The Oncologist, 2025, **30**, oyaf153
https://doi.org/10.1093/oncolo/oyaf153
Advance access publication 30 June 2025
Review Article

KRAS mutated NSCLC: past, present, and future directions in a rapidly evolving landscape

Austin Frisch[1], Eric Martin[1], So Yeon Kim[2], Jonathan W. Riess[3], Triparna Sen[*,4,5], Nagla Karim[*,6]

[1]Inova Fairfax Department of Internal Medicine, Inova Fairfax Hospital, Fairfax, VA 22042, United States,
[2]Yale Cancer Center, Yale School of Medicine, New Haven, CT 06510, United States,
[3]UC Davis Comprehensive Cancer Center, UC Davis School of Medicine, Sacramento, CA 95817, United States,
[4]Department of Oncological Sciences, Icahn School of Medicine, Mount Sinai, New York, NY, 10029, United States,
[5]Tisch Cancer Institute, Icahn School of Medicine, Mount Sinai, New York, NY 10029, United States,
[6]Inova Schar Cancer Center, Inova Fairfax Hospital, Fairfax, VA 22042, United States

[*]Corresponding authors: Nagla A Karim, MD, George Washington University Cancer Center, 800 22nd Street NW, Washington DC, 20052, USA. E-mail: nagla.karim5@gmail.com; Triparna Sen, PhD, Department of Oncological Sciences, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, Office 15-70E, New York, NYork 10029, USA. E-mail: triparna.sen@mssm.edu

Abstract

Non-small cell lung cancer (NSCLC) is among one of the most common and deadliest malignancies worldwide. With this new era of precision medicine, oncogenic driver genes and immunotherapy have changed the way we classify and treat this disease. Among these genes, the Kirsten rat sarcoma virus (KRAS) gene is the most mutated in NSCLC and has been the focus of numerous clinical trials for targeted therapy over the past few years. Here, we present an in-depth literature review of past, present, and future KRAS mutated NSCLC treatment with KRAS inhibitor monotherapy and combinatorial approaches including immunotherapy. The molecular biology behind KRAS targeted therapy is discussed while highlighting the difficulties of KRAS inhibitor treatment, including resistance, and the next steps needed to overcome them.

Key words: KRAS; NSCLC; co-mutation; resistance; review.

Implications for practice

There are only two approved FDA KRAS inhibitors for NSCLC, despite uncovering KRAS as a druggable target. The currently approved KRAS inhibitors are only for the G12C amino acid substitution that occurs in less than half of patients with KRAS-mutated lung cancer and, invariably, resistance develops in less than a year. The focus has turned to developing novel KRAS inhibitors and testing combination therapies that can better improve patient outcomes. For Oncologists, this review offers a complete up to date discussion on the current and developing landscape of KRAS-based therapy as it applies to NSCLC and highlights areas of unmet need that can spark interest for future studies.

Introduction

NSCLC is associated with high mortality, causing approximately 120 000 deaths in the United States in 2024.[1] Before the rise of immunotherapy, the 5-year survival rate for metastatic NSCLC was around 6% from 2010 to 2016.[2] With the data from KEYNOTE-189, the addition of pembrolizumab to standard chemotherapy while treating metastatic non-squamous cell NSCLC has proven successful. Overall survival at 12 months was 69.2% vs 49.4% in the control group and the progression free survival (PFS) in the pembrolizumab group was 8.8 months vs 4.9 months in the control group.[3] Over the past few years, new research has identified oncogenic driver genes that have allowed stratification and treatment of NSCLC based on actionable molecular alterations. KRAS is the most mutated oncogenic driver gene in NSCLC with mutation rates approaching 30% and patients with these mutations are known to have poor outcomes.[4]

Mutations seen in the early codon region and different splice variants of KRAS have sparked interest in medical researchers as targets for possible therapy. The most mutated codons, G12 (90% of KRAS cases), G13 (3%-6% of cases), and Q61 (1% of cases) are responsible for the dysfunctional GTPase protein leading to the constantly active state of GTP bound KRAS.[5] The G12 mutated codon has become the most clinically relevant and has different alterations depending on which amino acid is substituted: G12C (40% of KRAS mutated subtypes), G12V (21%), G12D (17%), G12A (6-8%), and G12R (2%).[6]

Co-mutations with *KRAS* mutated NSCLC

The tumor suppressor genes *STK11*, *KEAP1*, *TP53*, *SMARCA4*, and *CDKN2A* are the most seen genes co-mutated along with KRAS. Each different combination brings unique phenotypes and heterogeneity to this disease.[7]

Received: 22 March 2025; Accepted: 2 May 2025.

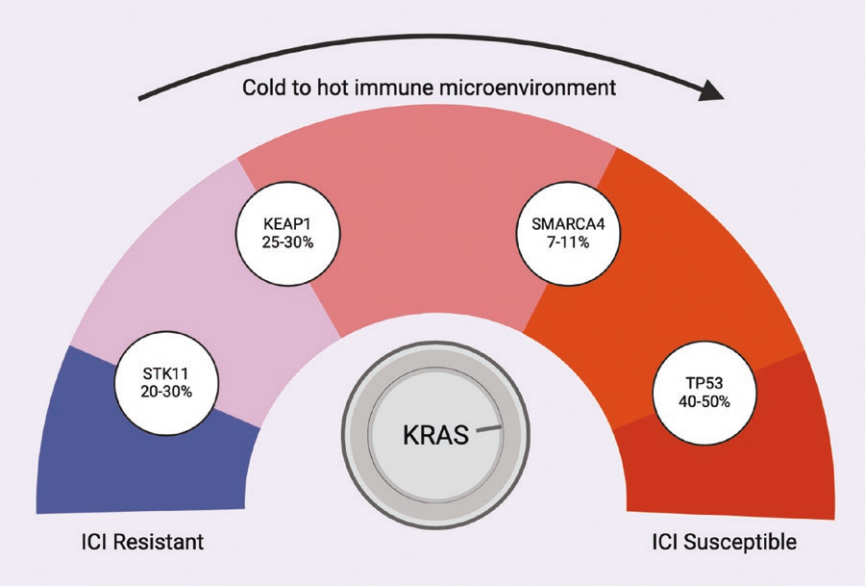

Figure 1: KRAS co-mutations displayed on a cold to hot immune environment spectrum based on their likelihood of response to immune checkpoint inhibitor therapy (ICI). KRAS-STK11 phenotype makes up roughly 20-30% of co-mutation cases and has the coldest immune phenotype making it highly resistant to ICI therapy. KRAS-TP53 on the other hand has the warmest immune phenotype with much higher ICI susceptibility and makes up 40-50% of co-mutation cases.Created in BioRender. Frisch, A. (2025) https://BioRender.com/c98t213

The *KRAS-STK11* mutated combination has been shown to create an immunosuppressive tumor microenvironment and lead to overall worse outcomes.[8,9] A particularly challenging subset of *KRAS*-mutant NSCLC arises when co-mutations occur in *STK11* and *KEAP1*, resulting in unique metabolic characteristics and treatment complexities.[10,11] These genetic changes interact to reshape cellular metabolism and disrupt redox homeostasis, profoundly influencing tumor behavior and therapy outcomes. The *STK11* gene, encoding the LKB1 protein, is a crucial metabolic regulator, activating AMPK to influence mTOR signaling and metabolic pathways.[12-15] Meanwhile, *KEAP1* acts as a central regulator of the cellular antioxidant response, modulating the activity of NRF2, a transcription factor that governs genes involved in antioxidant defenses and detoxification. *KRAS*-mutant NSCLC with *STK11* and *KEAP1* co-mutations has been shown to activate mechanisms that evade ferroptosis, a type of iron-dependent cell death. Targeting these ferroptosis resistance pathways has demonstrated potential in preclinical studies.[11,15,16]

TP53-KRAS co-mutations have been found in anywhere between 40% and 50% of KRAS mutated NSCLC. This subgroup has been found to have an increase in PD-L1 expression and create more of a favorable immune environment for immunotherapy.[17] Lab studies have shown a higher activation and expression of genes correlating with T cell mobilization and antigen expression in the tumor microenvironment which correlates with the data showing the *TP53-KRAS* co-mutation NSCLC group fare better with immunotherapy than the *KRAS-STK11* group.[18,19]

SMARCA4 is another gene frequently seen mutated with KRAS and has been known to correlate with poor outcomes in NSCLC patients and is found mutated in 7%-11% of NSCLC cases.[20,21] *SMARCA4* is a tumor suppressor gene that codes for the Brhama-Related Gene 1 (BRG1) protein which is heavily involved in gene transcription and histone modification. The limited data available suggests that SMARCA4 mutations have PD-L1 expression and do not create the cold immune environment to the degree that *STK11* or *KEAP1* mutations do, but outcomes are still poor with limited treatment options.[22,23]

Exploring the interactions between *KRAS, STK11, KEAP1* and other co-mutations holds significant promise for identifying new therapeutic avenues and developing tailored treatment strategies for patients with this oncogene-driven NSCLC subset. Early identification of these co-mutations can help clinicians recognize ICI sensitivity and predict outcomes. **Figure 1** shows the immune microenvironment spectrum with its corresponding KRAS co-mutation as either too cold or too hot regarding how susceptible the KRAS co-mutation phenotype is to ICI therapy.

