particularly immune checkpoint inhibitors, is an emerging strategy based on the possibility that KRAS inhibition may enhance antitumor immune responses. Preclinical evidence suggests that KRAS inhibition can modulate the TME, thereby improving the efficacy of immunotherapy. However, safety remains a critical concern, as seen with other targeted–immunotherapy combinations (e.g., EGFR inhibitors with checkpoint inhibitors causing pneumonitis).[83]

Table 2. KRAS G12C inhibitor combination strategies with SHP2, MEK, and EGFR inhibitors

Target	Combination (Trial/NCT)	Phase	Population	*N*	Key Toxicities	Efficacy
SHP2	TNO155 + JDQ443 (KontRASt-01)[68]	Ib	Advanced solid tumors	50	Edema, neutropenia; G3–4: 36%	ORR: 33% (NSCLC)
	RMC4630 + sotorasib (CodeBreaK 101)[69]	Ib	Advanced solid tumors	27	Diarrhea, fatigue; G3–4: 22%	ORR: 50% (naïve NSCLC)
MEK	trametinib + sotorasib (CodeBreaK 101)[73]	Ib	Advanced solid tumors	41	Diarrhea, rash; G3–4: 34%	ORR: modest (≤ 20%)
	avutometinib + sotorasib (RAMP203)[74]	Ib/II	Advanced NSCLC	15	Mostly grade 1–2; some G3 events	ORR: 40% (naïve), 14.3% (pretreated)
RTK (EGFR)	cetuximab + adagrasib (KRYSTAL-1)[77]	I/II	Pretreated mCRC (no prior KRAS G12C therapy)	32	Nausea, diarrhea, vomiting; G3–4: 16%	ORR: 46%; mPFS: 6.9 m
	cetuximab + divarasib (NCT04449874)[78]	Ib	Advanced/metastatic CRC	29	Rash, diarrhea, nausea; G3–4: 45%	ORR: 60% (pretreated), 62.5% (naïve); mPFS: 8.1 m
	cetuximab + D1553 (NCT04585035)[79]	II	Metastatic CRC (naïve)	40	Rash, ↑AST/ALT, paronychia; G3–4: 12.5%	ORR: 45%; mPFS: 7.6 m
	panitumumab + sotorasib (CodeBreaK 300)[81]	III	Pretreated mCRC	106	Hypomagnesemia, rash; G3–4: ~30%–36%	ORR: 26.4% (960 mg), 5.7% (240 mg); mPFS: 5.6 vs 3.9 m
	panitumumab + sotorasib (CodeBreaK 101)[79]	Ib	Pretreated mCRC	48	Dermatologic toxicity; G3–4: 27%	ORR: 30%; mPFS: 5.7 m; mOS: 15.2 m
	panitumumab + FOLFIRI + sotorasib (CodeBreaK 101)[80]	Ib	Pretreated mCRC	46	Skin toxicity, GI events; G3–4: 43%	ORR: 55%
	afatinib + sotorasib (CodeBreaK 101)[82]	Ib	Pretreated NSCLC	33	Diarrhea, nausea; G3–4: 30%	ORR: ~33%–35% (higher in naïve)

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRC: Colorectal cancer; EGFR: Epidermal growth factor receptor; FOLFIRI: Folinic acid, fluorouracil, and irinotecan; G3–4: Grade 3–4; GI: Gastrointestinal; KRAS: Kirsten-RAS; mCRC: Metastatic colorectal cancer; MEK: Mitogen-activated protein kinase kinase; mOS: Median overall survival; mPFS: Median progression-free survival; NCT: ClinicalTrial.gov identifier; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; RTK: Receptor tyrosine kinase; SHP2: Src homology 2 domain-containing protein tyrosine phosphatase 2.

Advantages

- Potential enhanced antitumor activity: KRAS G12C inhibition may enhance tumor immunogenicity and modify the tumor microenvironment, potentially improving the activity of immune checkpoint inhibitors.
- Improved treatment durability: Combining targeted therapy with immunotherapy may provide complementary mechanisms of tumor control and potentially prolong responses.
- Potential clinical applicability: The strategy may benefit patients with KRAS G12C-mutant NSCLC, including selected patients with high PD-L1 expression.
- Rational combination strategy: Preclinical evidence supporting immune modulation by KRAS G12C inhibition provides a biological rationale for combining targeted and immune-based therapies.
- Potential to overcome resistance: Immunotherapy may help address heterogeneous tumor-cell populations or emerging resistant clones that are not adequately controlled by KRAS G12C inhibition alone.

Limitations

- Increased toxicity: Concurrent administration may increase treatment-related adverse events, particularly hepatotoxicity, pneumonitis, and other immune-mediated toxicities.
- Uncertain optimal sequencing: Clinical studies suggest that sequential or lead-in strategies may have a more favorable safety profile than simultaneous treatment, but the optimal sequence remains unresolved.
- Limited long-term evidence: Many combination studies are early-phase trials with relatively small patient populations and limited mature survival data.
- Patient-selection challenges: The benefit may vary according to PD-L1 expression, tumor immune microenvironment, co-occurring genomic alterations, and other patient-specific factors.

- Risk of treatment discontinuation: Severe adverse events may require dose interruptions or permanent discontinuation, potentially compromising therapeutic benefit.
- Need for further validation: Larger randomized trials are required to establish the efficacy, safety, optimal dosing, and sequencing of KRAS G12C inhibitors and immune checkpoint inhibitors.

