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Kras-Targeted Therapies in Solid Tumors: From Undruggable to Clinical Application

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Abstract: For decades, KRAS the most frequently mutated oncogene in human cancers—remained a symbol of "undruggable" targets due to its smooth surface topology and high GTP/GDP affinity. However, recent breakthroughs in covalent inhibition, particularly for KRAS G12C, have redefined therapeutic possibilities across several solid tumors, including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and pancreatic ductal adenocarcinoma (PDAC). This review systematically explores KRAS structure, mutation-driven activation mechanisms, and the challenges of targeting KRAS. We analyze the emergence of direct inhibitors such as sotorasib and adagrasib, the development of next-generation compounds targeting G12D, G13D, and G12V, and the role of combination therapies to address resistance. We further evaluate resistance mechanisms, real-world clinical data, and predictive biomarkers, including circulating tumor DNA (ctDNA) and liquid biopsy. Finally, we discuss the integration of KRAS inhibitors into multi-modal oncology care and highlight future directions, including cost-effectiveness, pediatric applications, and pan-KRAS inhibition strategies. These advances collectively underscore a paradigm shift from "undruggable" to actionable, signaling a new era of biomarker-guided precision oncology.

Keywords: KRAS mutations, Solid tumors, Targeted therapy, Covalent inhibitors, Liquid biopsy, Precision oncology.

Introduction

KRAS (Kirsten rat sarcoma viral oncogene homolog), a member of the RAS family of small GTPases, has remained one of the most intensively studied oncogenes in cancer biology for over four decades. Mutations in KRAS drive oncogenesis in a wide spectrum of solid tumors, including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and pancreatic ductal adenocarcinoma (PDAC). These mutations result in constitutive activation of downstream signaling cascades, most

notably the MAPK and PI3K pathways, promoting unchecked cell proliferation, survival, and tumor progression (Pylayeva-Gupta, et al. 2011; Stephen, et al. 2014).
Historically, KRAS has been considered "undruggable" due to its smooth, shallow protein surface lacking the deep hydrophobic pockets necessary for high-affinity binding by small-molecule inhibitors. Furthermore, its high affinity for GTP/GDP (~picomolar range) makes competitive inhibition a formidable challenge (Cox, et al. 2014; Ostrem, et al. 2013). This pharmacological inaccessibility, coupled with functional redundancy among RAS isoforms and adaptive resistance mechanisms within cancer cells, stalled therapeutic advances for decades.
However, in recent years, a major scientific and clinical breakthrough occurred with the identification of an allosteric binding pocket unique to the KRAS G12C mutant—a common mutation in NSCLC and other cancers. This discovery has ushered in a new era of direct KRAS inhibition, culminating in the approval of the first mutant-selective KRAS inhibitors, such as sotorasib and adagrasib, and the emergence of a robust pipeline of next-generation agents (Canon, et al. 2019; Skoulidis, et al. 2021).
Given the centrality of KRAS in oncogenic signaling and the translational success of recent drug development efforts, it is essential to synthesize the evolving landscape of KRAS-targeted therapies. This review provides a comprehensive overview of KRAS biology in solid tumors, the structural and functional challenges that rendered it "undruggable," recent advancements in drug discovery, current clinical evidence, mechanisms of resistance, and the future directions that may eventually realize the full therapeutic potential of KRAS inhibition in precision oncology.

Kras Biology and Role in Solid Tumors

Structure and Function of KRAS Protein

KRAS (Kirsten rat sarcoma viral oncogene homolog) encodes a ~21 kDa small GTPase that belongs to the RAS superfamily, which also includes NRAS and HRAS. It functions as a binary molecular switch by alternating between an active GTP-bound state and an inactive GDP-bound state. Activation occurs upon stimulation by receptor tyrosine kinases (RTKs) via guanine nucleotide exchange factors (GEFs), most notably SOS1, facilitating GDP release and GTP binding. Conversely, GTP hydrolysis is catalyzed by intrinsic GTPase activity accelerated by GTPase-activating proteins (GAPs) (Figure 1) (Simanshu, et al. 2017; Prior, et al. 2020).
Upon activation, KRAS initiates downstream signaling through effector pathways, notably the RAF–MEK–ERK (MAPK) cascade and the PI3K–AKT–mTOR axis. These pathways collectively regulate essential cellular functions including proliferation, differentiation, apoptosis inhibition, and metabolic adaptation (Pylayeva-Gupta, et al. 2011).