Current and evolving therapies for *KRAS* mutated NSCLC

KRAS-mutated NSCLC has been shown to respond to ICI therapy. Sub group analysis of both the KEYNOTE-189 and Impower-150 trials show this. A follow-up study was done on the KEYNOTE-189 trial focusing on *KRAS* mutation status and its influence on the efficacy of pembrolizumab plus carboplatin and pemetrexed.[24] 31% of these patients had a KRAS mutation including 13% being the G12C variant and these patients had a higher PD-L1 TPS status. The mPFS did not change significantly depending on mutation status (9 months for both pembro + chemo with KRAS or without KRAS mutation). Similarly, the OS showed no significant change (mOS 21 vs 23 months in pembro + chemo with KRAS or without KRAS mutation). Overall, this follow-up analysis proved that pembrolizumab with carboplatin and pemetrexed is a reasonable first-line treatment option for metastatic NSCLC regardless of KRAS mutation status. Other active phase III clinical trials testing chemotherapy + ICI combinations in advanced NSCLC include the Impower-150 trial, which tested the humanized IgG1 anti-PDL-1 antibody Atezolizumab with carboplatin and

paclitaxel (ACP) vs bevacizumab plus carboplatin with paclitaxel (BCP) or atezolizumab plus BCP (ABCP).[25] This trial showed that the mPFS was greater in the ABCP group vs the BCP group (8.3 vs 6.8 months). Improvement in OS was shown as well as overall reliable tolerability. A follow-up analysis of the Impower-150 trial focused on KRAS and co-occurring STK11, KEAP1, and TP53 mutations. Roughly 25% of the patients had a KRAS mutation and ABCP proved superior to BCP in KRAS-mutated patients regarding mOS and mPFS (19.8 vs 9.9 months and 8.1 vs 5.8 months respectively).[26] Interestingly, in KRAS-wild-type patients, OS was longer in the ACP group than in the ABCP or BCP groups. KRAS-mutated patients who also had STK11 and KEAP1 co-mutations had a worse OS across all treatment groups vs wild type. However, among these KRAS patients with STK11 and/or KEAP1 co-mutations, the ABCP treatment group had the best OS.[26] Both the ORIENT-11 and GEMSTONE-301 trials, testing anti-PDL-1 antibodies Sintilimab and Sugemalimab respectively, also showed improved PFS with their ICI + chemotherapy combination groups vs standard chemotherapy alone.[27,28] These phase III trials testing chemotherapy + ICI combinations all focus on metastatic NSCLC patients who are EGFR/ALK-negative.

The double ICI trials such as POSEIDON and CheckMate-227 are hoping for a breakthrough in KRAS NSCLC patients with co-mutations that create a cold immune environment such as KEAP1/STK11.[29,30] The hope is that double ICI therapy will have synergistic effects that can truly awaken the immune system against KRAS-mutated NSCLC. Skoulidis et al discussed the advantages of double ICI therapy with anti-CTLA and PDL-1 or double PDL-1 treatment such as an increase in engagement of anti-tumor T cells driving an increase in "tumoricidal phenotypes" among immune cells causing a vulnerable TME.[31]

FDA approved KRAS G12C off inhibitors

Sotorasib was the first approved KRAS G12C off inhibitor. The CodeBreak 100 phase II trial included 126 NSCLC patients who have received either platinum chemotherapy and/or PD-L1 therapy.[32] The median progression free survival (PFS) was 6.8 months, overall survival (OS) was 12.5 months, and the objective response rate (ORR) being 37.1%.[32] The approval of Sotorasib for G12C mutations in KRAS mutated NSCLC marked a turning point in NSCLC therapy and initially proved its superiority over standard docetaxel therapy. Despite this breakthrough, a 2023 follow up study CodeBreak 200 phase III trial released data confirming improved PFS and ORR but not a statistically significant difference in OS.[33] Sotorasib also had a decrease in PFS when compared to the phase I and phase II trials with 5.6 months vs previous data showing 6.3 and 6.8 months. A follow up study from the CodeBreak 200 trial was presented at ASCO in 2023 discussing the intracranial efficacy of Sotorasib vs Docetaxel. Overall, this updated analysis shows Sotorasob having a benefit in NSCLC patients with treated, stable brain metastasis regarding PFS and having a delayed time to CNS recurrence.[34]

Adagrasib was the second KRAS G12C off inhibitor approved by the FDA and irreversibly binds to the switch two pocket region near where the GTP binds. As of December 2022, it has been another option for patients with locally advanced or metastatic NSCLC. The FDA decision was made based off the data from the KRYSTAL 1 phase I/II trial that enrolled 116 patients.[35] Results showed an ORR of 42.9% with a PFS of 6.5 months.[35] A more recent phase III trial continued to show Adagrasib with improved PFS and ORR over docetaxel.[36] A subgroup analysis of CNS metastasis identified 33 patients who had previously treated, stable central nervous system metastasis and the intracranial confirmed ORR for this group was 33.3%.[37] For the CNS group, 27/33 of these patients received radiation therapy before treatment with Adagrasib and the median intracranial PFS in these patients with CNS metastatis was 5.4 months.[37] **Table 1** shows active clinical trials for KRAS G12C inhibitors which include NSCLC patients.

KRAS G12C off inhibitors in development

Olomorasib, another G12C off inhibitor, was used in 184 patients of all solid tumor types in the LOXO-RAS-20001 study.[38] Treatment related adverse effects of grade 3 or higher were found in 7% of these patients. In 39 NSCLC patients who were previously treated with KRAS inhibitors, the ORR was 41% with a mPFS of 8.1 months.[38] New analysis was published in 2024 on a study testing Olomorasib in combination with pembrolizumab. 50 patients received the combination therapy and treatment-related adverse events led to 9% of patients being discontinued on Olomorasib or pembrolizumab and 9% had discontinued both with pneumonitis being seen in 3 patients. ORR was 63% with disease control rate (DCR) being 93% with mPFS not estimated with follow-up ongoing.[39] The SUNRAY-01 trial is currently ongoing testing Olomorasib with pembrolizumab or with pembrolizumab plus chemotherapy as a triple KRAS, ICI, and chemotherapy trial (NCT06119581).

Opnurasib was notably active against KRAS-mutated cell lines that acquired resistance to Sotorasib and Adagrasib.[40] It is currently being studied in the KontRASt-01 trial that included 49 NSCLC patients. The early analysis shows an ORR of 57% among the 14 NSCLC patients who took the 200mg BID dosing with the most common side effects being nausea, edema, diarrhea and fatigue.[41] Opnurasib is currently in a trial being tested against docetaxel in NSCLC patients.[42] A phase 1 trial evaluating the efficacy and safety of Garsorasib enrolled 79 patients and showed a ORR and DCR of 41% and 92%.[43] Furthermore, Garsorasib had been shown to have a high degree of CNS penetration in pre-clinical trials and this trial revealed an intracranial ORR and DCR of 17% and 100%, respectively.[43,44]

Glecirasib and Divarasib are two other examples of G12C off inhibitors currently being investigated in clinical trials. A phase II, single arm study studying the efficacy of Glecirasib was presented at ASCO in 2024.[45] This China based trial enrolled 119 patients with most patients (94%) having received prior platinum based or ICI therapy. 79% of the patients were male. Confirmed ORR was 47.9% while mPFS and mOS were 8.2 and 13.6 months, respectively while grade 3 or higher treatment related adverse events occurred in 39.5% of patients.[45] Overall, Glecirasib has shown promising early results and should be further tested in larger phase III trials. In a phase I trial testing safety, tolerability and anti-tumor activity, Divarasib was shown to have a confirmed response rate of 53% in the NSCLC group with a mPFS of 13.1 months.[46] 12% of patients reported a grade 3 or higher treatment related adverse event. Further trials exploring Divarasib as monotherapy are underway as well as an active combination trial studying Divarasib with pembrolizumab (NCT05789082).

Table 1. Active clinical trials involving NSCLC patients targeting the KRAS G12C mutation organized by trial phase.

