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REVIEW ARTICLE

Advances in the treatment of *KRAS*^{G12C} mutant non–small cell lung cancer

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Abstract

Kirsten rat sarcoma (*KRAS*) is one of the most frequently mutated oncogenic drivers in metastatic non–small cell lung cancer (NSCLC). The development of selective, covalent KRAS G12C (KRAS^{G12C}) inhibitors represents a breakthrough in the treatment for *KRAS*^{G12C} mutant NSCLC, but the durability of response and efficacy of these inhibitors are limited by the rapid emergence of drug resistance and their ability to only bind KRAS^{G12C} in the guanosine diphosphate-bound form. Importantly, co-occurring gene alterations, including *KEAP1*, *STK11*, and *CDKN2A*, may affect prognosis and response to therapies, including immunotherapy and KRAS^{G12C} inhibitors. New therapeutic approaches are needed to both delay and overcome treatment resistance. Moreover, developing KRAS inhibitors with novel mechanisms of action and alternative allele specificities is necessary to overcome emerging on-target resistance mechanisms to KRAS^{G12C} inhibitors. A literature search was performed using PubMed, the Food and Drug Administration website, and Google search. The inclusive dates in the literature search were between 1982 and July 2024. In this article, the authors reviewed the disease prevalence, biology and therapeutic options, including specific KRAS^{G12C} inhibitors and new pan-KRAS therapeutic agents for *KRAS*^{G12C} mutant NSCLC. KRAS inhibitor resistance mechanisms, treatment strategies, and multi-targeted treatment approaches are also discussed.

KEYWORDS
adaptive resistance, *KRAS*^{G12C} mutation, RAS OFF, RAS ON

INTRODUCTION

Kirsten rat sarcoma (*KRAS*) has long been recognized as one of the most frequently mutated oncogenic drivers in human cancers. The KRAS activating mutation is one of the most common molecular non–small cell lung cancer (NSCLC) subtypes comprising 25%–32% of lung adenocarcinoma and is mutually exclusive with other targetable alterations, including *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *RET*, *NTRK1-3*, and *HER2*.[1,2] Despite its prevalence and essential role in tumor cell growth and survival, KRAS was considered "undruggable" due to its high affinity for guanosine triphosphate (GTP). Significant efforts have been dedicated to targeting RAS proteins over the last several decades.[3] These efforts culminated in clinical success with the approval of the two KRAS^{G12C} inhibitors, sotorasib and adagrasib, in patients with NSCLC, both under the accelerated approval pathway based on phase 2 clinical trial results (Table 1).

TABLE 1 Clinical trials evaluating KRAS^{G12C} inhibitors in KRAS^{G12C} mutant NSCLC.

Clinical trial name	Study phase	KRAS^{G12C} inhibitor	NSCLC patients, No.	ORR (%)	mDOR (months)	mPFS (months)	mOS (months)	CNS activity (yes/no)	TRAEs ≥3 (%)	FDA (other) approval date	Reference
CodeBreaK100 19, NCT03600883	Phase 1	Sotorasib (AMG 510, Amgen)	59	32.2 (95% CI, 20.62–45.64)	NA	6.3 (95% CI, 5.3–8.2)	NA	NA	11.6	NA	Hong 2020[4]
CodeBreaK100 42, NCT03600883	Phase 2	Sotorasib	124	37.1	11.1	6.8 (95% CI, 5.1–8.2)	12.5 (95% CI, 10.0–could not be evaluable)	Yes; ORR, 13%	20.6	FDA, USA, 5/28/2021	Skoulidis 2021[5]
CodeBreak200 29, NCT04303780	Phase 3	Sotorasib vs. docetaxel	171 sotorasib, 174 docetaxel	28.1 (95% CI, 21.5%–35.4%) vs. 13.2 (95% CI, 8.6%–19.2%); $p < .001$	8.6 (95% CI, 7.1–18.0) vs. 6.8 (95% CI, 4.3–8.3)	5.6 (95% CI, 4.3–7.8) vs. 4.5 (95% CI, 3.0–5.7); HR, 0.66 (95% CI, 0.51–0.86); $p = .0017$	10.6 (95% CI, 8.9–14.0) vs. 11.3 (95% CI, 9.0–14.9)	Yes, IC DCR 87.5% in patients with stable BM, median time to CNS disease recurrence 15.8 (95% CI, 9.7–NE) vs. 10.5 (95% CI, 5.8–NE); HR, 0.52 (95% CI, 0.26–1.0)	33 vs. 40	NA	de Langen 2023[6]
Adagrasib, KRYSTAL-1 26, NCT03785249	Phase 1/1b	Adagrasib (MRTX849, Mirati Therapeutics)	18	53.3 (95% CI, 26.6–78.7)	16.4 (95% CI, 3.1–NE)	11.1 (95% CI, 2.6–NE)	NR (95% CI, 3.1–NE)	NA	36.0	NA	Ou 2022[7]
Adagrasib, KRYSTAL-1 41, NCT03785249	Phase 2	Adagrasib	116	42.9 (95% CI, 33.5–52.6)	8.5 (95% CI, 6.2–13.8)	6.5 (95% CI, 4.7–8.4)	12.6 (95% CI, 9.2–19.2)	Yes; ORR, 33.3%	44.8	FDA, USA, 12/12/2022	Janne 2022[8]
KRYSTAL-12 28, NCT04685135	Phase 3	Adagrasib vs. docetaxel	301 adagrasib vs. 152 docetaxel	31.9 (95% CI, 26.7–37.5) vs. 9.2 (95% CI, 5.1–15.0)	8.31 (95% CI, 6.05–10.35) vs. 5.36 (95% CI, 2.86–8.54)	5.49 vs. 3.84; HR, 0.58 (95% CI, 0.45–0.76); $p < .0001$	NA	Yes; 24% vs. 11%	47 vs. 45.7	NA	Mok 2024[9]
GO42144 31, NCT04449874	Phase 1	Divarasib (GDC-6036, Genentech)	60	53.4 (95% CI, 39.9–66.7)	14.0 (95% CI, 8.3–NE)	13.1 (95% CI, 8.8–NE)	NA	NA	12.0	NA	Sacher 2023[10]
LOXO-RAS-20001 33, NCT04956640	Phase 1/2	Olomorasib (LY3537982, LOXO Oncology/Eli-Lilly)	KRAS G12Ci naive, 36; active BM, 6; KRAS G12Ci treated, 41	41; KRAS G12Ci discontinued: due to toxicity, 46; due to PD or other: 39	NA	KRAS G12Ci naive: 7.9 (95% CI, 4.1–NE); KRAS G12Ci treated: mPFS 8.1 (95% CI, 5.6–15.6)	NA	Yes; ORR, 80% (4 of 5 patients had reduction in CNS disease)	7.0	NA	Heist 2024[11]
GFH925X1101 74, NCT05005234	Phase 2	Fulzerasib (IBI-351, GFH925, Innovent Biologics)	116	46.6 (95% CI, 37.2%–56.0%)	8.3 (95% CI, 6.3–NE)	8.3 (95% CI, 5.6–10.4)	NA	NA	40.5	NDA, China, 11/23/23	Zhou 2023[12]