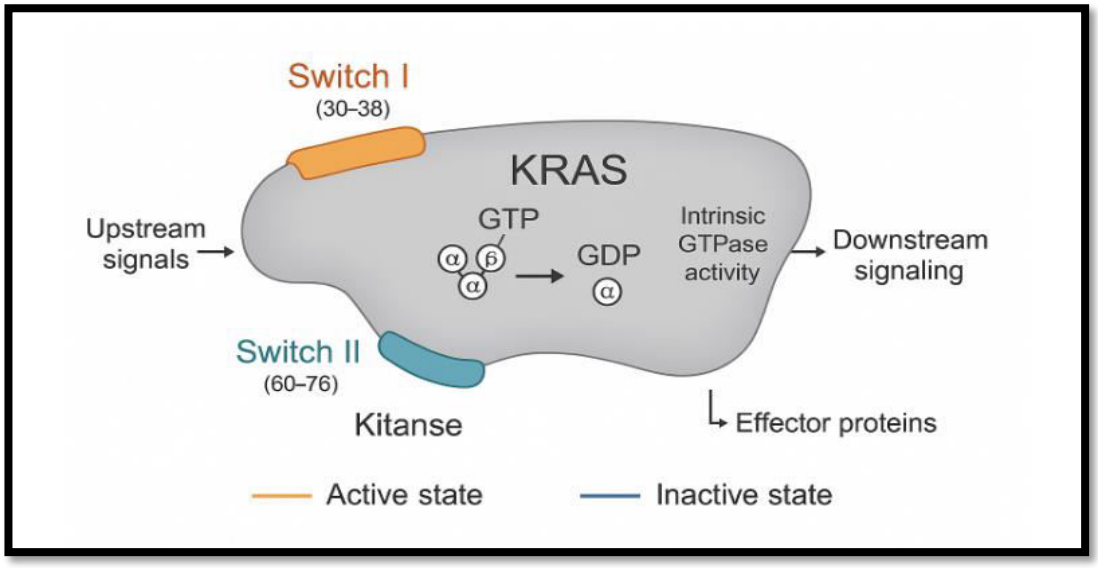

Figure 1. Structure and function of KRAS Protein

Mechanisms of KRAS Activation: Mutations and Upstream Signals

KRAS activation in oncogenesis is most frequently driven by somatic point mutations occurring in specific codons—particularly codons 12, 13, and 61—within the GTP-binding domain. These mutations impair the intrinsic GTPase activity of KRAS or render it resistant to regulation by GTPase-activating proteins (GAPs), such as neurofibromin (NF1), thereby locking the protein in a constitutively active GTP-bound state (Stephen, et al. 2014; Prior, et al. 2020). Among these, codon 12 mutations are the most prevalent and biologically significant, including G12D, G12V, and G12C. Each of these mutations leads to subtle yet distinct alterations in effector binding and downstream signaling amplitude. For instance, G12D preferentially activates PI3K-AKT signaling, while G12V is more biased towards RAF-MEK-ERK activation, contributing to differential tumor behavior and therapeutic vulnerabilities (Hunter, et al. 2015; Ihle, et al. 2012).

Beyond point mutations, KRAS can also be activated via upstream oncogenic signals in tumors where the gene is wild-type. In such cases, overexpression or hyperactivation of receptor tyrosine kinases (RTKs)—such as EGFR, FGFR, ALK, or HER2—leads to enhanced activation of the guanine nucleotide exchange factor (GEF) SOS1. This GEF promotes the exchange of GDP for GTP on KRAS, thereby shifting it into its active signaling conformation (Ebi, et al. 2011; Mainardi, et al. 2018). Similarly, mutations or amplifications in signaling adaptors like GRB2, SHC, and GAB1 can also potentiate KRAS activation in the absence of direct KRAS mutations. These upstream events are particularly relevant in cancers like glioblastoma, gastric cancer, and triple-negative breast cancer, where KRAS mutations are rare but MAPK signaling remains aberrantly active.

It is important to note that these mechanisms are not mutually exclusive. In many KRAS-mutant tumors, oncogenic signaling is further exacerbated by co-occurring alterations in upstream RTKs or parallel pathways. For example, EGFR amplification or MET overexpression has been observed in some KRAS-mutant NSCLC cases, potentially contributing to resistance to targeted therapies and altering the tumor's biological phenotype (Unni, et al. 2015; Awad, et al. 2021). Additionally, tumor suppressors such as PTEN or LKB1, when inactivated alongside KRAS mutations, further modulate the downstream signaling output, contributing to tumor heterogeneity, metabolic reprogramming, and therapeutic escape. These complex signaling networks underscore the necessity of integrative molecular profiling in KRAS-driven malignancies and provide rationale for combinatorial therapeutic approaches.

Prevalence and Distribution of KRAS Mutations in Solid Tumors

- **Non-Small Cell Lung Cancer (NSCLC)**

KRAS mutations are among the most frequent genetic alterations in NSCLC, occurring in approximately 25–30% of lung adenocarcinomas. The most common variant is the KRAS G12C mutation, accounting for ~13% of all NSCLC cases and ~40% of KRAS-mutated tumors, particularly associated with a history of tobacco use (Skoulidis, et al. 2015; Canon, et al. 2019).

- **Colorectal Cancer (CRC)**

In colorectal carcinoma, KRAS mutations occur in about 35–45% of cases, with the most frequent being G12D, G12V, and G13D. Unlike NSCLC, the G12C variant is rare in CRC. KRAS mutations are predominantly associated with resistance to EGFR-targeted therapies such as cetuximab and panitumumab (Douillard, et al. 2013; De Roock, et al. 2010).

- **Pancreatic Ductal Adenocarcinoma (PDAC)**

PDAC exhibits the highest prevalence of KRAS mutations among all human cancers, with rates exceeding 90%. The predominant variants are G12D (~50%) and G12V (~30%). These mutations are considered an initiating event in pancreatic carcinogenesis and are maintained throughout disease progression (Waddell, et al. 2015; Raphael, et al. 2017).

- **Other Tumors**

KRAS mutations are also reported, albeit at lower frequencies, in biliary tract cancers (~20%), endometrial cancers (~10–15%), ovarian mucinous carcinomas (~50%), and appendiceal cancers. The spectrum of mutations in these tumors can vary and may confer distinct biological behaviors (Barbareschi, et al. 2003; Nakamura, et al. 2015) (Table 1).