NCT ID	Title	Phase	KRAS Variants	Completion Date
NCT04330664	Adagrasib in Combination With TNO155 in Patients With Cancer (KRYSTAL 2)	PHASE1	G12C	2025-01-22
NCT05485974	A Dose Escalation Study of HBI-2438 (G12C inhibitor) in Patients With Solid Tumors Harboring KRAS G12C Mutation	PHASE1	G12C	2025-08
NCT06039384	A Study of INCB099280 in Combination With Adagrasib in Adults With Advanced Solid Tumors Harboring a KRASG12C Mutation	PHASE1	G12C	2025-11-03
NCT05462717	Dose Escalation and Dose Expansion Study of RMC-6291 (G12C inhibitor) Monotherapy in Subjects With Advanced KRASG12C Mutant Solid Tumors	PHASE1	G12C	2025-12
NCT04973163	A Study to Test Different Doses of **BI 1823911 (G12C inhibitor)** Alone and Combined With Other Medicines in People With Different Types of Advanced Cancer With KRAS Mutation	PHASE1	G12C	2025-12-27
NCT06127940	K-SAB Trial—Sotorasib Followed by SBRT to 1-3 Lesions in Advanced NSCLC With KRASG12C Mutation	PHASE1	G12C	2026-01-01
NCT06249282	Carfilzomib in Combination With Sotorasib for the Treatment of Patients With KRAS G12C Mutated Advanced or Metastatic Non-small Cell Lung Cancer	PHASE1	G12C	2026-03-19
NCT04449874	A Study to Evaluate the Safety, Pharmacokinetics, and Activity of GDC-6036 (G12C inhibitor) Alone or in Combination in Participants With Advanced or Metastatic Solid Tumors With a KRAS G12C Mutation	PHASE1	G12C	2026-03-31
NCT05840510	Adagrasib in Combination With Nab-Sirolimus in Patients With Advanced Solid Tumors and Non-Small Cell Lung Cancer With a KRAS G12C Mutation (KRYSTAL -19)	PHASE1	G12C	2026-06-30
NCT05815173	Ladarixin With Sotorasib in Advanced NSCLC	PHASE1	G12C	2026-08
NCT06128551	Study of RMC-6291 in Combination with RMC-6236 (pan but studying G12C population) in Participants with Advanced KRAS G12C Mutant Solid Tumors	PHASE1	G12C	2026-11-30
NCT06026410	KO-2806 (G12C inhibitor) Monotherapy and Combination Therapies in Advanced Solid Tumors	PHASE1	G12C	2027-04
NCT05504278	Efficacy and Safety of IBI351 (G12C inhibitor) in Combination With Sintilimab ± Chemotherapy in Advanced Non-squamous Non-small Cell Lung Cancer Subjects With KRAS G12C Mutation	PHASE1	G12C	2027-07-31
NCT06343402	Study of BBO-8520 (G12C inhibitor) in Adult Subjects with KRASG12C Non-small Cell Lung and Colorectal Cancer	PHASE1	G12C	2028-02
NCT04185883	Sotorasib Activity in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation (CodeBreak 101)	PHASE1	G12C	2028-03-13
NCT06447662	A Study to Learn About the Study Medicine PF-07934040 (KRAS inhibitor) When Given Alone or With Other Anti-cancer Therapies in People With Advanced Solid Tumors That Have a Genetic Mutation.	PHASE1	G12C	2028-06-07
NCT06130254	Phase Ib Trial of the KRAS G12C Inhibitor Adagrasib (MRTX849) in Combination with the PARP Inhibitor Olaparib in Patients with KRAS G12C Mutated Advanced Solid Tumors, with a Focus on Gynecological, Breast, Pancreatic and KEAP1 Mutated Non-small Cell Lung Cancers	PHASE1	G12C	2030-08-25
NCT05005234	A Study of GFH925 (G12C inhibitor) in Patients With Advanced Solid Tumors With KRAS G12C Mutations	PHASE1, PHASE2	G12C	2024-04-10
NCT05375994	Study of Avutometinib (VS-6766) + Adagrasib (**G12C inhibitor**) in KRAS G12C NSCLC Patients	PHASE1, PHASE2	G12C	2025-01-01
NCT06237400	A Study of ZG19018 (G12C inhibitor) in Patients With KRAS G12C Mutant Advanced Solid Tumors.	PHASE1, PHASE2	G12C	2025-05
NCT05756153	A Study of GFH925 (G12C inhibitor) in Combination with Cetuximab in Previously Untreated Advanced NSCLC Harboring KRAS G12C Mutation	PHASE1, PHASE2	G12C	2025-08
NCT05009329	A Study of JAB-21822(G12C inhibitor) in Adult Patients With Advanced Solid Tumors Harboring KRAS p.G12C Mutation in China	PHASE1, PHASE2	G12C	2025-12
NCT05358249	Platform Study of JDQ443 (G12C inhibitor) in Combinations in Patients With Advanced Solid Tumors Harboring the KRAS G12C Mutation	PHASE1, PHASE2	G12C	2025-12-22
NCT05276726	A Study of JAB-21822 (G12C inhibitor) in Advanced or Metastatic NSCLC With KRAS p.G12C and STK11 Co-mutation and Wild-type KEAP1	PHASE1, PHASE2	G12C	2026-02
NCT05288205	Phase 1/2a Study of JAB-21822 Plus JAB-3312 (G12C inhibitor) in Patients With Advanced Solid Tumors Harboring KRAS p.G12C Mutation	PHASE1, PHASE2	G12C	2026-03
NCT04699188	Study of JDQ443 (G12C inhibitor) in Patients With Advanced Solid Tumors Harboring the KRAS G12C Mutation	PHASE1, PHASE2	G12C	2026-04-30
NCT04956640	Study of LY3537982 (G12C inhibitor) in Cancer Patients With a Specific Genetic Mutation (KRAS G12C)	PHASE1, PHASE2	G12C	2026-06

Table 1. Continued

NCT ID	Title	Phase	KRAS Variants	Completion Date
NCT05074810	Phase 1/2 Study of Avutometinib (VS-6766) + Sotorasib With or Without Defactinib in KRAS G12C NSCLC Patients	PHASE1, PHASE2	G12C	2027-04
NCT05789082	A Study Evaluating the Safety, Activity, and Pharmacokinetics of Divarasib (G12C inhibitor) in Combination With Other Anti-Cancer Therapies in Participants With Previously Untreated Advanced or Metastatic Non-Small Cell Lung Cancer With a KRAS G12C Mutation	PHASE1, PHASE2	G12C	2027-05-10
NCT06244771	A Study Evaluating FMC-376 (G12C inhibitor) in Participants with KRAS G12C Mutated Solid Tumors	PHASE1, PHASE2	G12C	2028-04
NCT03600883	A Phase 1/2, Study Evaluating the Safety, Tolerability, PK, and Efficacy of Sotorasib (AMG 510) in Subjects With Solid Tumors With a Specific KRAS Mutation (CodeBreaK 100)	PHASE1, PHASE2	G12C	2028-05-30
NCT05993455	A Phase 2 Basket Trial in Which Patients With Advanced Solid Tumors Carrying the KRAS G12C mutation Receive Treatment With a Combination of Sotorasib and Panitumumab	PHASE2	G12C	2023-12-31
NCT05311709	Sotorasib in Advanced KRASG12C-mutated Non-small Cell Lung Cancer Patients With Comorbidities	PHASE2	G12C	2025-03-01
NCT05853575	Trial of Two Adagrasib Dosing Regimens in NSCLC With KRAS G12C Mutation (KRYSTAL 21)	PHASE2	G12C	2025-03-31
NCT05118854	A Phase II Study of Neoadjuvant Sotorasib in Combination with Cisplatin or Carboplatin and Pemetrexed for Surgically Resectable Stage IIA-IIIB Non-Squamous Non-Small Cell Lung Cancer with a KRAS P.G12C Mutation	PHASE2	G12C	2025-10-20
NCT04933695	A Study of Sotorasib (AMG 510) in Participants With Stage IV NSCLC Whose Tumors Harbor a KRAS p.G12C Mutation in Need of First-line Treatment	PHASE2	G12C	2026-01-13
NCT05673187	Adagrasib in Patients With KRASG12C-mutant NSCLC Who Are Elderly or Have Poor Performance Status	PHASE2	G12C	2026-03-01
NCT06582771	A Study of Sotorasib in People with Non-Small Cell Lung Cancer	PHASE2	G12C	2026-08
NCT05609578	Combination Therapies With Adagrasib in Patients With Advanced NSCLC With KRAS G12C Mutation	PHASE2	G12C	2026-12-01
NCT06333678	A Study Comparing Sotorasib With Durvalumab in People With Non-Small Cell Lung Cancer (NSCLC)	PHASE2	G12C	2027-03
NCT05631249	Sotorasib in Previously Treated Locally Advanced or Metastatic NSCLC Subjects With Mutated KRAS p.G12C	PHASE2	G12C	2027-06-13
NCT05445843	Study of Efficacy and Safety of JDQ443 (G12C inhibitor) Single-agent as First-line Treatment for Patients With Locally Advanced or Metastatic KRAS G12C- Mutated Non-small Cell Lung Cancer With a PD-L1 Expression < 1% or a PD-L1 Expression ≥ 1% and an STK11 Co-mutation.	PHASE2	G12C	2027-11-30
NCT04625647	Testing the Use of Targeted Treatment (AMG 510) for KRAS G12C Mutated Advanced Non-squamous Non-small Cell Lung Cancer (A Lung-MAP Treatment Trial)	PHASE2	G12C	2027-12-31
NCT06248606	Adagrasib + SRS for Patients With Metastatic KRAS G12C-mutated NSCLC With Untreated Brain Metastases	PHASE2	G12C	2028-08
NCT05398094	Clinical Trial of AMG510 (Sotorasib) in Stage III Unresectable NSCLC KRAS p.G12C Patients and Ineligible for Chemo-radiotherapy	PHASE2	G12C	2028-12-31
NCT05472623	Neoadjuvant KRAS G12C Directed Therapy With **Adagrasib** (MRTX849) With or Without Nivolumab	PHASE2	G12C	2029-02-01
NCT04613596	Phase 2 Trial of Adagrasib Monotherapy and in Combination With Pembrolizumab and a Phase 3 Trial of Adagrasib in Combination in Patients With a KRAS G12C Mutation KRYSTAL-7	PHASE2, PHASE3	G12C	2029-10-31
NCT04685135	Phase 3 Study of MRTX849 (Adagrasib) vs Docetaxel in Patients With Advanced Non-Small Cell Lung Cancer With KRAS G12C Mutation	PHASE3	G12C	2024-12-31
NCT05132075	Study of JDQ443 (G12C inhibitor) in Comparison With Docetaxel in Participants With Locally Advanced or Metastatic KRAS G12C Mutant Non-small Cell Lung Cancer	PHASE3	G12C	2025-04-24
NCT04303780	Study to Compare AMG 510 "Proposed INN **Sotorasib (G12C inhibitor)**" With Docetaxel in Non Small Cell Lung Cancer (NSCLC) (CodeBreak 200).	PHASE3	G12C	2026-04-27
NCT06416410	JAB-21822 (Glecirasib - G12C inhibitor) Combined With JAB-3312 Compared SOC in the First Line for Treatment of Advanced Non-small Cell Lung Cancer With KRAS p.G12C Mutation	PHASE3	G12C	2027-02-28
NCT06300177	D-1553 (G12C inhibitor)Tablet Versus Docetaxel Injection for KRAS G12C Mutation-positive Locally Advanced or Metastatic Non-small Cell Lung Cancer After Prior Standard Therapy Failure	PHASE3	G12C	2027-12

