

KRAS-targeted therapy in oncology: From four decades of failed attempts to a new era of precision medicine

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Abstract

Mutations in the KRAS (Kirsten Rat Sarcoma Viral Proto-oncogene) gene represent among the most prevalent oncogenic drivers in human malignancies, occurring in approximately 25% of all solid tumors. For more than four decades, KRAS was considered pharmacologically intractable due to the protein's picomolar affinity for GTP/GDP and the absence of accessible allosteric binding sites. The identification of the switch-II pocket (S-IIP) and subsequent development of mutation-selective covalent inhibitors targeting the KRAS G12C mutant fundamentally altered this paradigm. Sotorasib and adagrasib, the first approved KRAS G12C inhibitors, have demonstrated meaningful clinical activity in NSCLC and, in combination with anti-EGFR agents, in colorectal cancer. However, both drugs achieve only modest objective response rates of 30–43% in NSCLC with median progression-free survival of approximately six months, substantially below outcomes achieved with targeted therapies directed at EGFR or ALK. Acquired resistance emerges rapidly through on-target KRAS mutations, bypass signaling, and phenotypic plasticity. An expanding pipeline of next-generation agents targeting G12D, G12V, and pan-KRAS approaches offers the first plausible therapeutic options for pancreatic and other KRAS-driven cancers beyond G12C. This narrative review critically evaluates the biological basis of KRAS oncogenesis, the pharmacological obstacles that delayed drug development, the clinical performance and limitations of approved inhibitors, resistance mechanisms and rational combination strategies, and the evidence base and uncertainties surrounding next-generation therapeutic approaches.

Keywords: KRAS; Oncology; Targeted therapy; Sotorasib; Adagrasib; KRAS G12C; KRAS G12D; Pan-KRAS inhibitors; Resistance; RAS(ON) inhibitors; Pancreatic cancer

1. Introduction

KRAS mutations occupy a central position in the molecular pathology of human cancer. The gene encodes a 21-kDa GTPase that cycles between an active GTP-bound state and an inactive GDP-bound state, functioning as a binary molecular switch that regulates cell proliferation, survival, and metabolic adaptation [1, 3]. Downstream effector cascades activated by GTP-bound KRAS include the RAF/MEK/ERK mitogen-activated protein kinase (MAPK) pathway, the PI3K/AKT/mTOR axis, and the RALGDS signaling network [17, 18]. Oncogenic point mutations at codons 12, 13, and 61 impair intrinsic GTPase activity and abrogate responsiveness to GTPase-activating proteins (GAPs), locking KRAS in a constitutively active conformation that sustains unrestrained mitogenic signaling [1, 3, 4].

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KRAS mutations are present in approximately 90% of pancreatic ductal adenocarcinomas (PDAC), 30–40% of colorectal cancers (CRC), and 25–30% of non-small cell lung cancers (NSCLC) [2, 19]. The specific amino acid substitutions show striking tumor-type selectivity: KRAS G12D predominates in PDAC (~40%), G12C is most prevalent in NSCLC (~13%), and G12V is common in both CRC and PDAC [2, 20]. This allelic distribution has fundamental pharmacological implications, as each substitution confers distinct biochemical properties that determine susceptibility to inhibitor classes [21].

Despite KRAS being identified as a human oncogene in 1982, clinically useful pharmacological inhibition remained elusive for nearly four decades [3]. The protein's structural features – a shallow nucleotide-binding site with picomolar affinity for GTP and a surface largely devoid of tractable allosteric pockets – led to widespread use of the term 'undruggable' [3, 4]. This review examines the transition from that era of pharmacological pessimism to the current landscape of approved therapies and an active development pipeline, while also engaging critically with the limitations of current approaches and the barriers that remain.

2. KRAS Biology and Oncogenic Mechanisms

2.1. Structural Features of KRAS

The KRAS protein belongs to the RAS superfamily of small GTPases and shares the canonical G-domain architecture comprising five phosphate-binding elements and the switch I (residues 30–38) and switch II (residues 59–76) regions [3, 22]. These switch regions undergo conformational changes upon GTP/GDP exchange that determine effector binding competence. The P-loop (G1 motif) coordinates the β - and γ -phosphates of GTP, while the DxxG motif in switch II engages the γ -phosphate and the catalytic water molecule essential for hydrolysis [3, 22]. The C-terminal CAAX motif undergoes farnesylation, a modification essential for membrane association and biological activity [23].

Wild-type KRAS possesses an intrinsic GTPase rate of approximately 0.02 min^{-1} , augmented up to 100,000-fold by GAPs including neurofibromin (NF1) [3, 22]. This stimulation depends on an arginine 'finger' residue from the GAP inserting into the active site. Mutations at Gly12 introduce steric hindrance that prevents arginine finger coordination, effectively abolishing GAP-stimulated hydrolysis [3, 4]. Mutations at Gln61 remove the catalytic glutamine required for nucleophilic water activation [3]. These biochemical distinctions between alleles have direct relevance to drug tractability: G12C retains relatively higher GTPase activity and GDP-state dwell time compared to G12D or G12V, which is the structural rationale enabling the switch-II covalent inhibitor strategy [21, 22].

2.2. Downstream Effector Pathways and Feedback Signaling

Active GTP-bound KRAS engages multiple effector proteins via their RAS-binding or RAS association domains [17,18]. The three major downstream axes are: (1) the RAF/MEK/ERK MAPK cascade, governing transcriptional programs for proliferation and survival [17]; (2) the PI3K/AKT/mTOR axis, which coordinates growth, protein synthesis, and metabolic adaptation via PIP3 generation [18]; and (3) RALGDS family proteins, which activate RAL GTPases to modulate vesicle trafficking and transcriptional responses [18]. Feedback regulation profoundly complicates therapeutic targeting [24, 25]. Pharmacological inhibition of downstream effectors reliably induces compensatory RTK upregulation, activating SOS1 – the principal KRAS guanine nucleotide exchange factor (GEF) – through SHP2 adaptor signaling, thereby restoring GTP-loaded active KRAS [24, 25]. This feedback loop represents a fundamental mechanistic constraint that limits the durability of monotherapy targeting any single node in this network [24].

SHP2 (encoded by PTPN11) functions as a critical relay between activated receptor tyrosine kinases (RTKs) and RAS activation [25, 26]. SOS1 in turn promotes nucleotide exchange, reloading oncogenic KRAS with GTP within hours of drug-induced RAS pathway suppression [24, 27]. Understanding this adaptive signaling has directly motivated the development of SHP2 and SOS1 inhibitors as combination partners for KRAS inhibitors [25–27].