Table 1: Prevalence and Mutation Spectrum of KRAS in Solid Tumors

Tumor Type	Common KRAS Mutations	Approximate Prevalence (%)
NSCLC	G12C, G12V, G12D	25–30
Colorectal Cancer (CRC)	G12D, G13D, G12V	35–45
Pancreatic Cancer (PDAC)	G12D, G12V	>90
Biliary Tract Cancers	G12D, G13D	~20
Endometrial Cancer	G12D, G12A	10–15
Ovarian Mucinous Tumors	G12D, G12V	~50

Prognostic and Predictive Significance of KRAS Mutations

The prognostic value of KRAS mutations is highly tumor-type dependent. In NSCLC, KRAS mutations were once considered poor prognostic markers; however, recent evidence suggests that specific mutations like G12C have therapeutic implications and may be associated with distinct immunologic profiles (Skoulidis, et al. 2018). In CRC, KRAS mutations predict lack of response to anti-EGFR therapies, making molecular profiling essential before initiation of targeted treatment (Van Cutsem, et al. 2011). In PDAC, KRAS mutations are ubiquitous and associated with aggressive clinical behavior and limited responsiveness to standard chemotherapeutics.

Furthermore, co-mutations in genes such as TP53, STK11, KEAP1, or SMAD4 significantly alter the tumor phenotype and treatment responses in KRAS-mutant cancers. For instance, in NSCLC, co-mutations in STK11 are associated with poor response to immune checkpoint inhibitors, whereas TP53 co-mutations may indicate higher tumor immunogenicity (Skoulidis, et al. 2018; Romero, et al. 2020).

The "Undruggable" Nature of Kras: Challenges in Targeting

Lack of Deep Binding Pockets for Small Molecules

One of the most formidable challenges in targeting KRAS has been its structural intractability. Unlike kinases or hormone receptors that contain well-defined, druggable binding pockets, KRAS presents a relatively smooth and shallow surface with no prominent hydrophobic clefts to accommodate high-affinity small molecules (Cox, et al. 2014; Ostrem, et al. 2013). The absence of such a pocket precludes the classical lock-and-key model that underpins the success of most small-molecule inhibitors. This structural limitation significantly delayed the discovery of compounds that could selectively bind to and inhibit mutant KRAS in a biologically meaningful way.

High Affinity for GTP/GDP

KRAS functions as a molecular switch, cycling between its inactive GDP-bound and active GTP-bound conformations. In its wild-type or mutant form, KRAS exhibits picomolar affinity for both GDP and GTP, making it nearly impossible to competitively displace these nucleotides with a pharmacologic agent (Shields, et al. 2000; Stephen, et al. 2014). Furthermore, the high intracellular concentrations of GTP compared to GDP favor a constitutively active GTP-bound state in mutant KRAS, compounding the challenge of designing competitive inhibitors. These biochemical properties have historically deterred pharmaceutical efforts to directly interfere with the nucleotide-binding site.

Functional Redundancy with Other RAS Isoforms

KRAS shares significant sequence and structural homology with other RAS isoforms—HRAS and NRAS—which complicates the development of isoform-specific inhibitors. All three isoforms are capable of engaging similar downstream effectors such as RAF kinases, PI3K, and RalGDS (Matallanas, et al. 2011). Consequently, inhibitors targeting conserved regions risk cross-reactivity, potentially leading to off-target toxicities or diminished therapeutic index. Moreover, in certain cancers, alternative RAS isoforms may compensate for KRAS inhibition by maintaining downstream signaling, thereby reducing the efficacy of monotherapeutic approaches (Downward, et al. 2003; Jeng, et al. 2012).

Tumor Heterogeneity and Adaptive Resistance

Even when direct KRAS inhibition is achieved, intratumoral heterogeneity and dynamic adaptive responses limit the durability of treatment. KRAS-mutant tumors often harbor co-occurring mutations in tumor suppressor genes such as TP53, STK11, KEAP1, or SMAD4, which define molecular subtypes with distinct signaling dependencies and treatment outcomes (Skoulidis, et al. 2015; Romero, et al. 2020). Additionally, upon KRAS inhibition, feedback reactivation of receptor tyrosine kinases (e.g., EGFR, FGFR) or parallel signaling pathways (e.g., PI3K/AKT, JAK/STAT) can re-establish proliferative and survival signals, contributing to rapid emergence of resistance (Awad, et al. 2021). This plasticity underscores the need for combination therapies and adaptive treatment strategies to achieve sustained responses in KRAS-driven malignancies.

Breakthroughs in Direct Kras Inhibition

Discovery and Design of KRAS G12C Inhibitors

For decades, KRAS was labeled "undruggable" due to its lack of deep pockets for small-molecule binding and the picomolar affinity it holds for GTP/GDP. This paradigm was disrupted by the groundbreaking discovery of a cryptic allosteric

pocket—termed the switch-II pocket—found uniquely in the GDP-bound conformation of the KRAS G12C mutant. This cavity, transiently exposed due to a cysteine substitution at codon 12, enabled the rational design of covalent inhibitors that could selectively and irreversibly bind to mutant KRAS without affecting the wild-type protein (Ostrem, et al. 2013; Patricelli, et al. 2016).

The G12C mutation, in which glycine is replaced with a cysteine residue, accounts for approximately 13% of non-small cell lung cancers (NSCLC) and smaller fractions of colorectal and pancreatic cancers. Leveraging this substitution, medicinal chemists developed electrophilic inhibitors that form a covalent bond with the mutant cysteine side chain, locking KRAS in its inactive GDP-bound state and thereby preventing downstream signal transduction (Canon, et al. 2019). This approach marked the first instance of direct pharmacological KRAS inhibition with clinical efficacy.