Example 1: In the KRYSTAL-7 trial, pembrolizumab combined with adagrasib in treatment-naïve NSCLC patients demonstrated promising efficacy, with an ORR of ~63% in patients with high PD-L1 expression, although adverse events such as liver enzyme elevation and rare severe pneumonitis were reported.[84]

Example 2: In the CodeBreaK 100/101 studies, sotorasib was combined with checkpoint inhibitors such as pembrolizumab or atezolizumab using both sequential (lead-in) and concurrent approaches. While efficacy was moderate (ORR ~28–31%), toxicity was significantly higher in the concurrent setting, highlighting the importance of treatment sequencing.[85]

Example 3: In a phase I trial (NCT05067283), MK1084 combined with pembrolizumab showed encouraging early efficacy (ORR ~71%) in untreated NSCLC patients, although a substantial proportion experienced grade 3–4 toxicities leading to treatment discontinuation.[86]

5.6. Combination with chemotherapy

Combination of KRAS G12C inhibitors with chemotherapy is being explored to enhance antitumor efficacy by integrating cytotoxic effects with targeted pathway inhibition. This strategy has been successful in several malignancies and may improve response rates and progression-free survival in *KRAS*-mutant cancers, although toxicity remains a key concern.[87] Table 3 highlights combination strategies of KRAS G12C inhibitors with immunotherapy and chemotherapy, emphasizing their potential to enhance antitumor efficacy, modulate the TME, and overcome therapeutic resistance.

Advantages

- Complementary mechanisms of action: Chemotherapy provides broad cytotoxic activity, whereas KRAS G12C inhibitors selectively suppress oncogenic KRAS signaling, potentially producing complementary antitumor effects.
- Enhanced response rates: Early clinical studies suggest that combining KRAS G12C inhibitors with platinum-based chemotherapy may improve objective response rates compared with targeted therapy alone.
- Potential improvement in disease control: The combination may provide broader tumor-cell suppression and potentially delay progression.
- Utility in treatment-naïve patients: Chemotherapy combinations are particularly attractive in the first-line setting, where substantial tumor burden and intratumoral heterogeneity may require multimodal treatment.
- Potential to address tumor heterogeneity: Cytotoxic chemotherapy can eliminate tumor-cell populations that may be less dependent on KRAS G12C signaling, potentially complementing the selective activity of KRAS G12C inhibitors.
- Established clinical framework: Platinum-based chemotherapy regimens, particularly carboplatin plus pemetrexed in NSCLC, have well-established dosing and safety-monitoring protocols, facilitating clinical translation.

Limitations

- Increased hematologic toxicity: Combination treatment can substantially increase grade 3–4 adverse events, particularly neutropenia, thrombocytopenia, and anemia.
- Cumulative toxicity: Concurrent administration may increase overall treatment burden and may result in dose interruptions, dose reductions, or treatment discontinuation.
- Risk of severe adverse events: Although uncommon, serious or fatal treatment-related events have been reported, emphasizing the need for careful patient selection and monitoring.
- Uncertain optimal treatment schedule: The optimal dose, treatment duration, and sequencing of KRAS G12C inhibitors and chemotherapy remain to be established.
- Limited mature comparative data: Current evidence is largely derived from early-phase studies and study subgroups, and definitive randomized comparisons with established standard-of-care regimens remain limited.
- Potential impact on treatment tolerability: Increased toxicity may compromise quality of life and the ability to maintain adequate dose intensity.

Example 1: In a sub-cohort of the CodeBreaK 101 trial, sotorasib was combined with carboplatin and pemetrexed in advanced NSCLC patients. The combination showed notable efficacy, with an ORR of ~65% in the first-line and ~54% in the second-line setting. However, hematologic toxicities such as neutropenia and thrombocytopenia were common, with a high incidence of grade 3–4 adverse events.[88]

Example 2: The SCARLET trial evaluated sotorasib in combination with carboplatin and pemetrexed in treatment-naïve advanced NSCLC patients. This regimen demonstrated high efficacy, with an ORR of ~88.9%, although substantial hematologic toxicities and rare severe adverse events, including treatment-related mortality, were observed.[89]

Among currently evaluated combinations, KRAS G12C plus EGFR inhibition has some of the strongest clinical evidence, as it utilizes an excellent biological rationale together with strong clinical data, where KRAS G12C inhibition triggers EGFR-dependent feedback stimulation, leading to reactivation of the MAPK pathway and resistance; simultaneous EGFR inhibition prevents the adaptation mechanism.[95] In comparison, KRAS G12C plus SHP2 inhibition also has a strong mechanistic rationale because SHP2 mediates RTK-driven RAS reactivation; however, its clinical benefit remains under evaluation.[96] On the other hand, the KRAS G12C inhibitor in combination with a MEK inhibitor allows for efficient vertical blockade of the MAPK signaling cascade but fails to demonstrate clinical utility.[97] In conclusion, in light of recent evidence, KRAS G12C inhibitor–EGFR inhibitor combinations emerge as the most clinically proven approach, while SHP2 inhibitor combinations are highly promising for future treatment.

6. Next-generation KRAS inhibitors

6.1. Pan-KRAS inhibitors

Following the successful development of inhibitors targeting KRAS G12C, research efforts have increasingly focused on other clinically relevant *KRAS* mutations, particularly KRAS G12D, which is highly prevalent in colorectal and pancreatic cancers. A notable advancement was made by Mirati Therapeutics with the development of MRTX1133, a highly selective KRAS G12D inhibitor. Although MRTX1133 demonstrated promising preclinical efficacy, its clinical translation has been hindered by an unfavorable pharmacokinetic profile, highlighting the persistent challenges in drug development for *KRAS*-mutant cancers.[98] Daraxonrasib (RMC-6236) is an orally administered RAS(ON) multi-selective inhibitor that targets active, GTP-bound KRAS, NRAS, and HRAS through a cyclophilin A-mediated tri-complex mechanism, which forms a non-covalent complex with active RAS proteins and blocks the interaction between these proteins and their downstream effectors, such as RAF and PI3K, ultimately leading to the inhibition of the MAPK and PI3K/AKT pathways.[99] Currently, daraxonrasib is under investigation in the Phase I/II trial RMC-6236-001 (NCT05379985) for advanced solid tumors harboring mutant *RAS* genes, such as PDAC, NSCLC, and CRC.[100] Despite these advances, therapeutic targeting of KRAS remains inherently complex due to the extensive heterogeneity of *KRAS* mutations and their distinct biochemical properties. In addition to common mutations, a significant proportion of tumors harbor less frequent variants or exhibit *KRAS* wild-type amplification, for which effective targeted therapies are still lacking. This underscores the need for continued development of allele-specific inhibitors to achieve broader therapeutic coverage across diverse KRAS-driven malignancies.[101]