Table 1. Continued

NCT ID	Title	Phase	KRAS Variants	Completion Date
NCT06497556	A Study Evaluating the Efficacy and Safety of Divarasib Versus Sotorasib or Adagrasib in Participants With Previously Treated KRAS G12C-positive Advanced or Metastatic Non-Small Cell Lung Cancer	PHASE3	G12C	2029-09-30
NCT06119581	A Study of First-Line Olomorasib (LY3537982 - G12C inhibitor) and Pembrolizumab With or Without Chemotherapy in Patients With Advanced KRAS G12C-Mutant Non-small Cell Lung Cancer	PHASE3	G12C	2029-10
NCT06345729	A Study of MK-1084 (G12C inhibitor) Plus Pembrolizumab (MK-3475) in Participants With KRAS G12C Mutant, Metastatic Non-small Cell Lung Cancer (NSCLC) With Programmed Cell Death Ligand 1 (PD-L1) Tumor Proportion Score (TPS) ≥ 50% (MK-1084-004)	PHASE3	G12C	2031-02-18
NCT05920356	A Study Evaluating Sotorasib Platinum Doublet Combination Versus Pembrolizumab Platinum Doublet Combination as a Front-Line Therapy in Participants With Stage IV or Advanced Stage IIIB/C Nonsquamous Non-Small Cell Lung Cancers (CodeBreaK 202)	PHASE3	G12C	2031-03-01

This new generation of G12C off inhibitors in development generally have stronger binding capabilities than Sotorasib or Adagrasib along with being highly selective.[47] For example, in laboratory studies, Opnurasib has been shown to be effective against G12C lines that showed resistance to Sotorasib and Adagrasib and hopefully, future results with Garsorasib will show efficacy against brain metastasis as mentioned above. Overall, these new G12C off inhibitors have shown numerous advantages in pre-clinical studies and could offer an exciting next step beyond Sotorasib and Adagrasib.

KRAS G12C on inhibitors in development

KRAS off inhibitors are the predominant type of KRAS therapy currently in development, but RMC-6291 is an example of a KRAS G12C on inhibitor currently being studied. RMC-6291 forms a tri-complex with cyclophilin and GTP-bound KRAS G12C which blocks the interaction between RAS and RAF. KRAS "on" inhibitors target the GTP-bound, active state of the KRAS protein. The hope is that these new on inhibitors can provide an option for patients who become resistant to the classic off inhibitor therapy since these inhibitors are likely to be more potent than the off inhibitors mentioned above. A study is currently underway evaluating the efficacy and safety of RMC-6291 and as of August 2023, 47 NSCLC patients have been treated with 35 still on treatment and the ORR was 57% in NSCLC patients who were previously treated with Adagrasib (off inhibitor).[48] RM-018 is another KRAS G12C on inhibitor being tested in pre-clinical studies and has proven resilient against the Y96D mutation.[49,50]

KRAS G12D and Pan-KRAS therapies in development

The G12D variant has been much more difficult to make an inhibitor against because of the substitution with aspartic acid causing a negative charge and repulsive forces in the popular GTP binding region.[51] The switch II pocket region in KRAS G12D does not have a reactive cysteine target and aspartic acid makes a covalent bonding approach difficult. It has been called a much "colder" nucleophile region as compared to the G12C binding region of interest.[52] However, compounds were identified and modified to react to form a salt bridge with aspartic acid in the switch II region leading to increased affinity. As a result, MRTX1133 and TSN1611 are two G12D inhibitors that are in active phase I/II trials. MRTX1133, a G12D off inhibitor, has been shown to have anti-tumor activity as well as the ability to manipulate the tumor microenvironment in pancreatic cancer cell lines.[53] HRS-4642 (off inhibitor) and RMC-9805 (on inhibitor) are two other G12D inhibitors that have shown some promise in early clinical data.[54,55] ASP3082 is a proteolysis-targeting chimera (PROTAC) molecule that is targeted against KRAS G12D and was recently presented at ESMO this past year in 2024. PROTAC molecules efficiently degrade proteins that are marked for destruction through the ubiquitin-proteosome system in cells.[56] Preliminary data was released showing an appropriate safety profile and antitumor activity among 98 patients (67 pancreatic cancer, 16 colorectal, 13 NSCLC, and 2 other cancers).[57] At the highest dose (300mg), an ORR of 33% was achieved along with a disease control rate of 75% among 12 patients.

RMC-6236 is an exciting multi-selective, tri-complex pan-KRAS inhibitor that targets active GTP bound KRAS and creates a protein complex between RAS and cyclophilin A. By combining RAS with cylophilin A, it prevents the interaction needed between RAS and other signaling proteins required to trigger the MAPK/PI3K pathways. RMC-6236 showed promise in preclinical data causing suppression of multiple RAS mutated cell lines of NSCLC, PDAC, and CRC and created an added benefit when coupled with immune checkpoint inhibition.[58] ORR of 38% and mOS of 17.7 months among NSCLC patients in a phase 1 study that included both NSCLC and PDAC tumors.[58,59] An updated analysis from October 2024 focused on PDAC patients and revealed that patients in the second line (2L) treatment setting with G12X mutations had a mPFS and mOS of 8.5 and 14.5 months, respectively.[58,60,61] RMC-LUNG-101 is a currently active phase 1b trial testing RMC-6236 in combination with pembrolizumab and chemotherapy in patients with RAS-mutated advanced NSCLC (NCT06162221).

KRAS G12V and other variants

The G12V variant accounts for around 21% of NSCLC KRAS mutated cases and 3% of overall NSCLC cases.[62] It has been associated more with smokers as well as a higher early recurrence rate of disease.[63] QTX3544 is a multi-KRAS inhibitor with more selectivity towards the G12V variant

Table 2. Active clinical trials involving NSCLC patient targeting KRAS non-G12C mutations organized by trial phase.

NCT ID	Title	Phases	KRAS variants	Completion date
NCT06078800	A Study of YL-17231 (pan RAS inhibitor) in Patients with Advanced Solid Tumors	PHASE1	KRAS	2025-12
NCT06043713	Autologous CD8 + and CD4 + Transgenic T Cells Expressing High Affinity KRASG12V Mutation-Specific T Cell Receptors (FH-A11KRASG12V-TCR) in Treating Patients with Metastatic Pancreatic, Colorectal and Non-Small Cell Lung Cancers with KRAS G12V Mutations	PHASE1	G12V; KRAS	2025-12-31
NCT04853017	A Study of ELI-002 (vaccine targeted G12D, G12R) in Subjects with KRAS Mutated Pancreatic Ductal Adenocarcinoma (PDAC) and Other Solid Tumors	PHASE1	G12R; G12D; KRAS	2026-03
NCT05379985	Study of RMC-6236 (pan-KRAS) in Patients with Advanced Solid Tumors Harboring Specific Mutations in RAS	PHASE1	KRAS	2026-06-30
NCT06585488	A First-in-human Study of BGB-53038, a Pan-KRAS Inhibitor, Alone or in Combinations in Participants with Advanced or Metastatic Solid Tumors with KRAS Mutations or Amplification	PHASE1	G12R; KRAS	2026-12
NCT05254184	KRAS-Targeted Vaccine with Nivolumab and Ipilimumab for Patients with NSCLC	PHASE1	G12R; G12A; KRAS; G12C; G12V; G12D; G13D	2027-04-01
NCT06403735	A Phase I Clinical Study of QLC1101 (G12D inhibitor) in Patients With Advanced Solid Tumors	PHASE1	G12D; KRAS	2027-04-30
NCT06364696	A Study to Find a Suitable Dose of ASP4396 (G12D inhibitor) in Adults with Solid Tumors	PHASE1	G12D; KRAS	2027-04-30
NCT06040541	Study of RMC-9805 (G12D inhibitor) in Participants with KRAS G12D-Mutant Solid Tumors	PHASE1	G12D; KRAS	2027-04-30
NCT06447662	A Study to Learn About the Study Medicine PF-07934040 (KRAS inhibitor) When Given Alone or With Other Anti-Cancer Therapies in People With Advanced Solid Tumors That Have a Genetic Mutation.	PHASE1	KRAS; G12C	2028-06-07
NCT06625775	Dose Escalation and Expansion of BBO-10203 (pan-RAS) in Advanced Solid Tumors (BREAKER-101)	PHASE1	KRAS	2028-11
NCT06586515	A Study of LY3962673 (G12D inhibitor) in Participants With KRAS G12D-Mutant Solid Tumors	PHASE1	G12D; KRAS	2029-03
NCT06607185	A Study of the Pan-KRAS Inhibitor LY4066434 in Participants With KRAS Mutant Solid Tumors	PHASE1	G12A; G12S; KRAS; G12C; G12V; G12D; G13D	2030-01
NCT06253520	Autologous **T-cells Genetically Engineered** to Express Receptors Reactive **Against KRAS Mutation**s in Conjunction With a Vaccine Directed Against These Antigens in Participants With Metastatic Cancer	PHASE1	G12V; G12D; KRAS	2033-06-15
NCT06218914	A Study of NT-112 (T-cell therapy targeting KRAS G12D mutation) in HLA-C*08:02-Positive Adult Subjects With Unresectable, Advanced, and/ or Metastatic Solid Tumors Positive for the KRAS G12D Mutation	PHASE1	G12D; KRAS	2040-08-30
NCT06237413	A Study of ZG2001 (pan-KRAS inhibitor) in Participants With KRAS Mutated Advanced Solid Tumours	PHASE1, PHASE2	KRAS	2026-02
NCT05578092	A Phase 1/2 Study of MRTX0902 (KRAS inhibitor) in Solid Tumors With Mutations in the KRAS MAPK Pathway	PHASE1, PHASE2	KRAS; G12C	2026-07-30
NCT05737706	Study of MRTX1133 (G12D inhibitor) in Patients With Advanced Solid Tumors Harboring a KRAS G12D Mutation	PHASE1, PHASE2	G12D; KRAS	2026-08-30
NCT06385925	A Study of TSN1611 (G12D inhibitor) Treating Patients With Advanced Solid Tumors Harboring KRAS G12D Mutation	PHASE1, PHASE2	G12D; KRAS	2027-04-30
NCT06599502	A Phase I/IIa Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Efficacy of AZD0022 (G12D inhibitor) as Monotherapy and in Combination With Anti-cancer Agents in Adult Participants With Tumours Harbouring a KRASG12D Mutation	PHASE1, PHASE2	G12D; KRAS	2028-02-03
NCT03745326	Administering Peripheral Blood Lymphocytes Transduced With a Murine T-Cell Receptor Recognizing the **G12D Variant of Mutated RAS** in HLA-A*11:01 Patients	PHASE1, PHASE2	G12D; KRAS	2028-12-01
NCT06015724	Anti-CD38 Antibody With KRAS Vaccine and Anti-PD-1 Antibody in Subjects With Pancreatic Ductal Adenocarcinoma and Refractory Non-Small Cell Lung Cancer	PHASE2	KRAS; G12C	2026-01