Mechanism of Covalent Inhibition Targeting the Switch-II Pocket

KRAS G12C inhibitors function by exploiting the unique chemical reactivity of the cysteine residue in the mutant protein. These molecules bind within the switch-II pocket adjacent to the nucleotide-binding site and covalently modify the thiol side chain of Cys12, effectively trapping KRAS in its inactive GDP-bound conformation (Ostrem, et al. 2013). This conformational arrest disrupts downstream effector interactions with RAF, PI3K, and RalGDS, thereby blunting mitogenic and survival signaling. Importantly, this mechanism is conformation-specific, with efficacy limited to the GDP-bound form of KRAS—a state maintained only in tumors with the G12C mutation. As such, continuous cycling between GDP and GTP is a prerequisite for inhibitor engagement (Table 2)(Lito, et al. 2016).

Key Clinical Candidates

- **Sotorasib (AMG 510)**

Sotorasib, developed by Amgen, was the first KRAS G12C inhibitor to gain regulatory approval. In the phase II Code BreaK 100 trial, sotorasib demonstrated an objective response rate (ORR) of 37.1% and median progression-free survival (PFS) of 6.8 months in previously treated NSCLC patients with KRAS G12C mutations (Skoulidis, et al. 2021). Based on these results, the U.S. FDA granted accelerated approval in 2021 for sotorasib in advanced NSCLC. Beyond lung cancer, sotorasib has shown modest activity in KRAS G12C-mutant colorectal cancer (CRC), with lower response rates likely due to compensatory EGFR signaling in CRC cells (Hong, et al. 2020).

- **Adagrasib (MRTX849)**

Adagrasib, developed by Mirati Therapeutics, is another potent KRAS G12C inhibitor characterized by a longer half-life (~24 hours) and favorable

pharmacokinetic profile. In the KRYSTAL-1 study, adagrasib achieved a confirmed ORR of 43% and a median PFS of 6.5 months in patients with KRAS G12C-mutated NSCLC (Jänne, et al. 2022). The drug also demonstrated intracranial activity and durability of response, making it a promising candidate for brain-metastatic disease. In colorectal cancer, adagrasib combined with the EGFR inhibitor cetuximab improved response rates, validating the rationale for combination strategies to overcome resistance (Weiss, et al. 2023).

Table 2: Clinical Performance of KRAS G12C Inhibitors

Agent	Cancer Type	ORR (%)	PFS (months)	Trial	Status
Sotorasib	NSCLC	37.1	6.8	CodeBreaK 100	FDA Approved
Adagrasib	NSCLC	43.0	6.5	KRYSTAL-1	Phase II Complete
Adagrasib + Cetuximab	CRC	46.0	6.9	KRYSTAL-1	Ongoing

Limitations of G12C-Focused Therapies

While KRAS G12C inhibitors have demonstrated unprecedented progress in targeting a long-considered undruggable oncogene, several limitations persist. First, the therapeutic scope is inherently mutation-specific; these inhibitors are ineffective against other common KRAS mutations such as G12D, G12V, or Q61H, which are prevalent in pancreatic and colorectal cancers (Hallin, et al. 2020). Second, early clinical experience has revealed the emergence of both primary and acquired resistance mechanisms, including secondary mutations in the switch-II pocket, increased RTK signaling, and phenotypic changes such as epithelial-to-mesenchymal transition (Tanaka, et al. 2021; Awad, et al. 2021).

These challenges underscore the need for next-generation KRAS inhibitors targeting non-G12C mutations, as well as rational combination strategies involving RTK inhibitors, SHP2 inhibitors, or immune checkpoint blockade to enhance response durability and overcome resistance.

Next-Generation and Pan-Kras Inhibitors

Targeting KRAS G12D, G12V, and G13D Mutations

While KRAS G12C inhibitors have marked a paradigm shift in oncology, their utility is limited to a small subset of patients harboring this specific mutation. Other prevalent oncogenic KRAS variants such as G12D, G12V, and G13D—more common in colorectal and pancreatic cancers—remain without effective targeted therapies (Prior, et al. 2020). G12D is the dominant mutation in pancreatic ductal adenocarcinoma (PDAC) and colorectal cancer (CRC), and its targeting poses a

formidable challenge due to the lack of a reactive cysteine for covalent modification and the need for high selectivity against wild-type KRAS.

Recent advances have introduced non-covalent small molecules that exploit transiently accessible binding pockets in mutant KRAS G12D. One such agent, MRTX1133, developed by Mirati Therapeutics, has demonstrated nanomolar potency and selective inhibition of KRAS G12D in preclinical models, including patient-derived xenografts (Hallin, et al. 2020). Unlike covalent inhibitors of G12C, MRTX1133 targets the GDP-bound state via a reversible mechanism and shows minimal off-target effects. However, clinical trials are still pending, and issues such as bioavailability, feedback reactivation, and resistance need to be addressed.

Pan-KRAS Inhibitors and Broad Mutation Coverage

To overcome the allele-specific limitations of existing therapies, pan-KRAS inhibitors are being developed to target multiple KRAS mutant variants regardless of their specific codon substitution. One such approach involves disrupting KRAS–effector interactions or impeding post-translational modifications like farnesylation and palmitoylation, essential for KRAS membrane localization and function (Mazhab-Jafari, et al. 2015; Canon, et al. 2020). For example, BI-2852, a pan-KRAS inhibitor developed by Boehringer Ingelheim, binds to the KRAS switch-I/II pocket, blocking its interaction with downstream effectors such as RAF and PI3K (Kessler, et al. 2019).

Although these inhibitors demonstrate pan-mutant inhibition in vitro, their limited cell permeability, suboptimal pharmacokinetics, and modest antitumor efficacy in vivo have hindered clinical translation. Efforts are ongoing to refine the chemical scaffolds to improve their drug-like properties and facilitate oral administration. Meanwhile, other strategies under development aim to combine pan-KRAS inhibitors with immune checkpoint inhibitors or MAPK pathway inhibitors for synergistic outcomes.