2.3. Mutation-Specific Oncogenic Properties

Different KRAS alleles are not functionally equivalent. G12C retains higher intrinsic GTP hydrolysis rates than G12D or G12V, allowing GDP-state occupancy substantial enough to enable covalent engagement by switch-II pocket inhibitors [21, 22]. In contrast, G12D and G12V are more robustly locked in the GTP-bound active state, making them intrinsically less amenable to GDP-state-selective inhibition [21]. KRAS G12R shows impaired PI3K γ interaction and reduced RALGDS engagement, possibly contributing to the modestly better prognosis observed in some G12R-mutant PDAC compared to G12D [20, 21]. Comutations in STK11 (LKB1) and KEAP1, prevalent in KRAS-mutant NSCLC, suppress innate immune surveillance and oxidative stress response, attenuating responsiveness to immunotherapy [28, 29].

Table 1 Frequency of major KRAS mutant alleles by tumor type (% of KRAS-mutant tumors of that histological type).

Tumor Type	G12C (%)	G12D (%)	G12V (%)	G12R (%)	G13D (%)	Other / WT (%)
NSCLC	~13	~17	~21	~1	~2	~6 / 75
Colorectal Cancer	~3–4	~13	~9	<1	~8	~7 / 60
PDAC	~1	~40	~29	~15	<1	~15 / 8
Endometrial	<1	~16	~12	<1	~4	~8 / 60
Cholangiocarcinoma	<1	~10	~4	<1	<1	~6 / 80
Bladder Cancer	~2	~5	~4	<1	~2	~2 / 85
All solid tumors (overall)	~3–4	~10–12	~7–8	~2	~3	~5 / 75

Approximate values based on published epidemiological analyses, TCGA data, and large genomic profiling cohorts [2,19,20]. Percentages represent proportion among KRAS-mutant tumors; 'Other / WT (%)' column reports the approximate proportion of wild-type KRAS tumors overall for context. PDAC = pancreatic ductal adenocarcinoma; NSCLC = non-small cell lung cancer

3. Four Decades of Failed Therapeutic Approaches

3.1. Direct Active Site Inhibition: Thermodynamic Barriers

Early efforts to develop competitive inhibitors of the GTP/GDP-binding site were abandoned on thermodynamic grounds. Intracellular GTP concentrations in the millimolar range, combined with picomolar dissociation constants for RAS–nucleotide complexes, rendered competitive displacement impractical at achievable drug concentrations [3, 4]. Unlike kinases with deep hydrophobic ATP-binding pockets, the KRAS GTPase surface lacked obvious high-affinity allosteric cavities accessible to drug-like small molecules [3, 4]. Fragment-based screening in the early 2000s identified shallow surface sites near the switch I/II interface, but compounds showed poor affinity and no cellular activity [5].

3.2. Farnesyltransferase Inhibitors: A Cautionary Example

Recognizing KRAS membrane anchoring dependence on farnesylation, multiple companies developed potent farnesyltransferase inhibitors (FTIs), including tipifarnib and lonafarnib, in the 1990s and 2000s [23, 30]. These agents showed impressive preclinical activity but failed consistently in clinical trials [30]. The mechanistic explanation emerged post hoc: upon farnesyltransferase inhibition, KRAS4B and NRAS undergo alternative geranylgeranylation by geranylgeranyltransferase-I (GGT-I), preserving membrane anchoring [23, 30]. HRAS, not a GGT-I substrate, remained FTI-sensitive, explaining why preclinical efficacy in HRAS-driven models did not translate to KRAS-mutant human cancers [30]. This cautionary precedent illustrates the risk of insufficient mechanism-of-resistance characterization in translational oncology.

3.3. Indirect Pathway Targeting: Two Decades of Limited Progress

Extensive clinical investigation targeting downstream effectors yielded similarly disappointing results. MEK inhibitors (trametinib, selumetinib, cobimetinib) produced limited single-agent activity in KRAS-mutant cancers despite robust pathway engagement, attributable to rapid feedback RTK/SOS1 rebound [24, 25]. PI3K/mTOR combinations showed additive but clinically insufficient activity. The emerging field of SHP2 and SOS1 inhibitors demonstrated mechanistic rationale [25–27] but limited monotherapy activity, given their dependence on upstream RTK input. A recurring cycle of target selection, inhibitor development, modest or transient efficacy, resistance characterization, and target abandonment reinforced the impression that KRAS-driven oncogenic circuitry was inherently pharmacologically resilient – a conclusion ultimately disproven by structural biology rather than pathway logic.

4. The Switch-II Pocket and First-Generation KRAS G12C Inhibitors

4.1. Structural Discovery and Covalent Strategy

The field was transformed in 2013 when Ostrem, Shokat, and colleagues described a cryptic allosteric binding site in KRAS emerging transiently in the GDP-bound state, subsequently designated the switch-II pocket (S-IIP) [5]. This discovery was initially made in the context of KRAS G12C, where the mutant cysteine at position 12 creates an electrophilic handle in proximity to the S-IIP in the GDP conformation [5, 6]. Covalent engagement via an acrylamide

warhead eliminates the thermodynamic penalty of competing with GTP: instead of displacing a picomolar-affinity nucleotide, the inhibitor forms an irreversible thioether bond with Cys12 while KRAS cycles transiently through the GDP-bound state [5, 6]. This mutation-selective covalent strategy achieves exquisite allele specificity while simultaneously exploiting the higher GDP-state dwell time unique to the G12C allele [5, 21].

4.2. Sotorasib: First Approved KRAS Inhibitor

Amgen's AMG 510 (sotorasib) emerged from systematic optimization of S-IIP engagement and covalent chemistry [6]. In the Phase I/II CodeBreaK 100 trial, sotorasib achieved an ORR of 37.1% and median PFS of 6.3 months in previously treated NSCLC patients harboring KRAS G12C mutations [7]. These results led to FDA accelerated approval in May 2021. The confirmatory Phase III CodeBreaK 200 trial compared sotorasib to docetaxel in second-line NSCLC, demonstrating improved ORR (28% vs 13%) and PFS (5.6 vs 4.5 months) but no statistically significant overall survival (OS) benefit (10.6 vs 11.3 months) [31]. The absence of OS improvement despite superior response and PFS raises important questions about the adequacy of second-line KRAS inhibition as a strategy and the impact of post-progression treatments on survival endpoints.

4.3. Adagrasib: Differentiated Pharmacokinetics and CNS Activity

Mirati Therapeutics' MRTX849 (adagrasib) incorporated a longer half-life (~23 vs ~5 hours for sotorasib) enabling sustained target coverage, and demonstrated meaningful CNS penetration in preclinical studies [8,32]. In KRYSTAL-1, adagrasib achieved an ORR of 42.9% and median PFS of 6.5 months in second-line NSCLC – broadly comparable to sotorasib [8]. Among patients with active brain metastases, adagrasib achieved an intracranial ORR of 31.6% [32], establishing it as a viable option in a subpopulation historically excluded from targeted therapy trials. FDA accelerated approval was granted in December 2022. Adagrasib is a potent CYP3A4 inhibitor, requiring pharmacokinetic attention to co-medications including anticoagulants and other oncology drugs commonly co-prescribed in this patient population [8].