Table 3. KRAS G12C inhibitor combination strategies with immunotherapy and chemotherapy

Combination	Trial (ID)	Phase	Population	*N*	Safety (Key TRAEs)	Efficacy
Pembrolizumab + adagrasib[90]	KRYSTAL-7	II	Untreated advanced NSCLC	148	Nausea, diarrhea, ↑AST/ALT; Grade 5: pneumonitis, pneumonia; Discontinuation: 4–11%	ORR: 63% (PD-L1 ≥ 50%); mPFS: Not reached
Pembrolizumab/atezolizumab + sotorasib (lead-in vs concurrent)[91]	CodeBreaK 100/101	Ib	Advanced NSCLC (no prior KRAS G12C therapy)	58	G3–4 TRAEs: 45% (lead-in), 72% (concurrent); ↑AST/ALT; Discontinuation: 24% vs. 52%	ORR: 31% (lead-in), 28% (concurrent); mOS: 15.7 months
Pembrolizumab + MK1084[92]	MK1084 trial	I	Untreated advanced NSCLC	24	↑AST/ALT, diarrhea, pruritus; G3–4: 42%; Discontinuation: 25%	ORR: 71%
Carboplatin + pemetrexed + sotorasib[93]	CodeBreaK 101	Ib	Advanced NSCLC	38	Neutropenia, anemia, thrombocytopenia; G3–4: 58%	ORR: 65% (1L), 54% (2L)
Carboplatin + pemetrexed + sotorasib[94]	SCARLET trial	II	Untreated advanced NSCLC	30	Hematologic toxicity; rare fatal pneumonia	ORR: 88.9%; mPFS: 5.7 months

Abbreviations: 1L: First-line; 2L: Second-line; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; G3–4: Grade 3–4; ID: Identifier; KRAS: Kirsten-RAS; mOS: Median overall survival; mPFS: Median progression-free survival; N: Number of patients; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; PD-L1: Programmed death-ligand 1; TRAEs: Treatment-related adverse events.

Examples of challenging KRAS variants include:

(i) KRAS G12D: Targeted by MRTX1133, but limited by poor pharmacokinetics
(ii) KRAS G12R: Frequently observed in pancreatic cancer; lacks effective inhibitors
(iii) KRAS G12A: Limited research progress and no approved targeted therapies
(iv) KRAS Q61H: Biochemically distinct; difficult to inhibit
(v) *KRAS* wild-type amplification: Not mutation-driven; no direct KRAS-targeted options available.[102]

6.2. Allosteric modulators

Allosteric modulation has emerged as a pivotal strategy in the development of KRAS inhibitors, particularly in overcoming the intrinsic limitations of directly targeting the highly conserved and high-affinity nucleotide-binding site of KRAS. Unlike orthosteric inhibitors, allosteric modulators bind to distinct regulatory pockets within the KRAS protein, most notably the switch-II pocket, inducing conformational changes that stabilize the inactive GDP-bound state and impair effector interactions.[103] This approach enables selective inhibition while avoiding direct competition with GTP. The discovery of inducible allosteric pockets in mutant KRAS, especially KRAS G12C, marked a significant breakthrough in drug design. Small molecules such as ARS-1620 were among the first to exploit this strategy, demonstrating that covalent binding to an allosteric site could effectively lock KRAS in its inactive form.[104] This concept was further translated into clinically approved agents such as sotorasib and adagrasib, which irreversibly bind to the cysteine residue in KRAS G12C via the switch-II pocket, thereby inhibiting downstream signaling pathways.[105]

Beyond KRAS G12C, the application of allosteric modulation remains challenging due to the absence of reactive residues and differences in pocket accessibility. Consequently, current research is focused on identifying non-covalent allosteric modulators capable of targeting other KRAS variants such as KRAS G12D. Additionally, alternative allosteric strategies involve disrupting protein–protein interactions, such as the SOS1–KRAS interface, to prevent nucleotide exchange and maintain KRAS in an inactive state.[106]

Examples of KRAS allosteric modulators include:

(i) ARS-1620: First-generation covalent allosteric inhibitor targeting the switch-II pocket
(ii) Sotorasib (AMG 510): FDA-approved; stabilizes inactive KRAS G12C via allosteric binding
(iii) Adagrasib (MRTX849): Allosteric inhibitor with improved pharmacokinetic profile
(iv) BI-3406 (SOS1 inhibitor): Indirect allosteric modulation by blocking KRAS activation