TABLE 1 (Continued)

Clinical trial name	Study phase	$KRAS^{G12C}$ inhibitor	NSCLC patients, No.	ORR (%)	mDOR (months)	mPFS (months)	mOS (months)	CNS activity (yes/no)	TRAEs ≥3 (%)	FDA (other) approval date	Reference
KontRASt-01 38, NCT04699188	Phase 1b/2	Opnurasib (JDQ443, Novartis)	38	41–54	NA	NA	NA	NA	7.1	NA	Cassier 2023[13]
NCT05383898 37	Phase 1	Garsorasib (D-1553, InventisBio)	74	40.5 (95% CI, 29.3–52.6)	6.9 (95% CI, 5.42–NE)	8.18 (95% CI, 7.52–NE)	NA	Yes; ORR, 17%; DCR, 100%	38.0	NA	Ziming 2023[14]
NCT05009329 39	Phase 2	Glecirasib (JAB-21822, Jacobio)	119	47.9 (95% CI, 38.5%–57.3%)	NR (95% CI, 7.2–NE)	8.2 (95% CI, 5.5–13.1)	13.6 (95% CI, 10.9–NE)	NA	38.7	NA	Yuankai 2024[15]

Abbreviations: AMG, Amgen; CI, confidence interval; CNS, central nervous system; DCR, disease control rate; FDA, Food and Drug Administration; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; NA, not applicable; NDA, new drug application; NSCLC, non–small cell lung cancer; NR, not reached; ORR, objective response rate; PD, progression of disease; TRAEs, treatment-related adverse events; USA, United States of America.

However, treatment responses to $KRAS^{G12C}$ inhibition are generally transient; almost all advanced $KRAS^{G12C}$ mutant NSCLC will ultimately progress due the rapid emergence of de novo adaptive resistance, on-target or off-target to resistance mechanisms. Tumor cells with on-target resistance or adaptive resistance remain dependent on KRAS signaling, whereas those with off-target mechanisms activate bypass pathways to support proliferation and cell survival. Tissue and liquid biopsies and genotyping of resistant clinical samples can elucidate resistance mechanisms and guide therapeutic decisions. However, challenges remain in addressing the diverse and polyclonal resistance mechanisms and preventing the emergence of resistance in the treatment-naive setting.

In this review, we provide an overview of the RAS pathway in NSCLC with an emphasis on $KRAS^{G12C}$ mutation and currently approved inhibitors, sotorasib and adagrasib. We explore potential strategies for additional therapeutic targeting for $KRAS^{G12C}$ and other KRAS alterations. Additionally, we examine several resistance mechanisms to $KRAS^{G12C}$ inhibition and possible therapeutic approaches to overcome them. Finally, we discuss the novel $KRAS^{G12C}$ inhibitors currently being evaluated in clinical studies.

KRAS MUTATIONS IN NSCLC

The RAS superfamily proteins (HRAS, KRAS, and NRAS) are G-proteins with intrinsic guanosine triphosphatase (GTPase) activity that act downstream of receptor tyrosine kinases (RTKs) and, on activation, induces the mitogen-activated protein kinase (MAPK/ERK) and phosphatidylinositol 3-kinase (PI3K) pathways as well as many others key signaling pathways (Figure 1). KRAS is an enzyme that cycles between the GTP wild type (WT) (ON) and guanosine diphosphate (GDP) (OFF) states and regulates normal cell proliferation, growth, and survival.[16,17] Mutant KRAS has reduced intrinsic GTPase activity and decreased ability to efficiently interact with GTPase activating proteins (GAPS), resulting in abnormally high concentrations of GTP-bound KRAS, driving downstream activation of MAPK and PI3K pathway. *KRAS* mutations were first discovered in 1982 in NSCLC and are found in 5% of small cell lung cancer and ~25% of lung adenocarcinomas.[18,19,20,21] Oncogenic mutations most frequently affect codons G12, G13, and Q61. The $KRAS^{G12C}$ mutation is the most prevalent (41%), followed by G12V (21%) and G12F/D (17%) (Figure 1).[22] Mutations in $KRAS^{G12C}$ represent approximately 14% of adenocarcinomas, and 1%–4% of squamous NSCLCs are linked to a more aggressive clinical phenotype and are a prognostic factor for survival in NSCLC.[11,12]