A notable limitation of both approved G12C inhibitors is their positioning in the second-line or later setting for NSCLC, while first-line therapy remains chemoimmunotherapy or immunotherapy based on PD-L1 status [11]. This contrasts sharply with the standard-of-care for EGFR- and ALK-driven NSCLC, where targeted therapy is first-line and achieves substantially higher response rates and longer progression-free survival [11]. The reasons for this gap include uncertainty about synergy or toxicity interactions with immunotherapy partners in the first-line setting, and the modest absolute magnitude of G12C inhibitor efficacy compared to EGFR/ALK inhibitors that have established their dominance over chemotherapy in randomized trials.

5. Colorectal Cancer: EGFR Feedback and the Rationale for Combination Therapy

5.1. Why G12C Monotherapy Fails in Colorectal Cancer

KRAS G12C mutations account for approximately 3–4% of colorectal cancers [20]. Early monotherapy experience was disappointing: response rates of only 7–10% were observed [9, 10], a striking contrast to ~40% ORR in NSCLC. Translational analyses identified rapid and robust feedback reactivation of EGFR signaling as the dominant mechanism: KRAS G12C inhibition in CRC cells triggers compensatory EGFR upregulation and ligand-mediated RTK-SOS1 activation, restoring GTP-loaded KRAS within hours [24, 33]. NSCLC cells are relatively insensitive to this feedback mechanism due to lower baseline EGFR expression and more frequent co-mutations in other RTK pathways [24, 33]. This stark tumor-type difference illustrates the critical importance of the molecular context in which oncogenic KRAS operates.

5.2. FDA-Approved Combination Regimens

The logical therapeutic response – vertical combination with anti-EGFR agents – produced clinically meaningful results. The KRYSTAL-1 expansion cohort enrolled 94 patients with locally advanced or metastatic KRAS G12C-mutant CRC who had received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. Adagrasib combined with cetuximab achieved an ORR of 34% with a median duration of response of 5.8 months [9]. The FDA granted accelerated approval in June 2024, marking the first KRAS inhibitor approval outside lung cancer. In January 2025, sotorasib combined with panitumumab received FDA approval for the same indication based on the CodeBreaK 300 trial, which showed an ORR of 26% versus 0% in the control arm with a PFS benefit of 5.6 versus 2.2 months [10]. While these approvals represent meaningful advances for a previously untreatable subpopulation, response rates remain moderate and duration of response limited. The EGFR feedback rationale is now well-established mechanistically; whether further upstream targeting (SHP2, SOS1) on top of EGFR blockade will yield deeper or more durable responses remains an open clinical question.

6. Resistance to KRAS G12C Inhibitors: Mechanisms and Countermeasures

6.1. On-Target Resistance

Median PFS of 5–7 months with KRAS G12C inhibitor monotherapy reflects the near-inevitable emergence of acquired resistance. On-target resistance involves secondary mutations within KRAS that disrupt covalent bond formation or stabilize the GTP-bound conformation. Post-progression genomic analyses have identified resistance mutations at the S-IIP interface, including R68S, H95D/Q/R, and Y96C, which alter pocket geometry or reduce covalent adduct stability [12, 13]. A clinically important pattern is the emergence of non-G12C KRAS mutations (G12D, G12V, G13D) through clonal selection, reflecting bypass of the targeted allele rather than direct drug resistance [12]. KRAS amplification similarly bypasses the inhibitor by increasing the total pool of active KRAS signaling beyond inhibitor occupancy capacity [12, 13].

6.2. Off-Target and Phenotypic Resistance

Off-target bypass mechanisms are diverse and frequently co-occur. The most commonly identified genomic alterations include NRAS and BRAF activating mutations (particularly BRAF V600E and class III mutations), RAF1 fusions, and NF1 loss-of-function [12, 13]. RTK amplifications – notably MET, ERBB2, and FGFR3 – restore upstream KRAS activation or engage parallel survival pathways [12, 13]. Parallel PI3K pathway activation through PIK3CA mutation, PTEN loss, or AKT amplification provides MAPK-independent survival signaling that sustains tumor growth despite KRAS suppression [13].

Phenotypic resistance mechanisms not driven by genetic mutation include epithelial-mesenchymal transition (EMT) and the emergence of drug-tolerant persister (DTP) cell populations [34, 35]. EMT involves transcriptional reprogramming orchestrated by ZEB1, SNAI1, and other EMT-transcription factors, with loss of E-cadherin and gain of mesenchymal markers including vimentin and fibronectin [34]. EMT cells activate YAP/TAZ co-transcriptional activators and FAK signaling to maintain survival independently of KRAS-MAPK continuity [34,35]. DTP cells survive pharmacological KRAS suppression through chromatin remodeling and transcriptional plasticity rather than through stable genetic alterations, representing a reservoir from which genetically resistant clones may emerge during prolonged drug exposure [35].

Table 2 Mechanisms of acquired resistance to KRAS G12C inhibitors and therapeutic countermeasures. Approximate frequencies from pooled analyses of post-progression biopsies; mechanisms are not mutually exclusive and may co-occur in the same patient [12,13].

Category	Mechanism	Specific Alterations	Frequency*	Therapeutic Counterstrategy
On-target	S-IIP secondary mutations	R68S, H95D/Q/R, Y96C/D	~15–20%	KRAS G12C (ON) inhibitors (elironrasib); 2nd-gen S-IIP agents
On-target	KRAS amp / allele switch	KRAS amp; emergence of G12D, G12V, G13D on new allele	~10–15%	Pan-KRAS inhibitors (daraxonrasib); allele-specific next-gen agents
Off-target (RAS/RAF)	RAS/RAF bypass mutations	NRAS G12/Q61; BRAF V600E/class III; RAF1 fusion; NF1 LOF	~20–30%	Pan-RAS inhibitors; BRAF + MEK combination (V600E); MEK in combo
Off-target (RTK)	RTK amplification / activation	MET amp; FGFR3 fusion; ERBB2 amp; EGFR reactivation (CRC)	~15–25%	SHP2 inhibitors (RMC-4630, TNO155); MET inhibitors; anti-EGFR (CRC); ERBB2-targeted agents
Off-target (PI3K axis)	Parallel pathway activation	PIK3CA mutation; PTEN loss; AKT amplification	~10%	PI3K/AKT/mTOR inhibitor combinations; rational co-targeting with KRAS inhibitor
Phenotypic	EMT / drug-tolerant persister (DTP)	E-cadherin loss; vimentin upregulation; YAP/TAZ activation	~10–15%	YAP/TAZ-TEAD inhibitors; FAK inhibitors; ferroptosis inducers; epigenetic agents

Upstream adaptive	SOS1/SHP2 feedback reactivation	Adaptive RTK→SOS1→KRAS GTP reloading within hours of drug exposure	Universal (adaptive, not genetic)	SHP2 inhibitors (RMC-4630, TNO155, BBP-398, JAB-3068); SOS1 inhibitors (BI 1701963); KRAS G12C (ON) inhibitors to trap reloaded active KRAS
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S-IIP = switch-II pocket; EMT = epithelial-mesenchymal transition; RTK = receptor tyrosine kinase; LOF = loss of function

6.3. Combination Strategies to Address Resistance

SHP2 inhibitors (RMC-4630, BBP-398, JAB-3068, TNO155) target the RTK-RAS relay upstream, preventing feedback GTP reloading [25, 26]. Clinical data from KonTRAS-01 demonstrated a confirmed ORR of 33% combining JDQ443 (KRAS G12C inhibitor) with TNO155 (SHP2 inhibitor) in KRAS G12C inhibitor-naïve NSCLC, and comparable activity (33% ORR) in post-G12Ci patients [36]. SHP2 inhibition additionally modifies the tumor microenvironment, potentially augmenting immune checkpoint inhibitor activity [25, 26]. SOS1 inhibitors (BI 1701963) provide a complementary upstream strategy targeting the GEF responsible for KRAS nucleotide exchange [27]. MEK inhibitors address downstream bypass but are limited by overlapping toxicity profiles with KRAS inhibitors [24].