Tables 1 and 2 comprise of active, ongoing clinical trials for KRAS mutated NSCLC. KRAS G12C is by far the most studied and researched genotype with clinical trials spanning all phases with many more trials involving combination strategies. An increase over the past year of trials involving non-G12C KRAS mutations shows how the field is changing. With new data being released on G12D, PROTAC, G12V, and Pan-KRAS targets, Table 2 would likely grow rapidly in the years to come.

that has shown some promise in pre-clinical trials. This drug showed appropriate affinity to G12V mutated cell lines in vitro and limited their growth along with having mild CNS penetration in mice models.[64] RMC-5127 is a G12V inhibitor that has done well in vitro and has shown success in CNS penetration in pre-clinical data.[65] Dose dependant exposure was observed in the brain of mice and revealed extensive anti-tumor activity. NSCLC patients harboring a G12V mutation who develop brain metastasis may have a targeted treatment option in the future if this preclinical data holds in phase I/II trials. AFNT-211 is a G12V based cellular therapy that uses re-engineered T cells to express a G12V specific T cell receptor that would be used to treat KRAS G12V mutated solid tumors. It is currently undergoing a phase 1 trial testing the safety and tolerability of this treatment.[66] There are currently no active clinical trials specifically targeting G12A. There are currently three active clinical trials that involve the G13 variant that include patients with metastatic lung cancer, but no active trials involving only the Q61 variant.[67] RMC-8839 is the only known G13C on inhibitor currently in development. **Table 2** shows active clinical trials for KRAS non-G12C inhibitors which include NSCLC patients. **Figure 2** depicts KRAS-mutated NSCLC as separate diseases based on KRAS variants with their respective KRAS targeted therapies either approved or in development.

Mechanisms of resistance

KRAS G12C inhibitors, that is, Adagrasib and Sotorasib, have shown utility in targeting KRAS G12C-mutated cancers, however, resistance can develop through complex and diverse mechanisms that can emerge during treatment.[68] Primary resistance occurs before initiation of treatment and is likely facilitated by co-mutations that circumvent KRAS dependency, leading to intrinsic resistance and thus a poor initial response.[69] While these mechanisms remain mostly unknown, they are thought to involve reactivation of multiple MAPK effectors that are both upstream and downstream of RAS.[69] KRAS aberrations and variants, including G12D, G12R, G12V, G12W, G13D, Q61H, H95D, H95Q, H95R, Q61H, R68S, Y96D and Y96C, have been implicated in primary as well as acquired resistance that led to bypass mechanisms of KRAS dependency.[68] For example, KRAS R68S and Y96D mutations were found to manipulate the structure of the switch II pocket region by disrupting hydrogen bonding which prevents the inhibitor from binding.[70]

Acquired resistance develops during therapy and includes both "on-target" mechanisms, such as secondary mutations in KRAS, and "off-target" mechanisms, such as gain-of-function mutations in oncogenes (eg, RET, BRAF, NRAS) or loss-of-function mutations in tumor suppressors (eg, PTEN).[1,3,68,71] It has been reported that patients who initially responded to KRAS G12C inhibition developed subsequent downstream alterations of BRAF and MEK mutations combined with gene fusions, resulting in reduced efficacy of KRAS G12C inhibition.[72] Attempts to overcome resistance with combinational therapy have been met with challenges as preclinical studies indicate that KRAS G12C inhibitors coupled with SHP2 inhibitors result in MAPK/PI3K pathway reactivation as well as KRAS G12C amplification, contributing to acquired resistance.[73] This bypass or escape signaling method of resistance results from upstream RTK regulators (EGFR, HER2, or SHP2) and PIK3/mTOR pathways becoming continuously activated through negative feedback or phosphorylation while KRAS is suppressed.[74] Combinatorial strategies involving MEK, EGFR, or pan-RAS inhibitors are being tested in clinical trials with hopes to overcome these bypass signalling mechanisms.[75] For example, Sotorasib combined with the MEK inhibitor trametinib and the EGFR antibody panitumamab showed a partial response in 20% in NSCLC patients in the CodeBreak 101 trial.[76] The pan-KRAS inhibitor RMC-6236 is currently being studied in combination with another G12C inhibitor to block further activation of RAS subtypes (HRAS, NRAS) which aims to limit RTK-MAPK bypass signalling altogether (NCT06128551).

More broadly, phenotypic transitions, such as adeno-to-squamous transition (AST) and epithelial-to-mesenchymal transition (EMT), have also been implicated in KRASG12C inhibitor resistance. AST is associated with LKB1 co-mutations and resistance to Adagrasib in KRAS G12C-mutated adenocarcinomas.[77] EMT is linked to both primary and acquired resistance, with mechanisms that appear to bypass KRAS inhibition.[78] Unraveling the role of AST and EMT in KRAS inhibitor resistance may perhaps facilitate discovery of predictive biomarkers to help optimize KRAS-targeted therapies.

Future direction

Many of these trials mentioned in this review are dominated by white, non-Hispanic patients. 97/116 or 83% of the patients in the Krystal-1 trial were white whereas 141/174 patients or 82% in the CodeBreak trial were white.[37,79] A brand-new study this past year evaluated the distribution of racial/ethnic enrollment in NSCLC trials and of the 28 540 patients identified, 79.6% were white, 3% were black, 10.4% were of Asian descent, and 3.5% were Hispanic/Latino.[80] Future directions need to include better guidelines in detailing demographic/racial data in clinical trials, more minority representation in clinical trial recruitment, and more inclusive support and logistical systems that can help recruit and offer transport to patients in diverse communities. More specifically, setting up offices and resource centers in minority-majority neighborhoods that provide education around safety and benefits while creating trust. Having numerous language resources and making sure that all materials and information is available in multiple languages is crucial. In additional to offering transportation services to and from trial centers, having the option of hybrid/virtual meetings for enrollment and appointments can also increase participation.

Other exciting trials are in development that are addressing lower stage, resectable NSCLC with targeted therapy, including KRAS inhibitors. The NAUTIKA1 trial is a phase II trial evaluating multiple neoadjuvant and adjuvant targeted therapies for resectable stage 1B, II, IIIA or IIIB NSCLC patients. KRAS G12C is one of the mutations that qualify for inclusion to see if there is a role for KRAS inhibitors at earlier stages of NSCLC.[81] Other trials incorporating KRAS inhibitors in new treatment settings include the K-SAB trial. This trial is testing Sotorasib followed by stereotactic radiation therapy (SBRT) to 1-3 lesions in patients with advanced NSCLC (NCT06127940).