KRAS OFF INHIBITORS

Targeting KRAS directly has been challenging due to its essential role in normal tissue development and the toxicities associated with blanket inhibition of WT RAS protein. KRAS was previously considered to be an "undruggable" protein due to its surface structure until

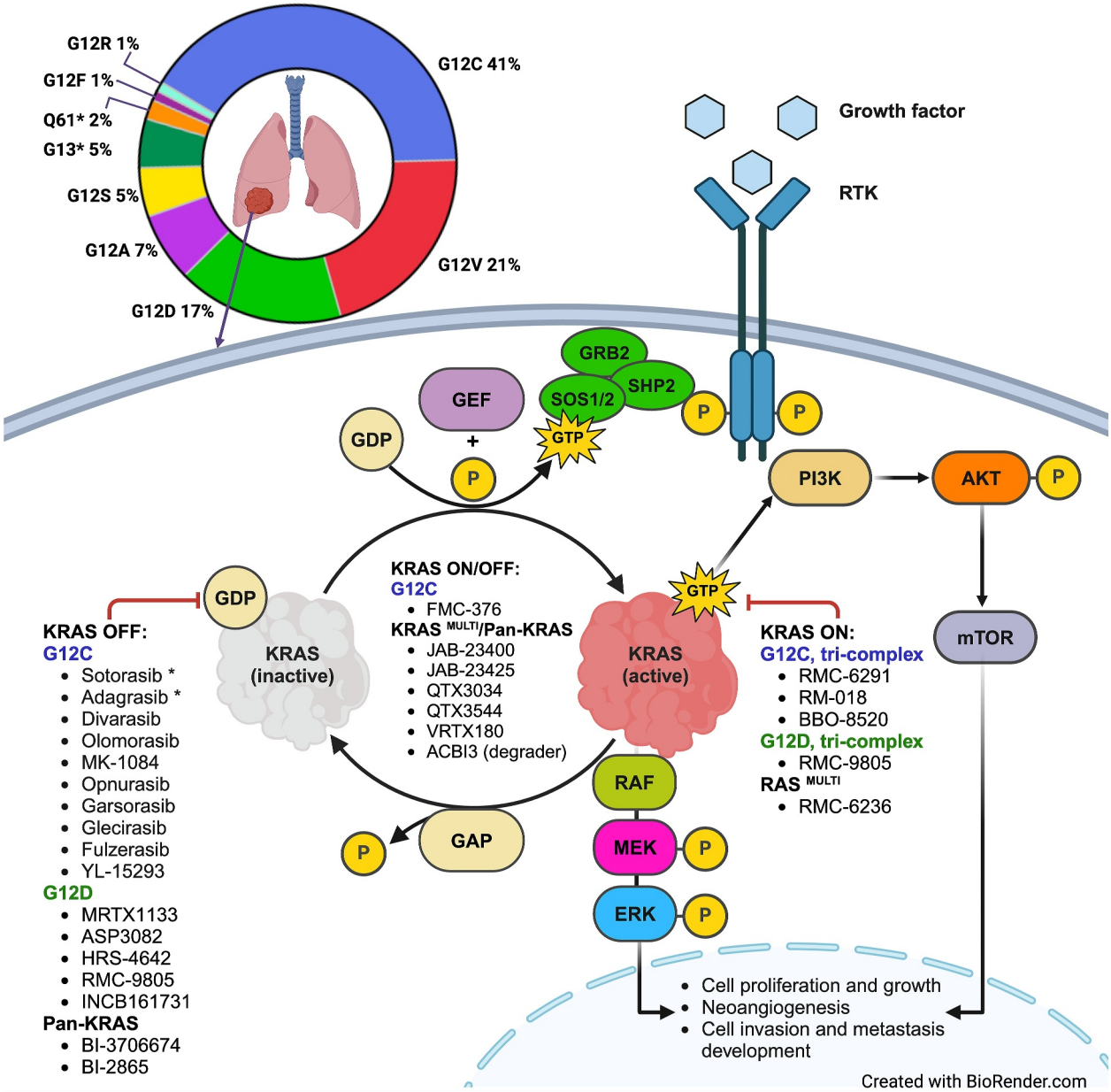

FIGURE 1 Targeting RAS with RAS-OFF and RAS-ON inhibitors in NSCLC. RAS is a G-protein that acts downstream of receptor tyrosine kinases (RTKs) and, on activation, induces the MAPK/ERK and PI3K pathways as well as many other key signaling pathways. Ras activation induces tumor cell proliferation, growth, angiogenesis, invasion, and metastasis. RAS activity is regulated through its intrinsic GTPase activity and thus cycles between the GTP (ON) state and GDP (OFF) state. *KRAS* alterations found in NSCLC affect codons G12, G13, and Q61. The *KRAS*^{G12C} mutation is found in NSCLC, the most prevalent (41%), followed by G12V (21%), G12D (17%), G12A (7%), G12S (5%), G13* (5%), Q61* (2%), and G12F/R (1%–2%). Multiple RAS-OFF (GDP-bound RAS) and RAS-ON (GTP-bound RAS) inhibitors have recently been developed to target KRAS G12C, KRAS G12D, or multiple KRAS mutant alleles. Many of these are currently being tested in the clinic. GDP indicates guanosine diphosphate; GTPase, guanosine triphosphatase; KRAS, Kirsten rat sarcoma; MAPK/ERK, mitogen-activated protein kinase; NSCLC, non–small cell lung cancer; PI3K, phosphatidylinositol 3-kinase; RTKs, receptor tyrosine kinases. *Food and Drug Administration approved.