Immune checkpoint inhibitor (ICI) combinations are among the most clinically advanced combination strategies. KRYSTAL-7 data (adagrasib + pembrolizumab, first-line NSCLC) demonstrated an overall ORR of 44.3% and median PFS of 11.0 months, with a particularly striking ORR of 63% in PD-L1 TPS ≥50% patients [37]. These results are hypothesis-generating but require Phase 3 validation before establishing a new standard of care. A meaningful concern is hepatotoxicity observed with KRAS inhibitor-ICI combinations, which must be carefully monitored in ongoing trials [37]. Patients with STK11 or KEAP1 co-mutations show attenuated ICI benefit [28, 29], and it remains uncertain whether KRAS inhibitor co-administration meaningfully rescues immunotherapy sensitivity in these molecular subgroups.

7. Beyond G12C: Targeting G12D, G12V, and Pan-KRAS Strategies

7.1. The Unmet Need

G12C accounts for only a minority of KRAS-mutant cancers. KRAS G12D (~40% of PDAC, ~13% of CRC, ~17% of NSCLC) and G12V (~29% of PDAC, ~9% of CRC, ~21% of NSCLC) collectively represent the majority of KRAS-driven malignancies and remain without approved targeted therapy [2,19,20]. PDAC in particular – where >90% of tumors carry KRAS mutations at G12D, G12V, or G12R – has historically had no effective targeted treatment, and median OS with current chemotherapy regimens remains below 12 months in the metastatic setting [38]. The pharmacological challenge is fundamental: G12D and G12V lack the reactive cysteine that enabled the G12C covalent inhibitor strategy, requiring different mechanistic approaches [14, 15, 21].

7.2. Non-Covalent KRAS G12D Inhibitors: MRTX1133

MRTX1133 (Mirati Therapeutics/Bristol Myers Squibb) is a non-covalent small molecule inhibitor that engages both GDP-bound and GTP-bound states of KRAS G12D by occupying a binding site bridging switch I and switch II regions, with direct contacts to Asp12 [15, 39]. Structural optimization achieved selectivity over wild-type KRAS by exploiting the altered binding geometry introduced by the D12 substitution [15]. Preclinical data in KRAS G12D-mutant PDAC, CRC, and NSCLC models demonstrated potent antiproliferative activity and tumor regression [15, 39]. MRTX1133 is currently in Phase 1/2 clinical evaluation. Translation of preclinical promise to clinical benefit in PDAC faces additional barriers beyond biochemical potency, including the dense desmoplastic stroma that impairs drug delivery and the immunosuppressive microenvironment that limits combination strategies [38].

7.3. Tri-Complex RAS(ON) Inhibitor Platform: Revolution Medicines

Revolution Medicines has developed a mechanistically distinct inhibitor class exploiting pharmacological recruitment of cyclophilin A (CYPA), an abundant intracellular chaperone [14, 16]. In the tri-complex paradigm, the drug simultaneously binds CYPA and oncogenic KRAS, creating a neomorphic protein-protein interface that traps active, GTP-bound RAS in a signaling-incompetent conformation [14, 16]. Because the interface incorporates structural contributions from the mutant residue at codon 12, these inhibitors achieve allele selectivity without requiring a reactive cysteine – enabling drug design against G12D, G12V, and other alleles not amenable to covalent strategies.

Daraxonrasib (RMC-6236), a multi-selective RAS(ON) inhibitor active against G12C, G12D, G12V, G13D, and other oncogenic alleles, has shown promising early-phase activity in PDAC and NSCLC across KRAS mutant subtypes [14]. In

June 2025, the FDA granted daraxonrasib Breakthrough Therapy Designation for previously treated metastatic PDAC with KRAS G12 mutations, based on Phase 1 data [14]. The Phase 3 RASolute 302 trial comparing daraxonrasib to investigator's choice standard-of-care in PDAC is closed to accrual with results pending. Important caveats apply: Breakthrough Designation reflects unmet medical need and preliminary data rather than proven clinical benefit; Phase 3 results will be essential to determine whether pan-KRAS inhibition translates to improved patient outcomes in PDAC.

Zoldonrasib (RMC-9805) is a covalent G12D-selective tri-complex inhibitor that engages the Asp12 residue via a neomorphic covalent mechanism facilitated by the cyclophilin A interface [16, 40]. In preclinical KRAS G12D xenograft models, zoldonrasib induced objective responses in 7 of 9 PDAC models [40]. Early clinical data presented at AACR 2025 from the Phase 1 trial (NCT06040541) demonstrated acceptable safety and preliminary antitumor activity in KRAS G12D-mutant NSCLC [16]. These are conference presentations rather than peer-reviewed publications; interpretation should be appropriately cautious pending full data disclosure and independent validation.

Elironrasib (RMC-6291), a RAS(ON) G12C-selective tri-complex inhibitor targeting the active GTP-bound form, is designed to overcome resistance to the approved GDP-state inhibitors by maintaining potency against S-IIP resistance mutations that shift KRAS toward the GTP-bound conformation [14]. This rationale is mechanistically compelling, though clinical evidence of efficacy in the post-G12C(OFF)-inhibitor setting is still maturing. RMC-5127 (G12V-selective) was described as progressing toward a Phase 1 first-in-human trial expected in 2026; this represents company-disclosed development plans rather than peer-reviewed clinical data [14].

7.4. Summary of KRAS-Targeting Agents in Clinical Use and Development

Table 3 Provides a detailed pharmacological reference summary of the principal KRAS-targeting agents, including allele selectivity, KRAS conformational state targeted, line of therapy, CNS penetration, toxicity profiles, and regulatory status. Color-coding distinguishes agents targeting the GDP-bound inactive state (OFF; amber), GTP-bound active state (ON; green), or both states. Pipeline agents are indicated in purple.