6.3. Proteolysis targeting chimera-mediated KRAS degradation

6.3.1. Direct KRAS degraders

Following the clinical success of KRAS G12C inhibitors, targeted protein degradation strategies such as proteolysis targeting chimeras (PROTACs) have been explored to directly eliminate mutant KRAS. KRAS-directed PROTACs recruit an E3 ubiquitin ligase to the target protein, promoting ubiquitination and proteasomal degradation. Unlike the KRAS inhibitors, which only inhibit KRAS activity, KRAS degraders may produce more sustained suppression of KRAS-dependent MAPK and PI3K/AKT signaling than reversible inhibition alone.[107] A notable example is LC-2, a heterobifunctional molecule generated by conjugating the KRAS G12C inhibitor MRTX849 with a von Hippel–Lindau (VHL) E3 ligase ligand. This design enables covalent binding to KRAS G12C and recruitment of the VHL ligase, resulting in efficient proteasomal degradation and suppression of MAPK signaling at submicromolar concentrations. Degradation efficiency was cell-type dependent, achieving ~50% in heterozygous cells and up to ~75% in homozygous models. Importantly, LC-2 demonstrated selectivity toward mutant KRAS over wild-type protein. In contrast, PROTACs utilizing cereblon (CRBN)-recruiting ligands (e.g., thalidomide derivatives) showed limited success in degrading endogenous KRAS G12C, despite effective target engagement, indicating that E3 ligase selection and ternary complex formation are critical determinants of degradation efficiency.[108]

6.3.2. Degraders of guanine nucleotide exchange factors and regulatory proteins

(a) SOS1-targeting degraders

The SOS1–KRAS interaction has been exploited using a novel ubiquitination-independent degradation strategy known as CANDDY (Chemical knockdown with affinity and degradation dynamics). SOS1-targeting degraders are novel targeted protein degraders (TPDs) that cause SOS1 degradation through the ubiquitination and proteasome pathway; SOS1 is a crucial GEF required for RAS activation. Suppression of SOS1 can reduce activation of mutant and wild-type RAS and attenuate RTK-driven MAPK reactivation, and overcome acquired resistance due to RTK feedback activation and high RAS-GTP load.[109] The conjugate TUS-007, derived from a RAS–SOS1 inhibitor, induces direct proteasomal degradation of KRAS G12D/V and exhibits dose-dependent tumor suppression in vivo.[110]

(b) SHP2 degraders

SHP2, a key mediator of RAS pathway activation, has

emerged as an important degradation target. Several PROTACs incorporating SHP2 inhibitors (e.g., SHP099 derivatives) and E3 ligase ligands (VHL or CRBN) have demonstrated potent degradation activity. Compounds such as SHP2-D26 exhibit low nanomolar DC_{50} values and achieve > 95% protein depletion, resulting in significantly enhanced inhibition of ERK phosphorylation and cancer cell proliferation compared to conventional inhibitors.[111] SHP2 degraders are protein degraders using the PROTAC platform for the selective ubiquitylation and proteasomal destruction of SHP2 (*PTPN11*), a critical player in RTK-induced activation of RAS. Unlike traditional SHP2 inhibitors that merely inhibit both catalytic and scaffolding functions, degraders destroy the protein entirely. As such, RTK-induced feedback loops and RAS and MAPK reactivation are prevented.[112]

6.3.3. RAF degraders

Targeted degradation of RAF kinases provides an additional strategy to suppress downstream signaling.[113-114] RAF degraders belong to the group of TPDs and are generally produced via the PROTAC strategy, where the RAF kinases (A-Raf proto-oncogene, serine/threonine kinase [ARAF], BRAF, and/or CRAF) undergo ubiquitination-mediated proteasomal degradation. As opposed to the usual RAF inhibitors, which are involved in just inhibiting the kinase function, RAF degraders destroy the RAF protein, thus preventing RAF dimerization, MEK phosphorylation, and subsequent MAPK signaling.[115] PROTACs derived from BRAF inhibitors such as vemurafenib have demonstrated efficient and selective degradation of mutant BRAF at nanomolar concentrations while sparing wild-type protein. Similarly, rigosertib-based PROTACs have shown potential as BRAF degraders.

Advantages over first-generation KRAS inhibitors include:

(i) Degradation of RAF protein, ensuring continuous suppression of the MAPK pathway instead of selective inhibition of mutant KRAS alone.
(ii) Prevention of RAF dimerization and scaffold-mediated signaling to circumvent the common adaptive resistance pathway.
(iii) Functional regardless of upstream modifications, such as RTK activation, *BRAF* amplification, and secondary *KRAS* mutation.
(iv) Inhibition of MAPK pathway rebound, which is likely to result in better antitumor effects.
(v) A strong case for combination with KRAS, SHP2, or EGFR inhibitors for complete pathway blockage.[116]

Recent advances in pan-RAF degraders targeting the simultaneous degradation of ARAF, BRAF, and CRAF proteins have demonstrated strong and sustained inhibition of MAPK signaling. The multi-isoform activity of these new-generation degraders may enable them to overcome resistance mechanisms arising from isoform switching and RAF dimerization.[117]

6.3.4. MEK1/2 degraders

MEK1/2 are critical components of the MAPK pathway and are frequently associated with resistance to MEK inhibitors. PROTAC-based degraders such as MS432 and its optimized analogs (MS928, MS934) have shown potent and selective degradation of MEK1/2, with DC_{50} values in the nanomolar range and improved antiproliferative activity.[118-119]. MEK1/2 degraders belong to the class of TPDs and have mainly been generated by means of the PROTAC method, which leads to the proteasome-mediated degradation of MEK1 and MEK2 through ubiquitination instead of their transient kinase inhibition. Through this process of elimination, the MEK proteins are prevented from participating in the RAF–MEK–ERK signaling pathway.[120]

Advantages over first-generation KRAS inhibitors include:

(i) Destroy the MEK1/2 protein instead of temporarily blocking kinase activity, producing a more persistent blockage of the MAPK pathway.
(ii) Surmount the resistance mechanism involving MAPK pathway reactivation via RTK-, BRAF-, and KRAS-dependent signaling.
(iii) Achieve better pathway rebound prevention through the inhibition of the re-accumulation of functional MEK proteins.
(iv) Maintain efficacy in tumors resistant to KRAS G12C inhibitors, especially with MAPK pathway dependency.
(v) Make a good combination therapy approach for KRAS, SHP2, or EGFR inhibitors.[121]

Recent advances in MEK1/2 degrader development have shown that PROTAC-mediated degradation of MEK1/2 has been found to provide strong and durable inhibition of ERK signaling that is more efficacious than traditional MEK inhibitors in preclinical studies.