the discovery of a switch II pocket that led to the development of several inhibitors targeting the G12C isoform.[23] Currently, two KRAS^{G12C} inhibitors, sotorasib (AMG 510, Amgen) and adagrasib (MRTX849, Mirati Therapeutics) are approved for second-line treatment of locally advanced or metastatic NSCLC (mNSCLC).[4,24] Sotorasib and adagrasib are highly specific, small molecules that irreversibly inhibit KRAS^{G12C} by trapping it in its inactive GDP-bound state.[4,24] This represents the major limitation of these drugs, as KRAS^{G12C} is predominantly GTP-bound in cancer cells (Figure 1).

Sotorasib, a potent, selective inhibitor of KRAS^{G12C}, binds to the cysteine residue of the switch II region and irreversibly inhibits KRAS signaling and downstream MAPK pathway. After a phase 1 study demonstrated activity in *KRAS*^{G12C} mutant solid tumors, including NSCLC in a single arm, the phase 2 CodeBreak100 study evaluated

sotorasib in patients with mNSCLC previously treated with anti-programmed death 1 (PD-1) or anti-programmed death ligand 1 (PD-L1) immunotherapy or platinum-based chemotherapy or after chemoimmunotherapy.[14,16] The majority of patients received both chemotherapy and immunotherapy (81%) and had two or more lines of treatment (57%). Patients with active or untreated brain metastasis (BM) were excluded. The study's primary end point was objective response (OR) by blinded, independent central review (BICR). Key secondary end points were duration of response (DOR), disease control, defined as complete response (CR), partial response (PR), or stable disease (SD) according to RECIST, version 1.1, time to response, progression-free survival (PFS), overall survival (OS), and safety.[4,5] The median follow-up was 15.3 months, with a median DOR of 5.5 months. In 124 evaluable patients, the objective response rate (ORR) was 37.1% (95% confidence interval [CI], 28.6–46.2) with a disease control rate of 80.6% (95% CI, 72.6–87.2). Sotorasib demonstrated a modified PFS (mPFS) of 6.8 months (95% CI, 5.1–8.2) with modified OS (mOS) of 12.5 months (95% CI, 10.0–not evaluable [NE]). Sotorasib was the first $KRAS^{G12C}$ inhibitor to receive accelerated Food and Drug Administration (FDA) approval for patients with $KRAS^{G12C}$-driven advanced NSCLC in the second-line settings (May 28, 2021).[5,25] The 2-year pooled analysis of CodeBreak100 was consistent with initially reported data; median DOR was 5.6 months with mPFS of 6.3 months (95% CI, 5.3–8.2) and mOS of 12.5 months (95% CI, 10.0–17.8).[26] Sotorasib was generally well tolerated, with the most commonly reported treatment-related adverse effects (TRAEs) being gastrointestinal toxicities, including diarrhea (31.7%), nausea (19.0%), increase in ALT/AST (15.1%), and fatigue (11.1%). The grade 3–4 TRAEs occurred in 20.6% of patients. Additionally, permanent drug discontinuation due to TRAEs occurred in 7.1% of patients, with diarrhea (7.9%) and AST/ALT elevation (7.9%) being the most frequent reason.[5]

As part of the post-marketing requirement to confirm the clinical benefit of sotorasib, the CodeBreak200, a randomized, phase 3 trial, evaluated the efficacy and safety of sotorasib compared to docetaxel, in $KRAS^{G12C}$ mutant NSCLC after progression on standard of care (SOC) platinum-based chemotherapy and/or PD-1/PD-L1 inhibitors.[6] The primary end point was PFS by BICR, and secondary end points included OS, ORR, DOR, DCR, time to response, safety, sotorasib pharmacokinetics, and patient-reported outcomes. The study demonstrated significant improvement in PFS in the Sotorasib arm at 5.6 months (95% CI, 4.3–7.8) compared to docetaxel at 4.5 months (95% CI, 3.0–5.7) with hazard ratio (HR), 0.66 (95% CI, 0.51–0.86); $p = .0017$.[6] However, OS did not differ between treatment arms, HR. 1.01 (95% CI, 0.77–1.33), 10.6 months (95% CI, 8.9–14.0) in the sotorasib group versus 11.3 months (95% CI, 9.0–14.9) in the docetaxel group (Table 1). Substantial dropout rate was observed in docetaxel arm, which potentially undermined the randomization and affected study results. Additionally, crossover from docetaxel to sotorasib occurred in 26% of patients, and an additional 7% of patients received $KRAS^{G12C}$ inhibitor after discontinuation from the study. Furthermore, patients treated with sotorasib were less affected by TRAEs and their quality-of-life remained stable compared to patients receiving docetaxel.[27] Grade ≥3 TRAEs were reported in 33% and 40% in sotorasib and docetaxel groups, respectively. Discontinuation due to TRAEs was seen in 10% and 11% of patients, with hepatotoxicity being the most common reason (2.4%) for sotorasib discontinuation due to TRAEs, particularly in those who had received prior immunotherapy within 2.6 months.[6]