Table 3 KRAS-targeting agents: pharmacological profiles, clinical data, and regulatory status (as of mid-2026). †BBB = blood-brain barrier penetration. *Adagrasib demonstrated clinically meaningful CNS penetration in KRYSTAL-1; intracranial ORR 31.6% in patients with active brain metastases [32]. †Daraxonrasib FDA Breakthrough Therapy Designation based on Phase 1 data (June 2025); full approval contingent on Phase 3 results [14]. †RMC-5127 Phase 1 timeline based on company disclosure; not yet peer-reviewed data [14].

Drug (code name)	KRAS state	Allele target	Mechanism	Line / Setting	ORR (%)	mPFS (mo)	BBB †	Key Toxicity	Regulatory Status
Sotorasib (AMG 510)	OFF (GDP)	G12C only	Irreversible covalent; switch-II pocket acrylamide	NSCLC 2L+; mCRC 2L+ (combination)	37 (NSCLC); 26 (CRC+pani)	6.3 / 5.6	Low	Diarrhea, hepatotox (↑AST/ALT), nausea	FDA approved May 2021 (NSCLC); Jan 2025 (CRC+pani)
Adagrasib (MRTX849)	OFF (GDP)	G12C only	Irreversible covalent; switch-II pocket; t _{1/2} ~23 h	NSCLC 2L+; mCRC 2L+ (combination); CNS mets	43 (NSCLC); 34 (CRC+cet)	6.5 / 6.9	Yes*	Diarrhea, nausea/vomiting, QTc prolong, hepatotox	FDA approved Dec 2022 (NSCLC); Jun 2024 (CRC+cet)
Elironrasib (RMC-6291)	ON (GTP)	G12C only	RAS(ON) tri-complex; cyclophilin A; overcomes OFF-	NSCLC, solid tumors (post-G12Ci)	Phase 1 (early)	NR	TBD	Under evaluation	Phase 1/2 clinical development

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Daraxonra sib (RMC- 6236)	ON (GTP)	Pan: G12C/D /V, G13D, Q61 (multi)	RAS(ON) multi- selective tri- complex; cyclophili n A	PDAC 2L+; NSCLC; CRC (any KRAS G12 mut)	Promising Ph1 PDAC/NSC LC (not yet mature)	NR	TBD	Rash, GI effects; dose- dependent	Phase 3 RASolute 302; FDA BT Designation PDAC 2025*
Zoldonrasi b (RMC- 9805)	ON (GTP)	G12D only (covalen t-Asp12)	Covalent RAS(ON) tri- complex; cyclophili n A; targets Asp12 via neomorp hic interface	PDAC, NSCLC (G12D)	Early Ph1 signals (AACR 2025†)	NR	TBD	Under evaluation	Phase 1 (NCT060405 41)
MRTX113 3	ON+O FF	G12D only (non- covalent bistate)	Non- covalent; engages switch I/II interface in both GDP and GTP states; direct Asp12 contact	PDAC, CRC (G12D)	Preclinical + early Ph1	NR	TBD	Under evaluation	Phase 1/2 (Mirati/BMS)
RMC-5127	ON (GTP)	G12V only	RAS(ON) G12V- selective tri- complex; cyclophili n A	Solid tumors (G12V)	Preclinical	–	–	Not yet established	Phase 1 planned 2026†

Color legend: amber = KRAS(OFF/GDP-state) inhibitors; green = KRAS(ON/GTP-state) inhibitors; purple = regulatory status of pipeline agents. ORR = objective response rate; mPFS = median progression-free survival; mo = months; NR = not reached; SoC = standard of care; BT = Breakthrough Therapy; t½ = half-life; CRC = colorectal cancer; NSCLC = non-small cell lung cancer; PDAC = pancreatic ductal adenocarcinoma

Table 4 Key clinical trials of KRAS-targeted therapy: design, efficacy, and regulatory outcomes.

Trial	Drug(s)	Phase	Tumor / Line	ORR (%)	mPFS (mo)	mOS (mo)	Status / Key Outcome
CodeBreak 100	Sotorasib mono	I/II	NSCLC 2L+	37.1	6.3	12.5	FDA accelerated approval May 2021 (NSCLC)
CodeBreak 200	Sotorasib vs docetaxel	III	NSCLC 2L	28 vs 13	5.6 vs 4.5	10.6 vs 11.3	Full approval confirmed; ORR/PFS improved, no OS benefit vs docetaxel
CodeBreak 300	Sotorasib + panitumumab	III	mCRC 2L+	26 vs 0	5.6 vs 2.2	NR	FDA approval Jan 2025; 1st KRAS-targeted approval in CRC for sotorasib
KRYSTAL-1 (NSCLC)	Adagrasib mono	I/II	NSCLC 2L+	42.9	6.5	12.6	FDA accelerated approval Dec 2022; CNS cohort: intracranial ORR 31.6%
KRYSTAL-1 (CRC exp.)	Adagrasib + cetuximab	I/II	mCRC 2L+	34	6.9	NR	FDA approval Jun 2024; first KRAS inhibitor approval outside lung cancer
KRYSTAL-7	Adagrasib + pembrolizumab	II	NSCLC 1L	44.3 overall; 63 (PD-L1 ≥50%)	11.0	NR	Ongoing; promising 1L signal; Phase 3 warranted for PD-L1-high subset
KontraST-01	JDQ443 + TNO155 (SHP2i)	Ib/II	NSCLC, solid tumors	33 (G12Ci-naïve); 33 (post-G12Ci)	NR	NR	Ongoing Phase 2 expansion; validates SHP2+G12Ci combination strategy
RASolute 302	Daraxonrasib vs SoC	III	PDAC 2L+	–	–	–	Closed to accrual (2025); results pending; first Phase 3 pan-KRAS trial in PDAC

Abbreviations: ORR = objective response rate; mPFS = median progression-free survival; mOS = median overall survival; mo = months; NR = not reached; SoC = standard of care; 1L/2L+ = first/second-line or later; G12Ci = KRAS G12C inhibitor; SHP2i = SHP2 inhibitor. All response rates are for KRAS G12C-mutant populations unless otherwise specified

7.5. Special Focus: KRAS Inhibition in Pancreatic Ductal Adenocarcinoma

PDAC exemplifies both the promise and the remaining challenges of KRAS-directed therapy. With a 5-year survival rate below 12% for metastatic disease and near-universal KRAS mutation prevalence – predominantly G12D (~40%), G12V (~29%), and G12R (~15%) – pancreatic cancer represents both the highest unmet need and the most formidable therapeutic target in this field [38, 41]. The dense desmoplastic microenvironment of PDAC, characterized by cancer-associated fibroblasts (CAFs), hyaluronan-rich extracellular matrix, hypovascularization, and profound cytotoxic T cell exclusion, creates pharmacokinetic barriers to drug delivery and pharmacodynamic barriers to immune sensitization that substantially exceed those encountered in NSCLC or CRC [38, 41, 42].