The treatment landscape for NSCLC is changing rapidly with the introduction of immunotherapy and targetable mutations. KRAS mutated NSCLC is an extremely heterogenous disease as outlined in the review. The future of KRAS

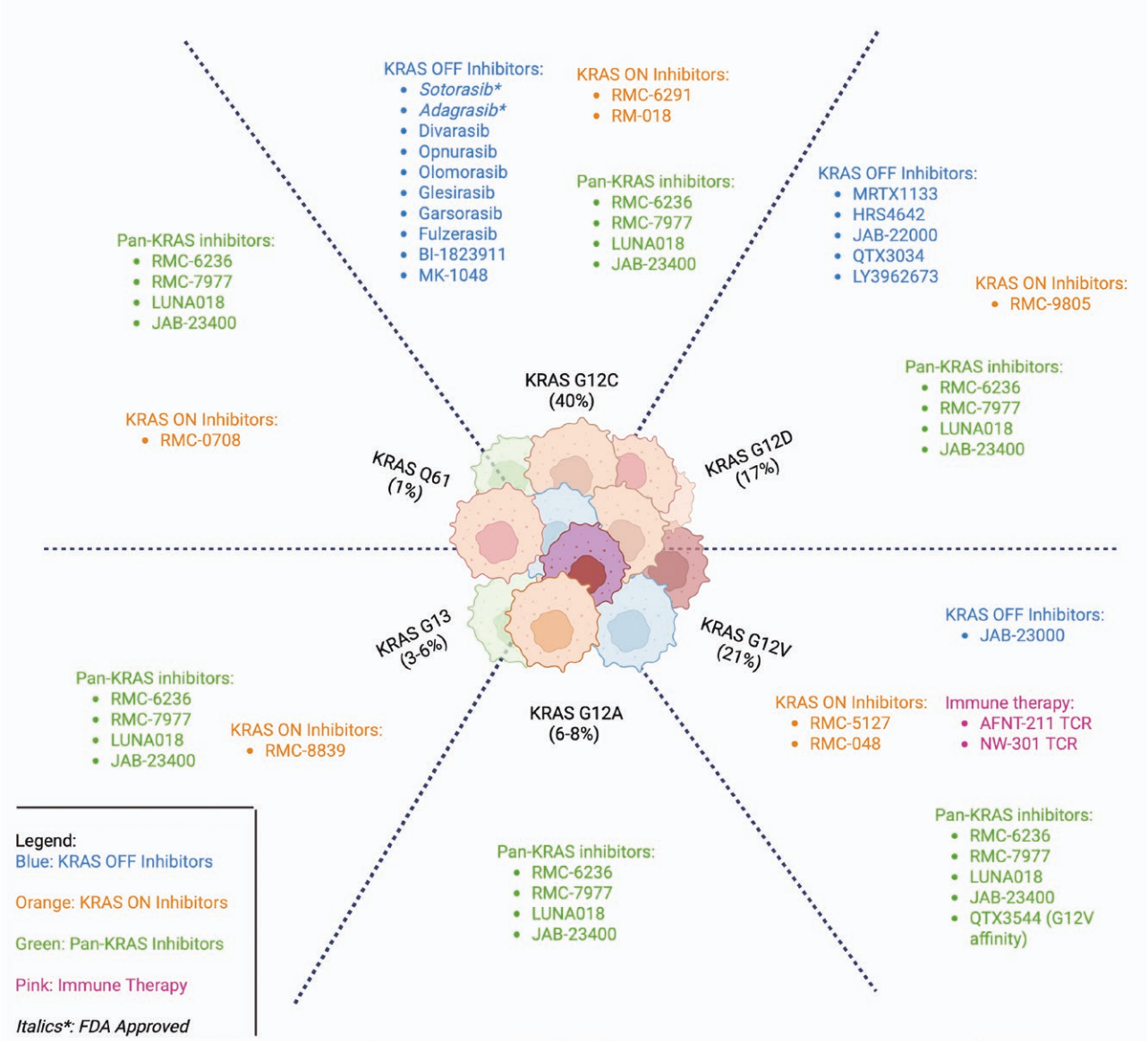

Figure 2. NSCLC KRAS mutated disease subtypes with associated targeted therapies and percent prevalence. Blue: KRAS OFF inhibitors; Orange: KRAS ON inhibitors; Green: Pan-KRAS inhibitors; Pink: Immune therapy; Italics and asterisk: FDA approval.Created in BioRender. Frisch, A. (2025) https://BioRender.com/t91n013

therapy is exciting yet largely unknown which is why it is crucial to outline these areas of unmet need.

Acknowledgement

The discussion and collaboration for the creation of this manuscript was made possible by the Evolving Therapies Symposium at Inova Schar Cancer Center organized by Dr Nagla Karim.

Author contributions

Austin Frisch (Writing-original draft, Writing- review and editing, conceptualization). Eric Martin (Writing -review and editing, data curation). So Teon Kim (Writing- review and editing). Jonathan W. Reiss (: Writing—review and editing). Triparna Sen (Writing—review and editing, supervision). Nagla Karim (Writing—review and editing, supervision).

Funding

No outside funding was used in design/conception of this manuscript

Conflicts of interest

A.F.: none. E.M.: none. S.Y.K.: Dr. Kim receives research funding (to institution) from Genentech, LoxoLilly, Mirati/BMS, BridgeBio, Genmab, Bioinvent, AstraZeneca, MonteRosa, BI, Dynamicure, Seagen, Gilead. Dr. Kim served on the advisory board for Genentech and Revolution Medicine. J.W.R.: Dr. Riess receives research funding (to insitutition) from AstraZeneca, Novartis, Summit, Merck, Nuvalent, IO Biotech, ArriVent, Revolution Medicines and Boehringer Ingelheim as well as consultant/advisory board fees from BMS, Daiichi Sankyo, Boehringer Ingelheim, Janssen, Pfizer, Oncohost, GSK, Catalyst and Amgen. T.S.: Dr. Sen has received grant

funding from Jazz Pharmaceuticals and Debiopharm as well as consultant/advisory board fees from Regeneron and BMS. N.K.: none.

Data availablity

Authors confirm that the data supporting the findings of this study are available within the article

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74:12-49. https://doi.org/10.3322/caac.21820
2. Ganti AK, Klein AB, Cotarla I, Seal B, Chou E. Update of incidence, prevalence, survival, and initial treatment in patients with non-small cell lung cancer in the US. *JAMA Oncol*. 2021;7:1824-1832. https://doi.org/10.1001/jamaoncol.2021.4932
3. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.
4. Rosell R, Codony-Servat J, Gonzalez J, et al. KRAS G12C-mutant driven non-small cell lung cancer (NSCLC). *Crit Rev Oncol Hematol*. 2024;195:104228. https://doi.org/10.1016/j.critrevonc.2023.104228
5. Punekar SR, Velcheti V, Neel BG, Wong KK. The current state of the art and future trends in RAS-targeted cancer therapies. *Nat Rev Clin Oncol*. 2022;19:637-655. https://doi.org/10.1038/s41571-022-00671-9
6. Miyashita H, Kato S, Hong DS. KRAS G12C inhibitor combination therapies: current evidence and challenge. *Front Oncol*. 2024;14:1380584. https://doi.org/10.3389/fonc.2024.1380584
7. Negrao MV, Araujo HA, Lamberti G, et al. Comutations and KRASG12C inhibitor efficacy in advanced NSCLC. *Cancer Discov*. 2023;13:1556-1571. https://doi.org/10.1158/2159-8290.CD-22-1420
8. Skoulidis F, Goldberg ME, Greenawalt DM, et al. STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma. *Cancer Discov*. 2018;8:822-835. https://doi.org/10.1158/2159-8290.CD-18-0099
9. 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 Thoracic Oncol*. 2022;17:399-410. https://doi.org/10.1016/j.jtho.2021.10.013
10. Sumii M, Namba M, Tokumo K, et al. Concurrent mutations in STK11 and KEAP1 cause treatment resistance in KRAS wild-type non-small-cell lung cancer. *Intern Med*. 2023;62:3001-3004. https://doi.org/10.2169/internalmedicine.1110-22
11. Wohlhieter CA, Richards AL, Uddin F, et al. Concurrent mutations in STK11 and KEAP1 promote ferroptosis protection and SCD1 dependence in lung cancer. *Cell Rep*. 2020;33:108444. https://doi.org/10.1016/j.celrep.2020.108444
12. Pons-Tostivint E, Lugat A, Fontenau JF, Denis MG, Bennouna J. STK11/LKB1 modulation of the immune response in lung cancer: from biology to therapeutic impact. *Cells*. 2021;10:3129. https://doi.org/10.3390/cells10113129
13. Hu L, Liu M, Tang B, et al. Posttranslational regulation of liver kinase B1 in human cancer. *J Biol Chem*. 2023;299:104570. https://doi.org/10.1016/j.jbc.2023.104570
14. Hollstein PE, Eichner LJ, Brun SN, et al. The AMPK-Related Kinases SIK1 and SIK3 mediate key tumor-suppressive effects of LKB1 in NSCLC. *Cancer Discov*. 2019;9:1606-1627. https://doi.org/10.1158/2159-8290.CD-18-1261
15. Sun Z, Jiang Q, Li J, Guo J. The potent roles of salt-inducible kinases (SIKs) in metabolic homeostasis and tumorigenesis. *Signal Transduct Target Ther*. 2020;5:150. https://doi.org/10.1038/s41392-020-00265-w
16. Sen U, Coleman C, Sen T. Stearoyl coenzyme A desaturase-1: multitasker in cancer, metabolism, and ferroptosis. *Trends Cancer*. 2023;9:480-489. https://doi.org/10.1016/j.trecan.2023.03.003
17. Dong ZY, Zhong WZ, Zhang XC, et al. Potential predictive value of TP53 and KRAS mutation status for response to PD-1 blockade immunotherapy in lung adenocarcinoma. *Clin Cancer Res*. 2017;23:3012-3024. https://doi.org/10.1158/1078-0432.CCR-16-2554
18. Cucurull M, Notario L, Sanchez-Cespedes M, et al. Targeting KRAS in lung cancer beyond KRAS G12C inhibitors: the immune regulatory role of KRAS and novel therapeutic strategies. *Front Oncol*. 2021;11:793121. https://doi.org/10.3389/fonc.2021.793121
19. Lim TKH, Skoulidis F, Kerr KM, et al. KRAS G12C in advanced NSCLC: prevalence, co-mutations, and testing. *Lung Cancer*. 2023;184:107293. https://doi.org/10.1016/j.lungcan.2023.107293
20. Bell EH, Chakraborty AR, Mo X, et al. SMARCA4/BRG1 is a novel prognostic biomarker predictive of cisplatin-based chemotherapy outcomes in resected non-small cell lung cancer. *Clin Cancer Res*. 2016;22:2396-2404. https://doi.org/10.1158/1078-0432.CCR-15-1468
21. Liu L, Ahmed T, Petty WJ, et al. SMARCA4 mutations in KRAS-mutant lung adenocarcinoma: a multi-cohort analysis. *Mol Oncol*. 2021;15:462-472. https://doi.org/10.1002/1878-0261.12831
22. Naito T, Udagawa H, Umemura S, et al. Non-small cell lung cancer with loss of expression of the SWI/SNF complex is associated with aggressive clinicopathological features, PD-L1-positive status, and high tumor mutation burden. *Lung Cancer*. 2019;138:35-42. https://doi.org/10.1016/j.lungcan.2019.10.009
23. Alessi JV, Ricciuti B, Spurr LF, et al. SMARCA4 and other SWItch/Sucrose non-fermentable family genomic alterations in NSCLC: clinicopathologic characteristics and outcomes to immune checkpoint inhibition. *J Thorac Oncol*. 2021;16:1176-1187. https://doi.org/10.1016/j.jtho.2021.03.024
24. Gadgeel S, Rodriguez-Abreu D, Felip E, et al. KRAS mutational status and efficacy in KEYNOTE-189: Pembrolizumab (pembro) plus chemotherapy (chemo) vs placebo plus chemo as first-line therapy for metastatic non-squamous NSCLC. *Ann Oncol*. 2019;30:xi64-xi65. https://doi.org/10.1093/annonc/mdz453.002
25. Socinski MA, Jotte RM, Cappuzzo F, et al; IMpower150 Study Group. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288-2301. https://doi.org/10.1056/NEJMoa1716948
26. West HJ, McCleland M, Cappuzzo F, et al. Clinical efficacy of atezolizumab plus bevacizumab and chemotherapy in KRAS-mutated non-small cell lung cancer with STK11, KEAP1, or TP53 comutations: subgroup results from the phase III IMpower150 trial. *J ImmunoTher Cancer*. 2022;10:e003027. https://doi.org/10.1136/jitc-2021-003027
27. Yang Y, Wang Z, Fang J, et al. Efficacy and safety of sintilimab plus pemetrexed and platinum as First-Line Treatment for locally advanced or Metastatic Nonsquamous NSCLC: a Randomized, Double-Blind, Phase 3 study (Oncology pRogram by InnovENT anti-PD-1-11). *J Thorac Oncol*. 2020;15:1636-1646. https://doi.org/10.1016/j.jtho.2020.07.014
28. Zhou C, Wu L, Fan Y, et al. Sintilimab Plus Platinum and Gemcitabine as First-Line Treatment for Advanced or Metastatic Squamous NSCLC: results from a Randomized, Double-Blind, Phase 3 Trial (ORIENT-12). *J Thorac Oncol*. 2021;16:1501-1511. https://doi.org/10.1016/j.jtho.2021.04.011
29. Johnson ML, Cho BC, Luft A, et al; for the POSEIDON investigators. Durvalumab with or without tremelimumab in combination with chemotherapy as First-Line Therapy for Metastatic non–small-cell lung cancer: the Phase III POSEIDON study. *J Clin Oncol*. 2023;41:1213-1227. https://doi.org/10.1200/jco.22.00975
30. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. *N Engl J Med*. 2019;381:2020-2031. https://doi.org/10.1056/NEJMoa1910231