Despite sotorasib showing better PFS, a more favorable toxicity profile than docetaxel several study design limitations raise concerns about the reliability of PFS and OS estimates. These limitations include the use of suboptimal control arm with docetaxel alone rather than combination of docetaxel and ramucirumab, sample size reduction, allowance of crossover without BICR, and imbalanced censoring rates. Furthermore, on October 5, 2023, the FDA's Oncologic Drug Advisory Committee determined that the PFS of sotorasib cannot be reliably interpreted in comparison to docetaxel due to these factors.[28] Last, several articles reported real-world data regarding tolerability and efficacy of sotorasib in patients with advanced NSCLC harboring $KRAS^{G12C}$ were similar to reported in the CodeBreak trials.[29,30]

Adagrasib, another covalent inhibitor of $KRAS^{G12C}$ mutant protein, was evaluated in KRYSTAL-1, a multicenter, phase 2 single-arm expansion cohort trial after demonstrating clinical activity in phase 1/1b study with 53.3% (95% CI, 26.6–78.7) in previously treated patients with NSCLC.[7,31] After the median follow-up of 15.6 months, adagrasib demonstrated an ORR of 42.9 (95% CI, 33.5–52.6) with a median DOR of 8.5 months (95% CI, 6.2–13.8), PFS was 6.5 months (95% CI, 4.7–8.4) and mOS was 12.6 (95% CI, 9.2–19.2).[31] Adagrasib received accelerated approval from the FDA for the treatment of advanced NSCLC harboring $KRAS^{G12C}$ in the second line setting (December 12, 2022). Although relatively well tolerated, the most commonly reported TRAEs were gastrointestinal toxicities, including diarrhea (62.9%), nausea (62.1%), vomiting (47.4%), fatigue (40.5%), and elevated liver enzymes (27.6%). The ≥3 TRAEs occurred in 44.8% of patients with the most noted fatigue (4.3%), nausea (4.3%), increased ALT (4.3%), and 1.7% grade 5 fatal cardiac events. Additionally, permanent discontinuation of adagrasib due to TRAEs occurred in 6.9% of patients. Interestingly, plasma circulating tumor DNA (ctDNA) analysis in 60 patients with $KRAS^{G12C}$ mutant NSCLC demonstrated that ctDNA clearance at cycle 2 was associated with ORR of 60.6% compared to patients with incomplete ctDNA clearance at 33.3%.[32] Furthermore, ctDNA clearance at cycle 4 was associated with improved OS 14.7 months versus 5.4 months, respectively, suggesting that ctDNA response has the potential to be a biomarker of treatment outcomes in patients with $KRAS^{G12C}$ mutant NSCLC.[32]

More recently, KRYSTAL-12, a randomized, phase 3 trial, compared adagrasib with docetaxel in patients with $KRAS^{G12C}$ mutant NSCLC after progression on chemoimmunotherapy.[9] The primary end point was PFS, assessed by BICR, and secondary end points were ORR, DOR, OS, 1-year OS, and safety. The study allowed crossover to adagrasib on progression on docetaxel. Adagrasib demonstrated significant improvement in PFS 5.49 versus 3.84 months compared to docetaxel (HR, 0.58; 95% CI, 0.45–0.76; $p < .0001$). Additionally, ORR

was 31.9% (95% CI, 26.7–37.5) versus 9.2% (95% CI, 5.1–15.0) and median DOR was 8.31 (95% CI, 6.05–10.35) versus 5.36 (95% CI, 2.86–8.54) months, respectively. In summary, adagrasib demonstrated improvement in both PFS and ORR compared to docetaxel in patients with previously treated *KRAS*^{G12C} NSCLC. Similar to the CodeBreak200, a lower ORR and PFS benefit was observed compared to KRYSTAL-1, and the PFS benefit compared to docetaxel was only marginally improved (Table 1). The most commonly observed TRAEs were more frequent with adagrasib versus docetaxel, including diarrhea (53% vs. 30%), vomiting (35% vs. 6%), and nausea (34% vs. 19%). Last, grade ≥3 TRAEs occurred in 47% of the adagrasib arm versus 45.7% in the docetaxel arm, with discontinuation of therapy in 7.7% and 14.3% of patients, respectively.

Given the relatively low activity of these agents, several studies have examined whether certain subsets of patients experienced greater or lesser benefit from the first-generation KRAS^{G12C} inhibitors. The CodeBreak100 study evaluated sotorasib response based on PD-L1 expression and common *KRAS*^{G12C} co-occurring mutations such as *TP53*, *STK11*, and *KEAP1*. The results demonstrated that patients with negative PD-L1 had ORR of 48% compared to 42% in the general population. Patients with WT *KEAP1* but *STK11* mutations had an ORR of 39%, compared to 50% in overall patient population. Additionally, for those with both *KEAP1* and *STK11* mutations, the treatment response was 23% compared to 14% for patients with *KEAP1* mutations but WT *STK11*. In the exploratory biomarker analysis of CodeBreak200, sotorasib showed consistent clinical benefit over docetaxel across several molecular subgroups including STK11, KEAP1, and TP53.[33] Although no definitive predictive biomarker was identified, high baseline plasma tumor burden correlated with early disease progression and KRAS G12C and NOTCH1 co-mutations may be associated with shorter PFS with sotorasib compared to docetaxel.[33] Multi-institutional real-world data of biomarker analysis in patients with *KRAS*^{G12C} mutant advanced NSCLC demonstrated that co-alterations in *KEAP1*, *CDKN2A*, and *SMARCA4* are independent factors for shorter PFS and OS, whereas mutations in DNA damage response genes were associated with improved efficacy of KRAS^{G12C} inhibitors treatment.[34] Furthermore, in KRYSTAL-1 study, exploratory biomarker analysis revealed that co-mutations in *STK11*, *KEAP1*, *TP53*, and *CDKN2A*, were associated with ORRs of 40.5%, 28.6%, 51.4%, and 58.3%, respectively. Additionally, adagrasib response rates ranged from 35.7% to 55.9% for patients with both *KEAP1* and *STK11* mutations compared to 14.3% for those with *KEAP1* mutations alone. Unlike sotorasib, adagrasib treatment response was not significantly associated with PD-L1 expression.