First-generation KRAS G12C inhibitors have minimal applicability in PDAC given the G12C allele's rarity (~1%). Daraxonrasib's pan-KRAS profile provides the first opportunity for direct KRAS inhibition in pancreatic cancer at meaningful scale [14]. Early Phase 1 signals of activity across G12D, G12V, and other KRAS-mutant PDAC patients are encouraging, but caution is warranted: similar early optimism surrounded EGFR inhibitors, immunotherapy, and PARP inhibitors in PDAC, most of which failed to demonstrate benefit in randomized evaluation [38]. The Phase 3 RASolute 302 results will be critical and informative regardless of outcome.

For G12D-dominant PDAC, zoldonrasib and MRTX1133 represent allele-selective options in clinical development [15, 16, 39, 40]. Whether allele-selective inhibitors achieve superior depth of response compared to pan-KRAS agents in the G12D-predominant PDAC context remains an open and important question for clinical evaluation. Combination approaches – particularly with stromal-targeting agents addressing CAF biology, or with immune-sensitizing strategies – may ultimately be required to achieve durable responses in this tumor type [38, 41, 42].

8. Future Perspectives

8.1. Combination Immunotherapy: Evidence and Uncertainties

The combination of KRAS inhibition with immune checkpoint blockade is mechanistically appealing: KRAS-mutant tumors are frequently immunosuppressive, with downregulated MHC-I antigen presentation, elevated IL-10 and TGF- β , and exclusion of cytotoxic T lymphocytes [43, 44]. Pharmacological KRAS suppression may reverse these defects, a hypothesis supported by KRYSTAL-7's 63% ORR in PD-L1-high first-line NSCLC [37]. However, several uncertainties demand acknowledgment. First, KRYSTAL-7 is a Phase 2 single-arm expansion without a concurrent randomized comparator; the apparently superior ORR relative to historical ICI monotherapy benchmarks may reflect patient selection rather than true synergy [37]. Second, adagrasib-ICI combinations carry hepatotoxicity risk that must be weighed against potential benefit [37]. Third, the mechanism by which KRAS inhibition enhances immunogenicity remains incompletely characterized – whether through increased antigen presentation, reduced immunosuppressive cytokine production, or indirect immune cell effects [43, 44]. Randomized Phase 3 data are needed before combination ICI-KRAS inhibitor regimens can be considered standard of care.

8.2. PROTAC and Targeted Protein Degradation Strategies

Proteolysis-targeting chimeras (PROTACs) designed to recruit E3 ubiquitin ligases (CRBN, VHL) to KRAS and direct it toward proteasomal degradation have shown preclinical proof-of-concept [45, 46]. The theoretical advantage of catalytic efficacy – one PROTAC molecule mediating multiple rounds of KRAS degradation – may overcome some resistance mechanisms driven by target amplification. However, clinical translation faces substantial challenges: KRAS PROTACs tend to be large, hydrophilic molecules with poor cell permeability; the hook effect at high concentrations may paradoxically reduce degradation efficiency; and ternary complex formation requires appropriate geometrical alignment in the intracellular environment [45, 46]. Several KRAS PROTAC programs are in preclinical or early-stage development, but none has yet demonstrated clinical activity.

8.3. RNA-Based Approaches and Allele-Selective Silencing

RNA interference (RNAi) and antisense oligonucleotide (ASO) approaches targeting KRAS mRNA offer allele-specific silencing through single-nucleotide discrimination – potentially preserving wild-type KRAS while suppressing oncogenic mutant alleles [47, 48]. Advances in lipid nanoparticle (LNP) and conjugate delivery have improved tumor penetration in preclinical models [47, 48]. The principal clinical challenge remains selective delivery to solid tumors with adequate efficiency to suppress target expression below the threshold needed for biological response. No KRAS-directed RNA therapeutic has yet demonstrated clinical efficacy in randomized evaluation.

8.4. Liquid Biopsy and Predictive Biomarkers

Serial circulating tumor DNA (ctDNA) analysis has emerged as a pharmacodynamic tool for monitoring KRAS inhibitor activity [49, 50]. Early on-treatment reductions in KRAS G12C variant allele fraction (VAF) correlate with depth of response and progression-free survival, while emerging resistance mutations in ctDNA precede radiographic progression by weeks to months [49, 50]. This temporal resolution positions ctDNA as a potential tool for adaptive trial designs, early treatment switching, and rational sequencing of combination regimens. Multiplexed ctDNA panels that simultaneously detect KRAS and co-mutations (STK11, KEAP1, CDKN2A) may enable refined patient stratification for combination strategies that are differentially effective in molecularly defined subgroups [28, 29, 50].

8.5. Toward Broader RAS Inhibition: Challenges Ahead

The longer-term aspiration for pan-RAS inhibition capable of suppressing all oncogenic RAS variants – including NRAS and HRAS – faces the fundamental concern of on-target toxicity against wild-type RAS, which is required for normal tissue homeostasis, particularly in the GI tract, skin, and hematopoietic compartment [14, 51]. The tri-complex platform exploits differential expression or activation kinetics between oncogenic and wild-type RAS to achieve selectivity, and preliminary clinical data suggest a tolerable safety window, but the therapeutic index of pan-RAS inhibition will require careful characterization as more patients are treated at therapeutic doses in longer-duration trials [14, 51]. Vertical combination of KRAS inhibitors – pairing G12C(OFF) with G12C(ON) inhibitors, or allele-selective with pan-KRAS

agents – represents a near-term strategy to achieve more complete on-target suppression while potentially limiting the toxicity of pan-RAS approaches [14].

9. Conclusions and Critical Assessment

The pharmacological development of KRAS inhibitors has progressed from four decades of conceptual pessimism to a field with two FDA-approved agents, multiple active Phase 3 trials, and an expanding pipeline targeting the full spectrum of KRAS alleles. The discovery of the switch-II pocket and the covalent mutation-selective inhibitor strategy rank among the most important mechanistic breakthroughs in targeted oncology of the past decade. The key concepts discussed throughout this review are summarized schematically in Figure 1.

However, an honest appraisal of the current evidence base warrants measured expectations alongside justified optimism. First-generation G12C inhibitors achieve ORRs of 30–43% and median PFS of approximately six months in second-line NSCLC – clinically meaningful improvements over chemotherapy, but substantially below outcomes achieved with EGFR or ALK inhibitors. The lack of OS benefit for sotorasib versus docetaxel in CodeBreak 200 is a sobering counterpoint to the enthusiasm generated by response data, and underscores that high response rates do not automatically translate to survival advantage in the context of post-progression treatment effects. In CRC, combinations with anti-EGFR antibodies have produced responses in a previously treatment-refractory population, but response rates of 26–34% and short durations highlight that much work remains.

The resistance landscape is complex, with on-target mutations, bypass signaling, and phenotypic plasticity all contributing to drug escape. No combination strategy has yet demonstrated durable suppression of acquired resistance in randomized clinical trials. The promising signals from SHP2 inhibitor combinations and ICI-KRAS inhibitor pairings require Phase 3 validation. For PDAC, the field is at an earlier stage, and past failures of promising PDAC-directed therapies counsel against premature confidence in pan-KRAS inhibitor data that remain predominantly from Phase 1 studies.