KRAS-Selective Degraders and PROTACs

An innovative avenue for KRAS targeting involves proteolysis-targeting chimeras (PROTACs) and other targeted protein degraders. These molecules are bifunctional—one end binds to the target protein (KRAS), and the other recruits an E3 ubiquitin ligase, leading to proteasome-mediated degradation of the KRAS protein (Bond, et al. 2020). Early-stage studies have demonstrated selective KRAS degradation, particularly for mutant isoforms, offering a route to overcome resistance mechanisms associated with catalytic inhibition.

Unlike small-molecule inhibitors that require persistent target engagement, degraders induce irreversible KRAS elimination, potentially reducing signaling rebound. Examples include KRAS G12C-selective degraders based on sotorasib backbones and pan-RAS degraders under preclinical validation. The major hurdles

for PROTACs in this context are achieving isoform and allele selectivity, maintaining intracellular stability, and avoiding degradation of wild-type RAS proteins critical for normal cell function.

Allosteric Inhibitors and SOS1 Interaction Disruptors

Another compelling approach involves targeting KRAS activation upstream by disrupting its interaction with SOS1, the guanine nucleotide exchange factor (GEF) that facilitates GDP-to-GTP exchange. Inhibitors of SOS1 prevent KRAS activation, effectively maintaining it in the inactive GDP-bound state and blunting downstream signaling (Hofmann, et al. 2021). Several small molecules, such as BAY-293 and BI-3406, have shown potent inhibitory activity against SOS1–KRAS interaction, especially in KRAS-mutant cell lines.

These agents may act synergistically with direct KRAS inhibitors or MEK inhibitors and are currently being evaluated in combination regimens. Notably, SOS1 inhibitors offer the advantage of non-allele-specific blockade, broadening their potential utility across diverse KRAS-mutant tumors. Challenges remain in optimizing bioavailability and minimizing systemic toxicity, given SOS1's role in wild-type KRAS signaling.

Clinical Trials and Real-World Applications

Summary of Pivotal Phase I–III Trials of KRAS-Targeted Agents

The transition of KRAS from an "undruggable" oncogene to a clinically actionable target has been substantiated by several landmark trials. Sotorasib (AMG 510) was the first KRAS G12C inhibitor to enter clinical testing. In the CodeBreaK 100 trial, a multicenter Phase I/II study, sotorasib demonstrated a confirmed objective response rate (ORR) of 37.1%, with a median progression-free survival (PFS) of 6.8 months and overall survival (OS) of 12.5 months in previously treated NSCLC patients harboring KRAS G12C mutations (Skoulidis, et al. 2021). This trial laid the groundwork for accelerated FDA approval in May 2021.

Similarly, Adagrasib (MRTX849), another selective KRAS G12C inhibitor, was evaluated in the KRYSTAL-1 Phase I/II trial. Among heavily pretreated NSCLC patients, adagrasib achieved an ORR of 43%, median PFS of 6.5 months, and demonstrated promising intracranial efficacy in patients with brain metastases (Jänne, et al. 2022). In colorectal cancer (CRC), KRAS inhibitors showed lower efficacy due to EGFR-mediated feedback; however, when adagrasib was combined with cetuximab, the ORR improved to 46% with a median PFS of 6.9 months (Table 3) (Weiss, et al. 2023).

Tumor-Specific Responses and Survival Outcomes

KRAS G12C-targeted agents have shown tumor-type specific variations in response. In NSCLC, monotherapy with sotorasib or adagrasib has achieved durable responses, even in patients previously treated with platinum-based chemotherapy and immunotherapy. In colorectal cancer, however, monotherapy efficacy was modest—likely due to compensatory EGFR signaling. Therefore, dual inhibition strategies (e.g., KRAS G12C + EGFR blockade) are emerging as standard in this setting (Yaeger, et al. 2022).

In pancreatic cancer, where KRAS mutations—especially G12D—are nearly ubiquitous, G12C-directed agents benefit only a small subset (~2%). Early signals from MRTX1133 (KRAS G12D inhibitor) in preclinical studies show potential, but clinical translation is still awaited (Hallin, et al. 2020).

Combination Regimens: Chemotherapy, Immunotherapy, and Targeted Drugs

Due to the emergence of resistance and limited monotherapy efficacy in certain tumors, several combination strategies are under active clinical exploration:

- **Chemotherapy + KRAS inhibitors:** Trials like CodeBreaK 101 are evaluating combinations of sotorasib with platinum-doublets.
- **Immunotherapy + KRAS inhibitors:** KRAS mutations, particularly G12C, are associated with immune-infiltrated phenotypes. Sotorasib plus anti-PD-1/PD-L1 agents such as pembrolizumab or atezolizumab is being explored in multiple trials (Spira, et al. 2022).
- **Targeted combinations:** SOS1 inhibitors (e.g., BI-3406), SHP2 inhibitors (e.g., TNO155), and MEK inhibitors are being paired with KRAS inhibitors to prevent adaptive signaling feedback.

These approaches aim to increase depth of response, delay resistance, and broaden the therapeutic window, especially in tumors with high heterogeneity or co-mutations (e.g., TP53, STK11, KEAP1).

FDA and EMA Approvals, Companion Diagnostics

Sotorasib received accelerated FDA approval in 2021 for advanced KRAS G12C-mutant NSCLC, based on CodeBreaK 100 data. In January 2023, the EMA also authorized sotorasib in the EU, following a positive opinion from the CHMP. In 2022, adagrasib was granted breakthrough therapy designation by the FDA for use in NSCLC and CRC.