6.3.5. Extracellular signal-regulated kinase degraders

To address limitations associated with conventional PROTACs, alternative approaches such as CLIPTACs (click-formed PROTACs) have been developed. These systems enable intracellular assembly of bifunctional degraders via bio-orthogonal click chemistry. The first ERK degrader, ERK-CLIPTAC, demonstrated effective degradation of ERK1/2 at micromolar concentrations,

highlighting a novel strategy for targeting downstream effectors.[122] ERK degraders represent a newer generation of TPDs, which mostly operate using PROTAC technology, to bring about the degradation of ERK1/2 via the ubiquitin-proteasome pathway. Instead of inhibiting the kinase activity of ERK, ERK degraders ensure the elimination of these proteins, thereby ensuring the long-term inhibition of MAPK signaling and inhibition of phosphorylation of transcription factors mediated by ERK.[123]

Advantages over first-generation KRAS inhibitors include:

(i) Inhibits ERK protein rather than reversible kinase inhibition, leading to more persistent suppression of the pathway.
(ii) It will be effective even against upstream resistance mechanisms such as secondary *KRAS* mutation and RTK-driven MAPK pathway reactivation.
(iii) Decreases adaptive MAPK pathway rebound, which may lead to improvement of the anti-tumor response persistence.
(iv) Has wide potential as therapeutics for many MAPK-driven tumors, regardless of the upstream resistance mutation.[124]
(v) Can serve as a rationale for combining this therapy with KRAS, SHP2, or EGFR inhibitors.

Recent advances in preclinical research indicate that the use of PROTACs in developing ERK degraders results in stronger inhibition of MAPK pathway signaling and improved antitumor efficacy when compared to the effects of traditional ERK inhibitors on tumor cells resistant to KRAS G12C inhibitors.

6.3.6. Tri-complex inhibitor

RMC-6291 represents a next-generation RAS(ON) tri-complex inhibitor that specifically targets active KRAS G12C bound to GTP. As opposed to first-generation inhibitors of KRAS G12C (such as sotorasib and adagrasib), which are irreversible inhibitors that bind specifically to the inactive form of the protein complexed with GDP, RMC-6291 specifically binds active KRAS G12C and the chaperone cyclophilin A. Cyclophilin A is a bridging protein that maintains the stability of the inhibitor-KRAS complex and interferes with KRAS interaction with its effectors like RAF, thus inhibiting MAPK pathway activation despite KRAS being in its active state of signaling.[125]

Advantages over first-generation KRAS G12C inhibitors include:

(i) Targets active (GTP-bound) KRAS G12C mutation, eliminating the requirement for GDP-bound KRAS that is necessary for first-generation inhibitors.
(ii) It forms a stable tri-complex with cyclophilin A, leading to robust and lasting inhibition of KRAS-effector protein interactions.
(iii) Less prone to RTK-driven acquired resistance due to its activity even at the time when KRAS is mostly in the ON condition.
(iv) Creates greater inhibition of MAPK pathway activation that could prevent tumor regrowth.
(v) It creates a strong basis for combined therapy strategies with SHP2, EGFR, SOS1, or immune checkpoints.[126]

Recent advances in active-state KRAS targeting have positioned RMC-6291 as a potential strategy for overcoming limitations associated with first-generation KRAS G12C inhibitors. Preclinical research has shown that RMC-6291 can induce quick and persistent tumor regression in models where KRAS G12C drives tumor formation. Clinical trials at the early stage are being conducted to determine its safety profile, pharmacokinetics, and efficacy against tumors. As an ON-state tri-complex inhibitor, RMC-6291 therefore represents a distinct therapeutic approach that may achieve more effective KRAS inhibition and delay the emergence of resistance.[127]

7. Clinical trials and translational advances

Clinical trials of KRAS G12C inhibitors have evolved from early monotherapy studies to combination-based approaches, particularly in colorectal cancer where single-agent efficacy is limited. As summarized in Table 4,[128-129] several KRAS-targeted and pan-KRAS inhibitors are currently under clinical development as monotherapies, highlighting the expanding therapeutic landscape. Combinations with EGFR inhibitors such as cetuximab have demonstrated improved clinical outcomes and are being evaluated in advanced-phase trials. Additionally, strategies involving SHP2 and SOS1 inhibitors are under investigation to overcome adaptive resistance by targeting upstream signaling pathways. As outlined in Table 5,[130] multiple combination regimens are being explored in clinical trials to enhance efficacy and delay resistance. Translational research, including genomic profiling and circulating tumor DNA analysis, is playing a key role in identifying biomarkers and monitoring resistance. These advances highlight the shift toward biomarker-driven, precision-based therapeutic strategies in *KRAS* G12C-mutant cancers.[131]

8. Current challenges and limitations

Although there have been clinical successes with KRAS G12C inhibitors, the durability of response remains hampered by complex and heterogeneous resistance mechanisms, which include secondary mutations in the

Table 4. KRAS-targeted and Pan-KRAS inhibitors monotherapy in clinical development