31. Skoulidis F, Araujo HA, Do MT, et al. CTLA4 blockade abrogates KEAP1/STK11-related resistance to PD-(L)1 inhibitors. *Nature*. 2024;635:462-471. https://doi.org/10.1038/s41586-024-07943-7
32. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. *N Engl J Med*. 2021;384:2371-2381. https://doi.org/10.1056/NEJMoa2103695
33. de Langen AJ, Johnson ML, Mazieres J, et al; CodeBreaK 200 Investigators. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRAS(G12C) mutation: a randomised, open-label, phase 3 trial. *Lancet*. 2023;401:733-746. https://doi.org/10.1016/S0140-6736(23)00221-0
34. Dingemans A-MC, Syrigos K, Livi L, et al. Intracranial efficacy of sotorasib versus docetaxel in pretreated KRASG12C-mutated advanced non-small cell lung cancer (NSCLC): Practice-informing data from a global, phase 3, randomized, controlled trial (RCT). *J Clin Oncol*. 2023;41:LBA9016-LBA9016. https://doi.org/10.1200/jco.2023.41.17_suppl.lba9016
35. Bekaii-Saab TS, Yaeger R, Spira AI, et al. Adagrasib in advanced solid tumors harboring a KRAS(G12C) Mutation. *J Clin Oncol*. 2023;41:4097-4106. https://doi.org/10.1200/JCO.23.00434
36. Mok TSK, Yao W, Duruisseaux M, et al. KRYSTAL-12: Phase 3 study of adagrasib versus docetaxel in patients with previously treated advanced/metastatic non-small cell lung cancer (NSCLC) harboring a KRASG12C mutation. *J Clin Oncol*. 2024;42:LBA8509-LBALBA8LBA.
37. Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non-small-cell lung cancer harboring a *KRASG12C* mutation. *N Engl J Med*. 2022;387:120-131. https://doi.org/10.1056/nejmoa2204619
38. Heist RS, Koyama T, Murciano-Goroff YR, et al. Pan-tumor activity of olomorasib (LY3537982), a second-generation KRAS G12C inhibitor (G12Ci), in patients with KRAS G12C-mutant advanced solid tumors. *Am Soc Clin Oncol*. 2024;42:3007-3007. https://doi.org/10.1200/jco.2024.42.16_suppl.3007
39. Burns TF, Dragnev KH, Fujiwara Y, et al. Efficacy and safety of olomorasib (LY3537982), a second-generation KRAS G12C inhibitor (G12Ci), in combination with pembrolizumab in patients with *KRAS* G12C-mutant advanced NSCLC. *J Clin Oncol*. 2024;42:8510.
40. Weiss A, Lorthiois E, Barys L, et al. Discovery, preclinical characterization, and early clinical activity of JDQ443, a structurally novel, potent, and selective covalent oral inhibitor of KRASG12C. *Cancer Discov*. 2022;12:1500-1517. https://doi.org/10.1158/2159-8290.CD-22-0158
41. Cassier PA, Dooms CA, Gazzah A, et al. KontRASt-01 update: safety and efficacy of JDQ443 in KRAS G12C-mutated solid tumors including non-small cell lung cancer (NSCLC). *Am Soc Clin Oncol*. 2023;118:e4-e5. https://doi.org/10.1016/j.ijrobp.2023.10.053
42. Cappuzzo F, Castro G, Kang J-H, et al. KontRASt-02: a phase III trial investigating the efficacy and safety of the KRASG12C inhibitor JDQ443 vs docetaxel in patients with previously treated, locally advanced or metastatic, KRAS G12C-mutated NSCLC. *Am Soc Clin Oncol*. 2023;118:e14. https://doi.org/10.1016/j.ijrobp.2023.10.073
43. Li Z, Song Z, Zhao Y, et al. D-1553 (Garsorasib), a potent and selective inhibitor of KRASG12C in patients with NSCLC: phase 1 study results. *J Thoracic Oncol*. 2023;18:940-951. https://doi.org/10.1016/j.jtho.2023.03.015
44. Shi Z, Weng J, Fan X, et al. Discovery of D-1553, a novel and selective KRas-G12C inhibitor with potent anti-tumor activity in a broad spectrum of tumor cell lines and xenograft models. *Cancer Res*. 2021;81:932-932. https://doi.org/10.1158/1538-7445.am2021-932
45. Shi Y, Fang J, Xing L, et al. A pivotal phase 2 single-arm study of glecirasib (JAB-21822) in patients with NSCLC harboring KRAS G12C mutation. *J Clin Oncol*. 2024;42:468214-468214. https://doi.org/10.1200/jco.2024.42.36_suppl.468214
46. Sacher A, LoRusso P, Patel MR, et al; GO42144 Investigator and Study Group. Single-Agent Divarasib (GDC-6036) in solid tumors with a *KRAS* G12C Mutation. *N Engl J Med*. 2023;389:710-721. https://doi.org/10.1056/NEJMoa2303810
47. Oya Y, Imaizumi K, Mitsudomi T. The next-generation KRAS inhibitors... What comes after sotorasib and adagrasib? *Lung Cancer*. 2024;194:107886. https://doi.org/10.1016/j.lungcan.2024.107886
48. Jänne PA, Bigot F, Papadopoulos K, et al. Preliminary safety and anti-tumor activity of RMC-6291, a first-in-class, tri-complex KRASG12C (ON) inhibitor, in patients with or without prior KRASG12C (OFF) inhibitor treatment. *Mol Cancer Ther*. 2023;22:PR014-PR014. https://doi.org/10.1158/1535-7163.targ-23-pr014
49. Tanaka N, Lin JJ, Li C, et al. Clinical acquired resistance to KRASG12C inhibition through a novel KRAS switch-II pocket mutation and polyclonal alterations converging on RAS–MAPK reactivation. *Cancer Discov*. 2021;11:1913-1922. https://doi.org/10.1158/2159-8290.CD-21-0365
50. Koga T, Suda K, Fujino T, et al. KRAS secondary mutations that confer acquired resistance to KRAS G12C inhibitors, sotorasib and adagrasib, and overcoming strategies: insights from in vitro experiments. *J Thoracic Oncol*. 2021;16:1321-1332. https://doi.org/10.1016/j.jtho.2021.04.015
51. Lokhandwala J, Smalley TB, Tran TH. Structural perspectives on recent breakthrough efforts toward direct drugging of RAS and acquired resistance. *Front Oncol*. 2024;14:1394702. https://doi.org/10.3389/fonc.2024.1394702
52. Vatansever S, Erman B, Gümüş ZH. Oncogenic G12D mutation alters local conformations and dynamics of K-Ras. *Sci Rep*. 2019;9:11730. https://doi.org/10.1038/s41598-019-48029-z
53. Wang X, Allen S, Blake JF, et al. Identification of MRTX1133, a non-covalent, potent, and selective KRAS(G12D) inhibitor. *J Med Chem*. 2022;65:3123-3133. https://doi.org/10.1021/acs.jmedchem.1c01688
54. Zhou C, Li W, Song Z, et al. LBA33 A first-in-human phase I study of a novel KRAS G12D inhibitor HRS-4642 in patients with advanced solid tumors harboring KRAS G12D mutation. *Ann Oncol*. 2023;34:S1273. https://doi.org/10.1016/j.annonc.2023.10.025
55. Jiang L, Menard M, Weller C, et al. Abstract 526: RMC-9805, a first-in-class, mutant-selective, covalent and oral KRASG12D(ON) inhibitor that induces apoptosis and drives tumor regression in pre-clinical models of KRASG12D cancers. *Cancer Res*. 2023;83:526-526. https://doi.org/10.1158/1538-7445.am2023-526
56. Hamilton G, Eggerstorfer MT, Stickler S. Development of PROTACS degrading KRAS and SOS1. *Oncol Res*. 2024;32:1257-1264. https://doi.org/10.32604/or.2024.051653
57. Park W, Kasi A, Spira A, et al. 608O Preliminary safety and clinical activity of ASP3082, a first-in-class, KRAS G12D selective protein degrader in adults with advanced pancreatic (PC), colorectal (CRC), and non-small cell lung cancer (NSCLC). *Ann Oncol*. 2024;35:S486-S487. https://doi.org/10.1016/j.annonc.2024.08.675
58. Jiang J, Jiang L, Maldonato BJ, et al. Translational and therapeutic evaluation of RAS-GTP inhibition by RMC-6236 in RAS-driven cancers. *Cancer Discov*. 2024;14:994-1017. https://doi.org/10.1158/2159-8290.CD-24-0027
59. Arbour K, Punekar S, Garrido-Laguna I, et al. 652O Preliminary clinical activity of RMC-6236, a first-in-class, RAS-selective, tri-complex RAS-MULTI (ON) inhibitor in patients with KRAS mutant pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC). *Ann Oncol*. 2023;34:S458. https://doi.org/10.1016/j.annonc.2023.09.1838
60. Revolution medicines presents updated data from RMC-6236 monotherapy study in patients with advanced pancreatic ductal adenocarcinoma [press release]. October 23, 2024 2024.
61. Garrido-Laguna I, Wolpin BM, Park W, et al.. Safety, efficacy, and on-treatment circulating tumor DNA (ctDNA) changes from a phase 1 study of RMC-6236, a RAS(ON) multi-selective, tri-complex inhibitor, in patients with RAS mutant pancreatic ductal adenocarcinoma (PDAC). *J Clin Oncol*. 2025;43 :722. https://doi.org/10.1200/JCO.2025.43.4_suppl.722