What is unambiguous is that the scientific trajectory is positive. The structural, chemical, and clinical insights accumulated over the past decade provide a robust foundation for next-generation drug development. The coming years will determine whether the pharmacological tractability established for G12C can be extended to G12D, G12V, and beyond – and whether the marginal benefit of first-generation inhibitors can be meaningfully amplified through rational combination, improved patient selection, and next-generation agents.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

- [1] Simanshu DK, Nissley DV, McCormick F. RAS Proteins and Their Regulators in Human Disease. *Cell*. 2017;170(1):17-33. doi:10.1016/j.cell.2017.06.009
- [2] Prior IA, Hood FE, Hartley JL. The Frequency of Ras Mutations in Cancer. *Cancer Res*. 2020;80(14):2969-2974. doi:10.1158/0008-5472.CAN-19-3682
- [3] Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. Drugging the undruggable RAS: Mission possible?. *Nat Rev Drug Discov*. 2014;13(11):828-851. doi:10.1038/nrd4389
- [4] McCormick F. KRAS as a Therapeutic Target. *Clin Cancer Res*. 2015;21(8):1797-1801. doi:10.1158/1078-0432.CCR-14-2662
- [5] Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature*. 2013;503(7477):548-551. doi:10.1038/nature12796
- [6] Fell JB, Fischer JP, Baer BR, et al. Identification of the Clinical Development Candidate MRTX849, a Covalent KRAS^{G12C} Inhibitor for the Treatment of Cancer. *J Med Chem*. 2020;63(13):6679-6693. doi:10.1021/acs.jmedchem.9b02052

- [7] Skoulidis F, Li BT, Dy GK, et al. Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation. *N Engl J Med*. 2021;384(25):2371-2381. doi:10.1056/NEJMoa2103695
- [8] Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in Non-Small-Cell Lung Cancer Harboring a *KRAS*G12C Mutation. *N Engl J Med*. 2022;387(2):120-131. doi:10.1056/NEJMoa2204619
- [9] Khan A, Chawla S, Hussain T, Haque MA. Adagrasib plus cetuximab - a novel therapy in the *KRAS* G12C mutated colorectal cancer treatment. *Ann Med Surg (Lond)*. 2025;87(1):11-12. Published 2025 Jan 9. doi:10.1097/MS9.0000000000002777
- [10] Fakih MG, Salvatore L, Esaki T, et al. Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated *KRAS* G12C. *N Engl J Med*. 2023;389(23):2125-2139. doi:10.1056/NEJMoa2308795
- [11] Hanna NH, Robinson AG, Temin S, et al. Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO and OH (CCO) Joint Guideline Update. *J Clin Oncol*. 2021;39(9):1040-1091. doi:10.1200/JCO.20.03570
- [12] Mohanty A, Nam A, Srivastava S, et al. Acquired resistance to *KRAS* G12C small-molecule inhibitors via genetic/nongenetic mechanisms in lung cancer. *Sci Adv*. 2023;9(41):eade3816. doi:10.1126/sciadv.ade3816
- [13] Tanaka N, Lin JJ, Li C, et al. Clinical Acquired Resistance to *KRAS*^{G12C} Inhibition through a Novel *KRAS* Switch-II Pocket Mutation and Polyclonal Alterations Converging on RAS-MAPK Reactivation. *Cancer Discov*. 2021;11(8):1913-1922. doi:10.1158/2159-8290.CD-21-0365
- [14] Revolution Medicines. Daraxonrasib (RMC-6236): clinical development updates. Annual Report and Investor Day Presentations. 2025. Available at: <https://ir.revmed.com>.
- [15] Wang X, Allen S, Blake JF, et al. Identification of MRTX1133, a Noncovalent, Potent, and Selective *KRAS*^{G12D} Inhibitor. *J Med Chem*. 2022;65(4):3123-3133. doi:10.1021/acs.jmedchem.1c01688
- [16] Revolution Medicines. Zoldonrasib (RMC-9805) initial data in *KRAS*G12D NSCLC. AACR Annual Meeting 2025, Chicago IL, April 27 2025. Oral presentation. [Conference abstract/press release; peer-reviewed publication pending].
- [17] Downward J. Targeting RAS signalling pathways in cancer therapy. *Nat Rev Cancer*. 2003;3(1):11-22. doi:10.1038/nrc969
- [18] Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K Pathway in Human Disease. *Cell*. 2017;170(4):605-635. doi:10.1016/j.cell.2017.07.029
- [19] Bailey P, Chang DK, Nones K, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature*. 2016;531(7592):47-52. doi:10.1038/nature16965
- [20] Corcoran RB, Chabner BA. Application of Cell-free DNA Analysis to Cancer Treatment. *N Engl J Med*. 2018;379(18):1754-1765. doi:10.1056/NEJMr1706174
- [21] Hunter JC, Manandhar A, Carrasco MA, Gurbani D, Gondi S, Westover KD. Biochemical and Structural Analysis of Common Cancer-Associated *KRAS* Mutations. *Mol Cancer Res*. 2015;13(9):1325-1335. doi:10.1158/1541-7786.MCR-15-0203
- [22] Vetter IR, Wittinghofer A. The guanine nucleotide-binding switch in three dimensions. *Science*. 2001;294(5545):1299-1304. doi:10.1126/science.1062023
- [23] Berndt N, Hamilton AD, Sebt SM. Targeting protein prenylation for cancer therapy. *Nat Rev Cancer*. 2011;11(11):775-791. Published 2011 Oct 24. doi:10.1038/nrc3151
- [24] Manchado E, Weissmueller S, Morris JP 4th, et al. A combinatorial strategy for treating *KRAS*-mutant lung cancer. *Nature*. 2016;534(7609):647-651. doi:10.1038/nature18600
- [25] Nichols RJ, Haderk F, Stahlhut C, et al. RAS nucleotide cycling underlies the SHP2 phosphatase dependence of mutant BRAF-, NF1- and RAS-driven cancers. *Nat Cell Biol*. 2018;20(9):1064-1073. doi:10.1038/s41556-018-0169-1
- [26] Ruess DA, Heynen GJ, Ciecieski KJ, et al. Mutant *KRAS*-driven cancers depend on PTPN11/SHP2 phosphatase. *Nat Med*. 2018;24(7):954-960. doi:10.1038/s41591-018-0024-8
- [27] Hallin J, Engstrom LD, Hargis L, et al. The *KRAS*^{G12C} Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of *KRAS*-Mutant Cancers in Mouse Models and Patients. *Cancer Discov*. 2020;10(1):54-71. doi:10.1158/2159-8290.CD-19-1167