Drug	Target	Sponsor	ClinicalTrials.gov ID	Disease Setting	Phase	Status	Intervention
Adagrasib (MRTX849)	KRAS G12C	Mirati Therapeutics	NCT03785249	Advanced solid tumors	I/II	Active, not recruiting (KRYSTAL-1)	Monotherapy
Adagrasib (MRTX849)	KRAS G12C	Mirati Therapeutics	NCT04685135	Advanced NSCLC	III	Active, not recruiting	vs. docetaxel
MRTX1133	KRAS G12D	Mirati Therapeutics	–	–	–	Recruiting	Selective G12D inhibitor
JNJ-74699157 (ARS-3248)	KRAS G12C	Johnson & Johnson	NCT04006301	Advanced solid tumors	I	Completed	Monotherapy
LY3499446	KRAS G12C	Eli Lilly and Company	NCT04165031	Advanced solid tumors	I/II	Terminated	Monotherapy
LY3537982	KRAS G12C	Eli Lilly and Company	–	–	–	Active/ Completed (depending on cohort)	–
JDQ443	KRAS G12C	Novartis	NCT04699188	Advanced solid tumors	Ib/II	Active, not recruiting	Monotherapy/ combination
GDC-6036	KRAS G12C	Genentech	NCT04449874	Advanced solid tumors	I	Active, not recruiting	Monotherapy
RG6330	KRAS G12C	Roche	–	Advanced solid tumors	I	Recruiting	–
D-1553	KRAS G12C	InventisBio	NCT04585035	Advanced solid tumors	I/II	Active, not recruiting	Monotherapy
BPI-421286	KRAS G12C	Betta Pharmaceuticals	–	Advanced solid tumors	–	IND stage	–
GH35	KRAS G12C	–	–	Advanced solid tumors	–	IND stage	–
BEBT-607	KRAS G12C	–	–	NSCLC, CRC	–	IND stage	–
JAB-21000	KRAS G12C	Jacobio Pharmaceuticals	–	Advanced solid tumors	–	IND stage	–
JAB-23E73	Pan-KRAS	Jacobio Pharmaceuticals	NCT06973564	NSCLC, CRC, PDAC, others	I/II	Recruiting	Monotherapy
AMG 410	Pan-KRAS	Amgen	NCT07094113	Solid tumors (*KRAS*-mutant)	I	Recruiting	± panitumumab, pembrolizumab
BGB-53038	Pan-KRAS	BeiGene	NCT06585488	Solid tumors (*KRAS*-mutant/amplified)	I	Terminated	± tislelizumab, cetuximab
BI-3706674	Pan-KRAS	Boehringer Ingelheim	NCT06056024	GAC, EAC, GEJAC	I	Completed	Monotherapy
PF-07934040	Pan-KRAS	Pfizer	NCT06447662	NSCLC, CRC, PDAC	I	Active, not recruiting	± chemotherapy, cetuximab, pembrolizumab
LY-4066434	Pan-KRAS	Eli Lilly and Company	NCT06607185	Advanced *KRAS*-mutant tumors	I	Active, not recruiting	± chemotherapy & immunotherapy
YL-17231	Pan-RAS (KRAS/ HRAS/NRAS)	Shanghai YingLi Pharmaceutical Co., Ltd.	NCT06096974	Advanced solid tumors	I	Recruiting	Monotherapy

Abbreviations: CRC: Colorectal cancer; EAC: Esophageal adenocarcinoma; GAC: Gastric adenocarcinoma; GEJAC: Gastroesophageal junction adenocarcinoma; HRAS: Harvey-HRAS; IND: Investigational new drug; KRAS: Kirsten-RAS; NRAS: Neuroblastoma-RAS; NSCLC: Non-small cell lung cancer; PDAC: Pancreatic ductal adenocarcinoma.

Table 5. Combination strategies with KRAS inhibitors in clinical trials at ClinicalTrials.gov

Target	Combination therapy	Trial (NCT no.)	Phase	Population	Status
RTK (EGFR)	Cetuximab + adagrasib (KRYSTAL-10)	NCT04793958	III	Advanced CRC (post 1L chemo)	Active, not recruiting
	Cetuximab + JDQ443 (KontRASt-03)	NCT05358249	I/II	Advanced solid tumors	Active, not recruiting
	Cetuximab + JAB21822	NCT05002270	I/II	Advanced solid tumors	Completed
	Cetuximab + IBI351	NCT05497336	I	Metastatic CRC	Recruiting
	Cetuximab + adagrasib + irinotecan	NCT05722327	I	Advanced CRC	Active, not recruiting
	Cetuximab/erlotinib + LY3537982	NCT04956640	I/II	Advanced solid tumors	Active, not recruiting
	Erlotinib + divarasib	NCT04449874	I	Advanced solid tumors	Active, not recruiting
	Panitumumab + sotorasib	NCT05638295	II	Advanced solid tumors	Active, not recruiting
	Tarloxotinib + sotorasib	NCT05313009	I	NSCLC (post G12C inhibitors)	Terminated
SHP2	TNO155 + sotorasib (CodeBreaK 101)	NCT04185883	I	Advanced solid tumors	Active, not recruiting
	TNO155 + adagrasib (KRYSTAL-2)	NCT04330664	I	Advanced solid tumors	Completed
	TNO155 + LY3537982	NCT04956640	I/II	Advanced solid tumors	Active, not recruiting
	TNO155 + tislelizumab + JDQ443	NCT04699188	I/II	Advanced solid tumors	Active, not recruiting
	BBP398 + sotorasib	NCT05480865	I	Advanced solid tumors	Terminated
	GDC1971 + divarasib	NCT04449874	I	Advanced solid tumors	Active, not recruiting
	JAB3312 + JAB21822	NCT05288205	I/II	Advanced solid tumors	Recruiting
	SAR442720 + adagrasib	NCT04418661	I/II	Advanced solid tumors	Terminated
	RMC4630 + sotorasib	NCT05054725	II	NSCLC (pretreated)	Completed
SOS1	BI1701963 + adagrasib (KRYSTAL-14)	NCT04975256	I	Advanced solid tumors	Terminated
	BI1701963 + sotorasib (CodeBreaK 101)	NCT04185883	I	NSCLC/CRC	Active, not recruiting
	BI1701963 + BI-1823911	NCT04973163	I	Advanced solid tumors	Active, not recruiting
	MRTX0902 + adagrasib	NCT05578092	I	Advanced solid tumors	Terminated
Wild-type RAS	RMC6236 + RMC6291	NCT06128551	I/II	Advanced solid tumors	Recruiting
MEK	Avutometinib + adagrasib (RAMP 204)	NCT05375994	I/II	NSCLC (post G12C therapy)	Completed
	Trametinib + JDQ443 (KontRASt-03)	NCT05358249	I/II	Advanced solid tumors	Recruiting
ERK	Temuterkib + LY3537982	NCT04956640	I/II	Advanced solid tumors	Active, not recruiting
	ERAS-007 + sotorasib (HERKULES-2)	NCT04959981	I	NSCLC	Completed
PI3K	Inavolisib + divarasib	NCT04449874	I	Advanced solid tumors	Active, not recruiting
mTOR	Everolimus + sotorasib (CodeBreaK 101)	NCT04185883	I	Advanced solid tumors	Active, not recruiting
	Nab-sirolimus + adagrasib (KRYSTAL-19)	NCT05840510	I	Advanced solid tumors	Terminated
CDK4/6	Palbociclib + adagrasib (KRYSTAL-16)	NCT05178888	I	Advanced solid tumors	Completed
	Palbociclib + sotorasib (CodeBreaK 101)	NCT04185883	I	Advanced solid tumors	Active, not recruiting
	Abemaciclib + LY3537982	NCT04956640	I/II	Advanced solid tumors	Active, not recruiting
	Ribociclib + JDQ443 (KontRASt-03)	NCT05358249	I/II	Advanced solid tumors	Active, not recruiting
AURKA	LY3295668 + LY3537982	NCT04956640	I/II	Advanced solid tumors	Active, not recruiting
ULK1/2	DCC-3116 + sotorasib	NCT04892017	I	NSCLC	Terminated
PARP	Olaparib + adagrasib	NCT06130254	I	Advanced solid tumors	Terminated
CXCR1/2	Ladarixin + adagrasib	NCT05815173	I	NSCLC	Recruiting