Several next-generation KRAS^{G12C} selective inhibitors with improved potency over first-in-class inhibitors (sotorasib and adagrasib) are currently under investigation in clinical trials. Many of these drugs have shown more favorable safety profile and superior pharmacological characteristics. In the phase 1 study, divarasib (GDC-6036), an oral KRAS^{G12C} inhibitor, demonstrated an ORR of 53.4% (95% CI, 39.9–66.7), mPFS of 13.1 months (95% CI, 8.8–NE), and the median DOR was 14.0 months (95% CI, 8.3–NE) in patients with previously treated mNSCLC.[10] Although cross-trial comparisons must be interpreted cautiously, divarasib appears to show less grade ≥3 TRAEs (11%) and numerically higher ORR (53.4%) and longer PFS (13.1 months) compared with sotorasib (ORR, 28%; mPFS, 5.6 months) and adagrasib (ORR, 43%; mPFS, 6.5 months).[4,5,10,35] Another second generation, highly selective KRAS^{G12C} inhibitor, olomorasib (LY3537982), was evaluated in LOXO-RAS-20001, a phase 1/2 study of *KRAS*^{G12C} mutant solid tumors including 83 patients with NSCLC.[11] In patients with NSCLC and prior KRAS^{G12C} inhibitor therapy, ORR was 41% and PFS was 8.1 months (95% CI, 5.6–15.6), with an overall favorable safety profile, including those patients with a history of prior KRAS^{G12C} inhibitor intolerance.[11] In summary, encouraging antitumor activity and safety profile make divarasib and olomorasib promising antitumor agents; however, it is still unknown if this improved efficacy will be maintained in the larger ongoing phase 3 clinical trials. Several other selective KRAS^{G12C} inhibitors, including opnurasib, fulzerasib, glecirasib, and garsorasib, are under investigation in clinical trials, summarized in Table 1.[12,13,14,15,36,37]

CENTRAL NERVOUS SYSTEM ACTIVITY OF KRAS OFF INHIBITORS

Several KRAS^{G12C} inhibitors have shown promising activity against untreated NSCLC-BM. Given the high incidence of BM (~40%) in patients with *KRAS*^{G12C} mutant NSCLC, therapeutic agents with superior central nervous system (CNS) efficacy will likely have improved efficacy.[38] In the KRYSTAL-1 trial, patients with untreated BM had a systemic ORR of 30% with a median intracranial DOR of 12.7 months, and in KRYSTAL-12, an intracranial ORR of 24% was observed.[9,39] Although CNS activity of sotorasib remains unknown, the retrospective post hoc analysis of CodeBreak100 demonstrated that 88% of patients with evaluable CNS disease achieved intracranial disease control.[40] Additionally, the mOS was 8.3 months (95% CI, 7.3–12.5) in patients with BM compared to 13.6 months (95% CI, 10–NE) in patients without BM.[40] Furthermore, Codebreak200 included patients with stable, treated BM, 40 (23%) in the sotorasib arm and 29 (17%) in the docetaxel arm.[41] Sotorasib demonstrated reduced risk of CNS PFS and delayed CNS recurrence compared to docetaxel with 6.1 months versus 4.5 months (HR, 0.57; 95% CI, 0.30–1.07; $p = .045$).[41] Lastly, early signs of clinical CNS efficacy were observed with garsorasib (D-1553) and olomorasib (LY3537982) monotherapy, with intracranial ORR of 17% and 80%, respectively.[11,14] Given the small number of patients, larger, dedicated BM trials are needed to determine the efficacy of current KRAS^{G12C} inhibitors in patients with untreated BM.

RAS ON INHIBITORS

Although first-generation KRAS^{G12C} (RAS OFF) inhibitors have been transformative steps forward in the treatment of *KRAS*^{G12C} mutant NSCLC, suboptimal treatment response and resistance remain

significant challenges. Substantial progress has been made in developing novel therapeutic strategies, including next-generation KRAS^{G12C} inhibitors and broader-acting RAS ON inhibitors.

Trimeric complex (tri-complex) RAS inhibitors are allele-specific and pan-allele targeting drugs that bind to RAS ON via a unique mechanism, acting as a molecular "glue" with cyclophilin A. RMC-6291, an oral inhibitor, binds to *KRAS*^{G12C} and cyclophilin A (CypA), leading to rapid disruption of RAS effector binding and halting *KRAS*^{G12C} mutant-mediated signaling (Figure 1). RMC-6291, in contrast to adagrasib and sotorasib, covalently binds to the active GTP-bound KRAS^{G12C} (ON) and CypA and forms an inactive tri-complex, providing a novel therapeutic approach to KRAS-driven tumors. RMC-6291 led to significant and lasting suppression of RAS signaling in *KRAS*^{G12C} mutated tumors and had greater efficacy than adagrasib in preclinical studies.[42] Preliminary data shows promising antitumor activity of RMC-6291 in NSCLC patients with *KRAS*^{G12C} and KRAS^{G12C} inhibitor exposure; thus, it potentially can be used to overcome the limitations of first-generation KRAS^{G12C} inhibitors.[42,43]