To ensure patient selection and therapeutic efficacy, companion diagnostics have become critical. The Guardant360 CDx and Thermo Fisher Oncomine Dx Target Test are FDA-approved liquid biopsy and tissue-based tests, respectively, for detecting

KRAS G12C mutations. These assays enable rapid stratification and treatment initiation in eligible patients.

Table 3: Key Clinical Trials of KRAS-Targeted and Pathway-Modulating Agents in Solid Tumors

Agent / Drug	Target / Type	Tumor Type	Study (Phase)	ORR (%)	PFS (months)	OS (months)	Combination
Sotorasib (AMG 510)	KRAS G12C Inhibitor	NSCLC	CodeBreaK 100 (II)	37.1	6.8	12.5	Monotherapy; approved by FDA/EMA
Adagrasib (MRTX849)	KRAS G12C Inhibitor	NSCLC	KRYSTAL-1 (II)	43.0	6.5	12.6	Monotherapy; pending full approval
Adagrasib + Cetuximab	KRAS G12C + EGFR	CRC	KRYSTAL-1 (II)	46.0	6.9	Not reported	Improved response in EGFR-driven CRC
JDQ443	KRAS G12C Inhibitor	NSCLC	KontRASt-01 (I/II)	~33.0	Ongoing	Ongoing	Novartis drug; under active trials
GDC-6036	KRAS G12C Inhibitor	NSCLC / Pan-Cancer	NCT04449874 (I)	~38.0 (NSCLC)	Ongoing	Ongoing	Genentech/Roche; early-phase trials
MRTX1133	KRAS G12D Inhibitor	Pancreatic / CRC	Preclinical	>90 (models)	Preclinical	Preclinical	Potent non-covalent G12D agent
BI 3406 + Trametinib	SOS1 Inhibitor + MEK	KRAS-mutant solid tumors	Ongoing (I/II)	Early signal	Ongoing	Ongoing	Prevents upstream activation of KRAS
TNO155 + Sotorasib	SHP2 Inhibitor + G12C	NSCLC / CRC	NCT04330664 (I)	Not reported	Ongoing	Ongoing	Blocks feedback reactivation loop

RMC-6291	KRAS G12C Inhibitor (BiS)	NSCLC	Phase I (ongoing)	Prelim signal	Ongoing	Ongoing	Bivalent, potent selective inhibitor
BI-2852	Pan-KRAS Inhibitor	In vitro / preclinical	Discovery	Variable	Preclinical	Preclinical	First pan-KRAS switch-I/II inhibitor

Mechanisms of Resistance to Kras Inhibitors

The clinical success of KRAS G12C inhibitors like sotorasib and adagrasib has marked a significant milestone in targeted therapy. However, their long-term efficacy is often curtailed by acquired resistance, arising from both on-target and off-target mechanisms. Understanding these resistance pathways is critical to developing durable treatment strategies and rational combination regimens.

On-Target Mutations: Secondary KRAS Mutations

One of the most direct resistance mechanisms involves secondary mutations in the KRAS gene itself, which impair the binding of covalent inhibitors to the switch-II pocket. These on-target mutations include alterations such as Y96D, H95Q, and G13D, which either modify the structural conformation of the binding site or affect the drug's covalent locking mechanism (Tanaka, et al. 2021; Awad, et al. 2021).

For example, the Y96D mutation disrupts the key hydrogen bonding network required for G12C inhibitor binding, leading to reduced potency of agents like sotorasib and adagrasib. These mutations can arise under therapeutic pressure and often exist alongside the original G12C driver mutation, resulting in heterogeneous KRAS allele profiles within the tumor. This complicates treatment decisions, as newer-generation inhibitors may be required to address multiple KRAS variants simultaneously.

Bypass Pathway Activation: EGFR, MET, BRAF, and Others

Another common resistance route is bypass pathway activation, where tumors rewire upstream or parallel signaling nodes to restore downstream MAPK or PI3K pathway activity, independent of KRAS inhibition. For instance, EGFR reactivation has been frequently observed in KRAS G12C-mutant colorectal cancer, leading to diminished responses to monotherapy and necessitating the use of EGFR inhibitors in combination regimens (Yaeger, et al. 2022; Johnson, et al. 2021).

Additionally, amplification or activation of other receptor tyrosine kinases (RTKs) such as MET, HER2, or FGFR1, or downstream effectors like BRAF or MEK, can re-

establish proliferative signals. In some resistant cases, NF1 loss or PIK3CA mutations have also been reported, especially in lung and pancreatic cancers (Tanaka, et al. 2021; Ryan, et al. 2022). These findings suggest that KRAS inhibition may create selective pressure for alternative oncogenic drivers, thereby promoting adaptive resistance.

Tumor Plasticity and Heterogeneity

KRAS-mutant tumors often display substantial inter- and intratumoral heterogeneity, shaped by co-occurring mutations in genes like TP53, STK11, KEAP1, and SMAD4, which contribute to variable therapeutic responses and immune landscapes (Skoulidis, et al. 2015; Romero, et al. 2020). Such heterogeneity fosters tumor plasticity, wherein subclonal populations dynamically adapt to targeted inhibition by undergoing lineage reprogramming or phenotype switching.

This plasticity is particularly evident in epithelial-to-mesenchymal transition (EMT), a process that reduces dependency on KRAS-driven pathways and is associated with resistance to both direct inhibitors and immune checkpoint blockade. Moreover, transdifferentiation into neuroendocrine phenotypes has been reported in certain resistant settings, especially in lung cancer (Chabon, et al. 2022). These findings underscore the complexity of KRAS-driven cancers and the need for multi-faceted therapeutic strategies.