(*Cont'd...*)

Table 5. (*Continued*)

Target	Combination therapy	Trial (NCT no.)	Phase	Population	Status
VEGF	Bevacizumab + FOLFIRI/FOLFOX + sotorasib	NCT04185883	I	CRC	Active, not recruiting
	Bevacizumab + divarasib	NCT04449874	I	Advanced solid tumors	Active, not recruiting
PD-1	Pembrolizumab + adagrasib	NCT04418661	I/II	Advanced solid tumors	Terminated
	Pembrolizumab + adagrasib (KRYSTAL-17)	NCT05609578	II	NSCLC	Active, not recruiting
	Pembrolizumab + divarasib	NCT05789082	I/II	NSCLC	Recruiting
	Pembrolizumab + LY3537982	NCT04956640	I/II	Advanced solid tumors	Active, not recruiting
	Pembrolizumab + RMC6291	NCT06162221	I/II	Advanced solid tumors	Recruiting
	Nivolumab + adagrasib (NeoKAN)	NCT05472623	II	Resectable NSCLC	Withdrawn
PD-L1	Durvalumab + adagrasib	NCT05848843	I	NSCLC/GI cancers	Withdrawn
	Atezolizumab + divarasib	NCT04449874	I	NSCLC	Active, not recruiting
	AMG404 + sotorasib	NCT04185883	I/II	Advanced solid tumors	Active, not recruiting
	Sintilimab ± chemotherapy + IBI351	NCT05504278	I	NSCLC	Recruiting
	Tislelizumab ± TNO155 + JDQ443	NCT04699188	I/II	Advanced solid tumors	Active, not recruiting
Chemotherapy	Carboplatin/cisplatin + pemetrexed + sotorasib	NCT05118854	II	NSCLC	Active, not recruiting
	Platinum doublet chemotherapy + Sotorasib (CodeBreaK 202)	NCT05920356	III	NSCLC	Recruiting

Abbreviations: 1L: First-line; AURKA: Aurora kinase A; CDK4/6: Cyclin-dependent kinases 4 and 6; CRC: Colorectal cancer; CXCR1/2: C-X-C motif chemokine receptors 1 and 2; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal-regulated kinase; FOLFIRI: Folinic acid, fluorouracil, and irinotecan; FOLFOX: Folinic acid, fluorouracil, and oxaliplatin; GI: Gastrointestinal; KRAS: Kirsten-RAS; MEK: Mitogen-activated protein kinase kinase; mTOR: Mechanistic target of rapamycin; NCT: ClinicalTrial.gov identifier; NSCLC: Non-small cell lung cancer; PARP: Poly(ADP-ribose) polymerase; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PI3K: Phosphatidylinositol 3-kinase; RTK: Receptor tyrosine kinase; SHP2: Src homology 2 domain-containing protein tyrosine phosphatase 2; SOS1: Son of sevenless homolog 1; ULK1/2: Unc-51-like autophagy activating kinases 1 and 2; VEGF: Vascular endothelial growth factor.