Novel RAS^{MULTI} (ON) inhibitors targeting all RAS isoforms have been developed and are tested in clinical trials. Similar to KRAS^{G12C} (ON) inhibitors, the drug forms a tri-complex between active RAS and CypA protein. RMC-6236 is a RAS^{MULTI} inhibitor that has shown activity against RAS WT and various other mutant proteins, including G12X, G13, and Q61.[44,45,46] Several case reports showed objective responses in patients with advanced KRAS G12X mutant NSCLC pancreatic and ovarian cancers.[44,45] Furthermore, a phase 1 clinical trial evaluated RMC-6236 safety and efficacy in patients with previously treated metastatic solid tumors harboring KRAS G12X (~50% KRAS G12D and excluding G12C) and showed radiographic tumor regression and reduction in KRAS mutant alleles in blood ctDNA across the tumor types indicating antitumor activity (NCT05379985).[44,45,46] The most common grade 3 TRAE was rash; only one patient experienced grade 4 intestinal perforation at the tumor site. Overall, these results are promising. However, phase 3 randomized trials are necessary to evaluate the efficacy and safety RMC-6236 compared to current SOC.

Last, several other tri-complex inhibitors are entering the clinic, and data regarding efficacy are pending. For instance, RM-018 a novel, tri-complex KRAS ON inhibitor, can overcome resistance to RAS OFF inhibitors by inhibiting KRAS^{G12C} and as well as a novel, secondary mutation KRAS Y96D affecting the switch-II pocket.[47] Last, several other RAS ON small molecule inhibitors targeting G12D or other variants, including KRAS G13C, are being tested, and more in-depth analysis of efficacy and toxicity is needed before concluding if they can be used in clinical settings[48] (Figure 1).

RESISTANCE MECHANISM TO KRAS^{G12C} INHIBITION

Contrary to EGFR and ALK inhibitors in NSCLC, sotorasib, and adagrasib do not provide frequent and durable responses, suggesting the presence of intrinsic tumor resistance.[49,50] Acquired resistance mechanism to KRAS^{G12C} inhibitors can be categorized into two major mechanisms: on-target resistance, such as secondary KRAS alterations, or off-target resistance, which includes upstream, downstream, or parallel bypass mechanisms, changes in tumor microenvironment (TME), and histological transformation.

Concurrent KRAS alterations

De novo secondary KRAS mutations or amplifications are present in 2.8% of cancers and potentially lead KRAS^{G12C} inhibitors resistance.[50,51,52,53] Second site non-G12C mutations such as G12D/V/R, G13D, and Q61H, as well as allelic rearrangement from G12C to G12W, can also induce acquired drug resistance. *KRAS*^{G12C} mutant tumors treated with sotorasib led to treatment-emergent alterations in 27 of 43 patients, including second site KRAS mutations and copy number gains.[50] Plasma biomarker analysis of CodeBreak100 revealed that acquired genomic alterations at disease progression were heterogeneous and polyclonal, including changes in multiple genes (EGFR, second site RAS, etc.) and RTK pathway dysregulation in NSCLC and colorectal cancer.[54] Similarly, adagrasib treatment resulted in several mutations in the drug binding pocket (Y96C, H95R, and H95D), leading to decreased sensitivity to therapy.[50,55] Notably, although H95 alteration showed reduced sensitivity to adagrasib, this did not affect sensitivity to sotorasib.

Vertical signaling pathway alteration

Resistance to KRAS^{G12C} inhibition can arise from alterations in the upstream signaling pathways such as SHP2, SOS, and RTKs and can lead to both adaptive and acquired resistance. Upregulation in upstream RTKs like EGFR, HER2, and MET leads to increased frequency of KRAS^{G12C} in the GTP bound form and MAPK signaling resulting in resistance to both sotorasib and adagrasib therapy.[56] Adaptive resistance is characterized by the rapid rebound activation of the RAS-MAPK pathway due to the induction of genes encoding RTKs and their ligands on inhibition of RAS signaling. Therefore, inhibiting upstream effector pathways, such as SHP2 and SOS1, reduces the activation of *KRAS*^{G12C} mutant cancer cells.[57,58] Furthermore, *MET* amplification, a common bypass mechanism in several oncogene-driven NSCLCs treated with TKIs, has also been observed in patients with *KRAS*^{G12C} mutant NSCLC treated with KRAS^{G12C} inhibitors.[59] Interestingly, these tumors do not generally have a polygenic resistance mechanism.[50] Emerging treatment approaches with concomitant inhibition of KRAS^{G12C} and upstream RTKs or other proteins such as SHP2 and SOS1 to bypass intrinsic drugs are under active investigation.[60]

Additional resistance mechanisms

Parallel pathways can bypass KRAS^{G12C} inhibition via different mechanisms, including changes in the cell-cycle regulation, phenotypic transformation, or modification of the TME. Histological

transformation, a well-described off-target resistance mechanism to multiple targeted therapies, was also described in patients treated with adagrasib.[50] Last, changes in TME, increased TGF-β signaling, EMT transformation, and neoangiogenesis contribute to resistance.[61]

In summary, diverse on- and off-target mechanisms can lead to KRAS^{G12C} inhibitors resistance, and several resistance mechanisms can frequently be present simultaneously. For example, one rapid autopsy case report of a patient with *KRAS*^{G12C} mutant NSCLC treated with sotorasib identified several resistance mechanisms in tumors, including decreased *KRAS*^{G12C} allele frequency, reactivation of MAPK pathway, and evidence of tumor immunologic evasion.[61] Thus, new therapeutic strategies are needed to improve outcomes in patients with *KRAS*^{G12C} mutant NSCLC who experience disease relapse. Several ongoing clinical trials are currently evaluating the combination of adagrasib and sotorasib with inhibitors of other RTK (e.g., MEKi trametinib and EGFRi panitumumab) or SHP2 (TNO155a, SHP2i). Moreover, the development of additional KRAS^{G12C} inhibitors with different mechanisms of action and alternative allele specificities is necessary to overcome emerging on-target resistance mechanisms. Last, combining two distinct classes of direct KRAS inhibitors could have an advantage in preventing both second site mutations and rebound activation of the RAS signaling pathway.