62. Drosten M, Barbacid M. Targeting KRAS mutant lung cancer: light at the end of the tunnel. *Mol Oncol*. 2022;16:1057-1071. https://doi.org/10.1002/1878-0261.13168
63. Zhu W, Han H, Ma Z, et al. Prognostic value of KRAS G12V mutation in lung adenocarcinoma stratified by stages and radiological features. *J Thorac Cardiovasc Surg*. 2024;168:1525-1537.e6. https://doi.org/10.1016/j.jtcvs.2024.03.025
64. Zhang YW, Vo ED, Gan P, et al. Abstract LB163: discovery and characterization of QTX3544, a potent, selective, and orally bioavailable allosteric G12V preferring multi KRAS inhibitor. *Cancer Res*. 2024;84:LB163-LB163. https://doi.org/10.1158/1538-7445.am2024-lb163
65. Chen Z, Eriksson A, Lee B, et al. RMC-5127, a first-in-class, orally bioavailable mutant-selective RASG12V (ON) inhibitor is central nervous system (CNS)-penetrant and demonstrates anti-tumor activity in a preclinical intracranial xenograft model. *Cancer Res*. 2024;84:3340-3340. https://doi.org/10.1158/1538-7445.am2024-3340
66. Mitchell S, Khan B, Payumo F, et al. AFNT-211: a phase 1 study of autologous CD4+ and CD8+ T cells engineered to express a high avidity HLA-A* 11: 01-restricted, KRAS G12V-specific, transgenic TCR, a CD8α/β coreceptor, and a FAS41BB switch receptor in patients with advanced/metastatic solid tumors. *Am Soc Clin Oncol*. 2024;42:TPS8650-TPS8650. https://doi.org/10.1200/jco.2024.42.16_suppl.tps8650
67. Pollin G, Lomberk GA, Mathison AJ, Zimmermann MT, Urrutia R. Mutant KRAS inhibitors enter the scene of precision therapeutics for pancreatic cancer. *J Gastrointest Oncol*. 2024;15:1996-2001. https://doi.org/10.21037/jgo-24-326
68. Awad MM, Liu S, Rybkin II, et al. Acquired Resistance to KRAS(G12C) Inhibition in Cancer. *N Engl J Med*. 2021;384:2382-2393. https://doi.org/10.1056/NEJMoa2105281
69. Akhave NS, Biter AB, Hong DS. Mechanisms of resistance to KRAS(G12C)-Targeted therapy. *Cancer Discov*. 2021;11:1345-1352. https://doi.org/10.1158/2159-8290.CD-20-1616
70. 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;11:1913-1922. https://doi.org/10.1158/2159-8290.CD-21-0365
71. Chour A, Toffart AC, Berton E, Duruisseaux M. Mechanisms of resistance to KRASG12C inhibitors in KRASG12C-mutated non-small cell lung cancer. *Front Oncol*. 2024;14:1328728. https://doi.org/10.3389/fonc.2024.1328728
72. Caruso C. Mechanisms of KRAS inhibitor resistance revealed. *Cancer Discov*. 2021;11:1311-1312.
73. Prahallad A, Weiss A, Voshol H, et al. CRISPR screening identifies mechanisms of resistance to KRASG12C and SHP2 inhibitor combinations in non-small cell lung cancer. *Cancer Res*. 2023;83:4130-4141. https://doi.org/10.1158/0008-5472.CAN-23-1127
74. Isermann T, Sers C, Der CJ, Papke B. KRAS inhibitors: resistance drivers and combinatorial strategies. *Trends Cancer*. 2025;11:91-116. https://doi.org/10.1016/j.trecan.2024.11.009
75. Molina-Arcas M, Moore C, Rana S, et al. Development of combination therapies to maximize the impact of KRAS-G12C inhibitors in lung cancer. *Sci Transl Med*. 2019;11:eaaw7999. https://doi.org/10.1126/scitranslmed.aaw7999
76. Hondo N, Kitazawa M, Koyama M, et al. MEK inhibitor and anti-EGFR antibody overcome sotorasib resistance signals and enhance its antitumor effect in colorectal cancer cells. *Cancer Lett*. 2023;567:216264. https://doi.org/10.1016/j.canlet.2023.216264
77. Tong X, Patel AS, Kim E, et al. Adeno-to-squamous transition drives resistance to KRAS inhibition in LKB1 mutant lung cancer. *Cancer Cell*. 2024;42:413-428.e7. https://doi.org/10.1016/j.ccell.2024.01.012
78. Adachi Y, Ito K, Hayashi Y, et al. Epithelial-to-Mesenchymal transition is a cause of both intrinsic and acquired resistance to KRAS G12C inhibitor in KRAS G12C-Mutant non-small cell lung cancer. *Clin Cancer Res*. 2020;26:5962-5973. https://doi.org/10.1158/1078-0432.CCR-20-2077
79. Dy GK, Govindan R, Velcheti V, et al. Long-Term outcomes and molecular correlates of sotorasib efficacy in patients with pretreated *KRAS* G12C-mutated non-small-cell lung cancer: 2-year analysis of CodeBreaK 100. *J Clin Oncol*. 2023;41:3311-3317. https://doi.org/10.1200/JCO.22.02524
80. Wheeler M, Karanth S, Divaker J, et al. Participation in non-small cell lung cancer clinical trials in the united states by race/ethnicity. *Clin Lung Cancer*. 2025;26:52-57.e2. https://doi.org/10.1016/j.cllc.2024.09.009
81. Lee JM, Toloza EM, Pass HI, et al. P2.01-06 NAUTIKA1 study: Preliminary efficacy and safety data with neoadjuvant alectinib in patients with stage IB-III ALK+ NSCLC. *J Thoracic Oncol*. 2023;18:S297-S298. https://doi.org/10.1016/j.jtho.2023.09.511