KRAS switch-II pocket (such as Y96C/D, H95Q/R and R68S), *KRAS* amplifications, alternative RAS mutations, and fast restoration of wild-type RAS signaling via the EGFR, HER2, MET, FGFR, SHP2 and SOS1 signaling pathways. Resistance to treatment is also facilitated by the PI3K-AKT pathway bypass, EMT and lineage plasticity, HGF/FGF/TGF-β/CXCL12 signaling from CAF, and ECM reorganization and integrin-FAK-SRC activation.[132] Additional findings have shown that FAK/SRC signaling and TOP2A-dependent DNA damage response constitute two other mechanisms for developing drug resistance and synthetic lethal vulnerability, respectively. Besides, polyclonal evolution, temporal and spatial tumor heterogeneity, and tumor-specific co-mutations including *STK11*, *KEAP1*, *TP53*, and *CDKN2A*/*B* make *KRAS* G12C alone insufficient to predict clinical outcomes. Intratumoral heterogeneity and epigenetic plasticity further complicate treatment by enabling rapid clonal evolution and phenotypic switching. Emerging challenges include lineage plasticity, non-genetic drug tolerance states, and adaptive rewiring of signaling networks revealed by single-cell and spatial omics approaches. However, even though drug combinations with EGFR, SHP2, SOS1, MEK, ERK, MET, FAK/SRC, or PI3K/AKT inhibitors are appealing from a mechanism perspective, they are hindered by common side effects, pharmacodynamic interactions, feed-forward signaling pathways, and a very narrow window of toxicity. Thus, the future clinical strategy is being developed, moving from empiric combination trials "KRAS inhibitor + one other partner" towards a biomarker-driven, adaptive, and multi-faceted approach combining next-generation KRAS inhibitors, TME modulation, synthetic lethality, and sequential ctDNA/multi-omics assessment.[133] Addressing these complexities requires AI-driven integration of multi-omics and clinical datasets to enable predictive modeling of resistance and rational design of therapies. Future strategies are increasingly focused on vertical and horizontal combination approaches, including co-targeting KRAS with SHP2, MEK, or PI3K inhibitors, dual orthosteric allosteric inhibition, epigenetic

modulation, and immunotherapy combinations, alongside the development of next-generation inhibitors capable of overcoming pan-KRAS and mutation-specific resistance, ultimately advancing the goal of durable precision oncology.

9. Future perspectives

The collective evidence demonstrates that the development of resistance to inhibitors of the KRAS G12C mutation is a result of a multifactorial interaction between genetic evolution, cell plasticity, and the adaptability of the TME, rather than a process governed by a single predominant mechanism.[134] Though the secondary mutation in *KRAS*, RTK-mediated bypass signaling, and MAPK pathway activation are regarded as the most clinically established mechanisms, there are several other factors that play an equally significant role in causing resistance. These findings indicate that durable clinical response will not be gained through KRAS inhibition only and stress the necessity for transitioning from a mutation-based approach to a biology-based strategy for treatment. Therefore, rational combinations against SHP2, SOS1, EGFR, PI3K/AKT/mTOR, YAP1, autophagy, and immune checkpoint signaling pathway along with novel KRAS inhibitors such as KRAS(ON)-state inhibitors, pan-KRAS inhibitors, tri-complex inhibitors, and KRAS degraders, are the most promising approaches in overcoming resistance.[135] The broad heterogeneity at the molecular level in *KRAS*-mutant tumors, along with concomitant genomic changes, clonal evolution within the tumor, and the lack of reliable biomarkers, still impede the achievement of long-lasting therapeutic responses. Additionally, numerous resistance pathways have been discovered mainly in preclinical studies. Indeed, future research needs to incorporate the use of multi-omics profiling, single-cell and spatial transcriptomics, longitudinal ctDNA profiling, and functional tools like patient-derived organoids and xenografts in order to determine the resistance mechanisms in real time and select personalized therapies.[136] In parallel, there is a need for further studies on the tumor immune microenvironment involving CAFs, myeloid immunosuppressive cells, and ECM remodeling. In terms of future prospects, the fusion of artificial intelligence-driven biomarker identification, systems biology, liquid biopsy-based adaptive clinical trials, and precision combination therapy may very well lead to changing the paradigm of KRAS treatment from dealing with resistance to preventing the development of resistance altogether.

10. Conclusion

The clinical development of KRAS G12C inhibitors has revolutionized the treatment paradigm of *KRAS*-mutant cancers, making KRAS an actionable drug target that was previously thought to be 'undruggable' for decades. Nonetheless, a body of evidence that has emerged from both preclinical and clinical trials unequivocally shows that the effectiveness of the treatment is limited due to the development of drug resistance. The most clinically relevant resistance drivers include development of secondary *KRAS* mutations, activation of RTK-dependent bypass signaling, feedback activation of MAPK/PI3K-AKT signaling, EMT, lineage plasticity, drug-tolerant persister cells, metabolic alterations, and adaptations to the TME. Taken together, all the above observations imply that resistance is an evolutionary process characterized by the interaction of multiple tumor intrinsic and extrinsic adaptive changes, instead of a single molecular change. Current evidence further suggests that the development of rationally designed combination therapy approaches is one of the most promising avenues toward providing clinically relevant benefits. These combinations may include inhibitors of EGFR, SHP2, SOS1, PI3K/AKT/mTOR, MEK, CDK4/6, YAP1, autophagy, and immune checkpoint targets, in addition to a novel generation of KRAS inhibitors, such as KRAS(ON)-state inhibitors, tri-complex inhibitors, pan-KRAS inhibitors, pan-RAS inhibitors, and KRAS degraders. Nonetheless, many of these methods require validation of their clinical utility in prospective studies using biomarkers, underscoring the importance of separating validated methodologies from potentially innovative therapies that are currently under investigation. Overall, the key learning that comes out of this literature is that effective management of *KRAS*-mutant tumors would require transcending monotherapeutic targeting of mutations to adopting more advanced precision oncology strategies that take into account and mitigate the development of resistance. Going forward, this would require convergence of multi-omics analyses, single-cell and spatial analyses, longitudinal monitoring using liquid biopsies, patient-derived functional models, and artificial intelligence-assisted biomarker identification, among other areas. These multi-disciplinary approaches would ensure rapid progress in the evolution of durable treatment paradigms based on biomarkers and the discovery of next-generation KRAS-directed therapies that will provide lasting clinical advantage in various KRAS-driven cancers.

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