Strategies to Overcome Resistance: Sequential Therapy and Dual Inhibition

Addressing resistance requires a mechanism-informed therapeutic design. One promising approach is sequential therapy, where alternating or rotating inhibitors with differing binding profiles may mitigate clonal selection and resistance (Canon, et al. 2019). Additionally, dual inhibition strategies—combining KRAS G12C inhibitors with upstream RTK inhibitors (e.g., EGFR, SHP2), downstream MAPK pathway inhibitors (e.g., MEK, ERK), or immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1)—are actively being investigated.

Clinical trials such as CodeBreaK 101 and KRYSTAL-7 are testing these combinations, aiming to delay or prevent the emergence of resistance. The incorporation of biomarker-driven monitoring using liquid biopsies (ctDNA) is also being explored for early detection of resistance mutations and real-time treatment adaptation (Awad, et al. 2021; Tanaka, et al. 2021).

Emerging Biomarkers and Precision Oncology Approaches

The advent of KRAS-targeted therapy has significantly advanced the field of personalized oncology. However, due to the molecular heterogeneity and dynamic evolution of KRAS-driven tumors, patient stratification and real-time monitoring using biomarkers have become critical for optimizing therapeutic outcomes.

Current efforts in precision oncology focus on identifying predictive and prognostic biomarkers using liquid biopsy, circulating tumor DNA (ctDNA), and comprehensive molecular profiling to guide treatment selection and resistance management.

Role of ct DNA, Liquid Biopsy, and Molecular Profiling

Circulating tumor DNA (ctDNA) represents fragmented tumor-derived nucleic acids present in the bloodstream, offering a non-invasive means to detect somatic mutations, track clonal evolution, and monitor treatment response. In the context of KRAS-mutant cancers, ctDNA assays enable real-time assessment of KRAS mutation alleles (e.g., G12C, G12D) and identification of emerging resistance mutations such as Y96D, H95Q, or G13D (Reckamp, et al. 2022; Awad, et al. 2021).

Liquid biopsies have demonstrated high concordance with tissue-based genotyping and are increasingly integrated into clinical trials and routine oncology practice. For instance, the Guardant360 CDx test has been approved as a companion diagnostic for detecting KRAS G12C mutations in non-small cell lung cancer (NSCLC), facilitating rapid eligibility assessment for sotorasib therapy (US FDA, 2021). In addition to mutation tracking, ctDNA kinetics serve as a surrogate marker for tumor burden and therapeutic efficacy, with declining allele frequencies correlating with radiologic response (Jänne, et al. 2022).

Comprehensive next-generation sequencing (NGS) platforms further enhance molecular characterization by identifying co-mutations (e.g., TP53, STK11, KEAP1) that influence immune responsiveness, drug metabolism, and pathway reactivation—factors critical to therapy personalization (Skoulidis, et al. 2015).

Predictive Biomarkers for Response/Resistance to KRAS-Targeted Therapy

KRAS mutation status alone is insufficient to predict uniform responses across all tumor types and settings. Several predictive biomarkers have emerged to refine patient selection and forecast treatment outcomes. In NSCLC, co-occurring mutations in STK11 and KEAP1 are associated with poor response to both immunotherapy and KRAS inhibitors, likely due to their role in creating an immune-suppressive tumor microenvironment (Skoulidis, et al. 2018).

Similarly, EGFR pathway activation—via receptor overexpression, ligand upregulation, or gene amplification—is a key resistance determinant in colorectal cancer, necessitating combination strategies with EGFR inhibitors (Yaeger, et al. 2022). Biomarkers such as PD-L1 expression, tumor mutational burden (TMB), and T-cell infiltration are also being evaluated to predict the synergistic benefit of combining KRAS inhibition with immune checkpoint blockade.

Importantly, ctDNA profiling of resistant clones has enabled early detection of secondary KRAS mutations and bypass pathway alterations, supporting adaptive therapeutic adjustments and early clinical intervention (Awad, et al. 2021).

Personalized Treatment Algorithms in KRAS-Mutant Tumors

The integration of molecular diagnostics, real-time biomarker surveillance, and tumor-specific biology has paved the way for precision treatment algorithms tailored to KRAS-mutant malignancies. In NSCLC, standard practice now involves NGS-based KRAS genotyping, followed by therapy selection: sotorasib or adagrasib for G12C, or immunotherapy/chemotherapy based on additional biomarkers such as PD-L1 or STK11 status (Lazzari, et al. 2023).

In colorectal cancer, the presence of KRAS G12C mutation alongside EGFR amplification may prompt the use of adagrasib + cetuximab combinations. For pancreatic cancer, where G12D mutations dominate, investigational agents like MRTX1133 and pan-KRAS pathway combinations (e.g., SOS1 or SHP2 inhibitors) are expected to shape future personalized regimens.

Furthermore, AI-driven platforms are being developed to integrate genomic, transcriptomic, and radiomic data to generate individualized response models and resistance risk scores (Li, et al. 2022). Such innovations will support dynamic treatment adaptation and improve long-term survival outcomes in this highly heterogeneous patient population.

Future Directions and Challenges

Despite the remarkable progress in targeting KRAS—once deemed "undruggable"—several critical gaps and emerging frontiers persist. As therapeutic pipelines mature, oncology must confront challenges related to broader mutation coverage, durable efficacy, accessibility, and translational expansion to underserved cancer types and patient populations.