- [28] Skoulidis F, Goldberg ME, Greenawalt DM, et al. *STK11/LKB1* Mutations and PD-1 Inhibitor Resistance in *KRAS*-Mutant Lung Adenocarcinoma. *Cancer Discov.* 2018;8(7):822-835. doi:10.1158/2159-8290.CD-18-0099
- [29] Zavitsanou AM, Pillai R, Hao Y, et al. KEAP1 mutation in lung adenocarcinoma promotes immune evasion and immunotherapy resistance. *Cell Rep.* 2023;42(11):113295. doi:10.1016/j.celrep.2023.113295
- [30] Basso AD, Mirza A, Liu G, Long BJ, Bishop WR, Kirschmeier P. The farnesyl transferase inhibitor (FTI) SCH66336 (lonafarnib) inhibits Rheb farnesylation and mTOR signaling. Role in FTI enhancement of taxane and tamoxifen anti-tumor activity. *J Biol Chem.* 2005;280(35):31101-31108. doi:10.1074/jbc.M503763200
- [31] de Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with *KRAS*^{G12C} mutation: a randomised, open-label, phase 3 trial. *Lancet.* 2023;401(10378):733-746. doi:10.1016/S0140-6736(23)00221-0
- [32] Negrao MV, Spira AI, Heist RS, et al. Intracranial Efficacy of Adagrasib in Patients From the KRYSTAL-1 Trial With *KRAS*G12C-Mutated Non-Small-Cell Lung Cancer Who Have Untreated CNS Metastases. *J Clin Oncol.* 2023;41(28):4472-4477. doi:10.1200/JCO.23.00046
- [33] Amodio V, Yaeger R, Arcella P, et al. EGFR Blockade Reverts Resistance to *KRAS*^{G12C} Inhibition in Colorectal Cancer. *Cancer Discov.* 2020;10(8):1129-1139. doi:10.1158/2159-8290.CD-20-0187
- [34] Roper N, Gao S, Maity TK, et al. APOBEC Mutagenesis and Copy-Number Alterations Are Drivers of Proteogenomic Tumor Evolution and Heterogeneity in Metastatic Thoracic Tumors. *Cell Rep.* 2019;26(10):2651-2666.e6. doi:10.1016/j.celrep.2019.02.028
- [35] Bhang HE, Ruddy DA, Krishnamurthy Radhakrishna V, et al. Studying clonal dynamics in response to cancer therapy using high-complexity barcoding. *Nat Med.* 2015;21(5):440-448. doi:10.1038/nm.3841
- [36] Negrao M, Cassier P, Solomon B.6 et al. MA06.03 KonTRAsT-01: Preliminary Safety and Efficacy of JDQ443 + TNO155 in Patients with Advanced, *KRAS* G12C-Mutated Solid Tumors. *Journal of Thoracic Oncology*, 18, S117-S118
- [37] Tian T, Li W. Advances on drug therapy for *KRAS*^{G12C}-mutant non-small-cell lung cancer. *Transl Oncol.* 2026;65:102668. doi:10.1016/j.tranon.2026.102668
- [38] Strickler JH, Satake H, George TJ, et al. Sotorasib in *KRAS* p.G12C-Mutated Advanced Pancreatic Cancer. *N Engl J Med.* 2023;388(1):33-43. doi:10.1056/NEJMoa2208470
- [39] Hallin J, Bowcut V, Calinisan A, et al. Anti-tumor efficacy of a potent and selective non-covalent *KRAS*^{G12D} inhibitor. *Nat Med.* 2022;28(10):2171-2182. doi:10.1038/s41591-022-02007-7
- [40] Li T, Gu C, Zhou C, et al. Insights into direct *KRAS* inhibition strategies for cancer treatment. *Future Med Chem.* 2024;16(22):2411-2429. doi:10.1080/17568919.2024.2424149
- [41] Whatcott CJ, Diep CH, Jiang P, et al. Desmoplasia in Primary Tumors and Metastatic Lesions of Pancreatic Cancer. *Clin Cancer Res.* 2015;21(15):3561-3568. doi:10.1158/1078-0432.CCR-14-1051
- [42] Feig C, Gopinathan A, Neesse A, Chan DS, Cook N, Tuveson DA. The pancreas cancer microenvironment. *Clin Cancer Res.* 2012;18(16):4266-4276. doi:10.1158/1078-0432.CCR-11-3114
- [43] Canon J, Rex K, Saiki AY, et al. The clinical *KRAS*(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature.* 2019;575(7781):217-223. doi:10.1038/s41586-019-1694-1
- [44] Liao W, Overman MJ, Boutin AT, et al. *KRAS*-IRF2 Axis Drives Immune Suppression and Immune Therapy Resistance in Colorectal Cancer. *Cancer Cell.* 2019;35(4):559-572.e7. doi:10.1016/j.ccell.2019.02.008
- [45] Bond MJ, Crews CM. Proteolysis targeting chimeras (PROTACs) come of age: entering the third decade of targeted protein degradation. *RSC Chem Biol.* 2021;2(3):725-742. Published 2021 Mar 19. doi:10.1039/d1cb00011j
- [46] Zeng M, Xiong Y, Safaee N, et al. Exploring Targeted Degradation Strategy for Oncogenic *KRAS*^{G12C}. *Cell Chem Biol.* 2020;27(1):19-31.e6. doi:10.1016/j.chembiol.2019.12.006
- [47] Mullard A. Amgen overcomes historically undruggable target, with FDA nod for first *KRAS* inhibitor. *Nat Rev Drug Discov.* 2021;20(7):496. doi:10.1038/d41573-021-00098-4
- [48] Xie YH, Chen YX, Fang JY. Comprehensive review of targeted therapy for colorectal cancer. *Signal Transduct Target Ther.* 2020;5(1):22. Published 2020 Mar 20. doi:10.1038/s41392-020-0116-z

- [49] Aredo JV, Padda SK, Kunder CA, et al. Impact of KRAS mutation subtype and concurrent pathogenic mutations on non-small cell lung cancer outcomes. *Lung Cancer*. 2019;133:144-150. doi:10.1016/j.lungcan.2019.05.015
- [50] Ricciuti B, Arbour KC, Lin JJ, et al. Diminished Efficacy of Programmed Death-(Ligand)1 Inhibition in STK11- and KEAP1-Mutant Lung Adenocarcinoma Is Affected by KRAS Mutation Status. *J Thorac Oncol*. 2022;17(3):399-410. doi:10.1016/j.jtho.2021.10.013
- [51] Hobbs GA, Der CJ, Rossman KL. RAS isoforms and mutations in cancer at a glance. *J Cell Sci*. 2016;129(7):1287-1292. doi:10.1242/jcs.182873
- [52] Miyashita H, Kato S, Hong DS. KRAS G12C inhibitor combination therapies: current evidence and challenge. *Front Oncol*. 2024;14:1380584. Published 2024 May 2. doi:10.3389/fonc.2024.1380584
- [53] Papke B, Der CJ. Drugging RAS: Know the enemy. *Science*. 2017;355(6330):1158-1163. doi:10.1126/science.aam7622
- [54] Waddell N, Pajic M, Patch AM, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature*. 2015;518(7540):495-501. doi:10.1038/nature14169