Expanding Target ability beyond G12C

The majority of current clinical success is limited to tumors harboring the KRAS G12C mutation, which represents only a subset of KRAS-driven malignancies. G12D and G12V mutations, prevalent in pancreatic, colorectal, and endometrial cancers, remain inadequately targeted due to the lack of a reactive cysteine residue necessary for covalent binding (Prior, et al. 2020; Canon, et al. 2019). Recent advances, such as MRTX1133, a non-covalent inhibitor of KRAS G12D, have shown high preclinical potency and selectivity, offering a promising new avenue (Hallin, et al. 2020). Nevertheless, challenges in oral bioavailability, metabolic stability, and resistance profiling need to be overcome before such agents enter mainstream clinical use.

Parallel approaches—such as pan-KRAS inhibitors, KRAS-selective degraders, and allosteric SOS1 or SHP2 inhibitors—aim to target common structural features or regulatory interactions of KRAS rather than specific mutations, potentially offering broader clinical utility (Kessler, et al. 2019; Hofmann, et al. 2021).

Long-Term Safety and Resistance Surveillance

With increased use of KRAS inhibitors in earlier lines of therapy and combination regimens, long-term safety profiles must be better understood. Early-phase trials report manageable toxicity, primarily gastrointestinal and hepatic (Jänne, et al. 2022), but extended exposure, especially in combination therapies, could pose cumulative or synergistic adverse effects. Furthermore, as patients remain on therapy longer, the risk of secondary resistance mutations and tumor evolution increases.

To mitigate this, integrating serial liquid biopsies, real-time ctDNA monitoring, and AI-driven mutation tracking into clinical care can provide early warnings of resistance development and inform dynamic treatment adjustments (Awad, et al. 2021; Reckamp, et al. 2022). Establishing global resistance registries and incorporating molecular surveillance into post-marketing studies will be essential for refining therapeutic durability and retreatment strategies.

Integrating KRAS Inhibitors into Multi-Modal Treatment Paradigms

While KRAS G12C inhibitors are approved as monotherapies, the future lies in their integration with chemotherapy, radiotherapy, immunotherapy, and other targeted agents. Preclinical and clinical studies have demonstrated synergy between KRAS inhibitors and immune checkpoint inhibitors, EGFR inhibitors, and MEK/SHP2 pathway blockers, particularly in tumors with complex mutational landscapes (Spira, et al. 2022; Yaeger, et al. 2023). This multi-modal approach could:

- Enhance response rates,
- Suppress feedback resistance,
- Address intra-tumoral heterogeneity,
- Reprogram the tumor microenvironment.

However, this will require careful toxicity management, optimized sequencing, and biomarker-driven patient selection to maximize benefit while minimizing harm.

Cost-Effectiveness and Access Considerations

KRAS inhibitors are high-cost therapies, raising significant concerns about accessibility and health economics, especially in low- and middle-income countries (LMICs). Sotorasib and adagrasib are priced at over $17,000/month in high-income settings (ICER, 2022), placing strain on public health systems and insurance frameworks. Although cost-effectiveness models suggest favorable quality-adjusted life years (QALY) when used in biomarker-enriched populations (Pearson, et al. 2022), broad adoption will require price negotiation, generic competition, and regulatory support.

Patient assistance programs and value-based reimbursement models may help, but disparities in molecular testing access, especially liquid biopsy infrastructure, remain significant hurdles in LMICs.

KRAS in Rare Tumors and Pediatric Oncology

While most clinical research focuses on NSCLC, CRC, and PDAC, KRAS alterations are also present in rare adult and pediatric cancers, including embryonal rhabdomyosarcoma, low-grade gliomas, cholangiocarcinomas, and appendiceal neoplasms (Kobayashi, et al. 2021; Pfister, et al. 2020). These populations often lack access to clinical trials or biomarker-based therapies due to rarity, age restrictions, or genomic variability.

Expanding KRAS-directed therapy into these areas will require:

- Dedicated basket trials stratified by mutation rather than tumor type,
- Age-appropriate pharmacokinetics and dosing studies,
- Cross-disciplinary collaboration among oncologists, pediatricians, and regulatory bodies.

Precision oncology for KRAS-mutant tumors must evolve toward a mutation-agnostic, tissue-inclusive model to serve these underrepresented cohorts.

Conclusion

The evolution of KRAS from an "undruggable" oncogene to a clinically actionable target marks one of the most transformative advances in contemporary oncology. For decades, the absence of a suitable binding pocket and the biochemical challenges posed by its high-affinity GTP/GDP binding thwarted drug development. However, the recent discovery and approval of KRAS G12C inhibitors, such as sotorasib and adagrasib, have broken this paradigm, demonstrating tangible clinical benefit in patients with non-small cell lung cancer and other solid tumors.

This progress underscores the importance of structure-guided drug design, molecular modeling, and high-throughput screening, which together catalyzed a renaissance in RAS-directed therapies. More importantly, it has revitalized research on non-G12C KRAS mutations (e.g., G12D, G13D, G12V), broadened the therapeutic landscape through pan-KRAS inhibitors, PROTACs, and upstream regulators (e.g., SHP2, SOS1), and highlighted the necessity of combination strategies to circumvent resistance and tumor heterogeneity.

The future of KRAS-targeted therapy lies not only in drug discovery but in the integration of biomarker-driven precision oncology. The role of ctDNA, liquid biopsies, and NGS platforms will be pivotal for patient stratification, response monitoring, and early detection of resistance. Furthermore, expanding access to KRAS inhibitors across tumor types, rare cancers, and pediatric settings—along with ensuring cost-effectiveness and global availability—remains an essential goal.

As innovation continues to unravel the complexities of KRAS biology, its therapeutic relevance will increasingly shift from niche use to routine integration in standard oncology care. This shift calls for robust clinical frameworks, multidisciplinary

collaboration, and a commitment to equitable precision medicine that ensures every eligible patient benefits from this historic breakthrough.

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