KRAS^{G12C} INHIBITOR THERAPY COMBINATION STRATEGIES

Immune checkpoint inhibitors (ICIs) have transformed the care of multiple tumors, including NSCLC, and are first-line treatment for nononcogenic driver metastatic NSCLC, including patients with *KRAS*^{G12C} mutant tumors. Oncogenic KRAS-driven tumors are characterized by immunosuppressive TME and reduced activity of tumor-infiltrating T cells. On the contrary, inhibition of KRAS has been associated with augmented cytotoxic T-cell tumor infiltration.[48,62,63] Thus, there has been an emerging excitement in leveraging the synergistic effects of KRAS inhibition with ICIs in patients with advanced *KRAS*^{G12C} mutant NSCLC to improve treatment outcomes. Preclinical studies have demonstrated that combining sotorasib with anti–PD-1 therapy increases CD8+ T-cell infiltration and augmented antitumor immunity.[48,64,65] Unfortunately, early clinical data from studies investigating combination strategies of KRAS^{G12C} inhibitors with anti–PD(L)-1 in patients with NSCLC has shown significant challenges mainly associated with increased TRAEs, most notably hepatotoxicity. Early reports from the CodeBreak100/101 study raised concerns that the combination of sotorasib with ICI was associated with a higher incidence of grade 3 or 4 hepatotoxicity compared to sotorasib monotherapy.[5] Severe sotorasib-related liver toxicity has also been observed in patients with prior ICI use, and one study recommended delaying sotorasib therapy 30 days after ICI administration.[66-68] Other ongoing studies with other KRAS^{G12C} inhibitors suggest that combining KRAS^{G12C} inhibitors with ICIs may be feasible. The phase 2 KRYSTAL-7 study evaluated adagrasib and pembrolizumab in treatment-naive patients with *KRAS*^{G12C} mutant NSCLC and PD-L1 greater than or equal to 50%.[69] This combination therapy led to an improved ORR of 63%, particularly in patients with TPS greater than or equal to 50%. In contrast to sotorasib data, adagrasib led to mainly low-grade hepatotoxicity and a more manageable toxicity profile, although ~50% of patients experienced either drug-dose reduction or interruption due to TRAEs. Adagrasib, in combination with pembrolizumab and chemotherapy, is further being tested in a phase 3 clinical trial (NCT05609578).

Preliminary data of a novel oral KRAS^{G12C} inhibitor, MK-1084, in combination with pembrolizumab, demonstrated antitumor efficacy and manageable safety profile in treatment-naive *KRAS*^{G12C} mutant NSCLC.[70] Currently, the MK-1084 and pembrolizumab combination is being evaluated in phase 3 trials in patients with PD-L1 positive (TPS greater than or equal to 50%), *KRAS*^{G12C} mutant NSCLC (NCT06345729). Additionally, the LOXO-RAS-20001, a phase 1/2 study, evaluated olomorasib, a highly selective second-generation inhibitor of KRAS^{G12C}, in combination with pembrolizumab in *KRAS*^{G12C} mutant NSCLC across any line of treatment (NCT04956640).[71] Results presented at ASCO 2024 demonstrated that among the 60 efficacy-evaluable patients with NSCLC harboring KRAS^{G12C}, olomorasib in combination with pembrolizumab demonstrated an ORR of 77% in treatment-naive patients ($n = 17$) and 40% in previously treated patients, including those that progressed on prior chemotherapy, immunotherapy, prior KRAS^{G12C} inhibitor ($n = 43$), and showed a favorable safety profile.[71] A global registrational study, SUNRAY-01, is currently investigating the combination of olomorasib with pembrolizumab or chemoimmunotherapy in the first-line NSCLC (NCT06119581). Despite the promising results from the above studies, the combination of KRAS^{G12C} inhibitors with ICIs may pose a higher risk for toxicity and will require larger phase 3 trials to define the safety of these combinations.

The use of concurrent chemotherapy to debulk tumors and prevent secondary mutation emergence has been explored in several studies. The CodeBreak100 evaluated the combination of sotorasib with pemetrexed and carboplatin in patients with *KRAS*^{G12C} mutant NSCLC and showed ORR of 65% and 54% in the first- and second-line settings, respectively.[72] Additionally, phase 2 SCARLET study showed that sotorasib combined with pemetrexed and carboplatin elicited an ORR of 88% in patients with *KRAS*^{G12C} mutant NSCLC.[73] The phase 3 Code-Break202 trial is currently evaluating sotorasib in combination with platinum doublet chemotherapy versus pembrolizumab with a platinum doublet in the frontline settings in patients with PD-L1 negative, *KRAS*^{G12C} mutant NSCLC. Last, reactivation of the EGFR pathway has been observed as an adaptive response to KRAS^{G12C} inhibition, and the combination of adagrasib and cetuximab has been associated with enhanced clinical benefit in patients with metastatic colorectal cancer.[74] A phase 2 KROCUS study evaluated efficacy of KRAS^{G12C} inhibitors fulzerasib in combination with cetuximab, in patients with metastatic NSCLC in the first line settings (NCT05756153).[75] The results demonstrated ORR was 80.0% and DCR was 100%. Additionally, five of seven patients with BM demonstrated partial response. Grade 3 TRAEs occurred in five patients (18.5%), and no grade 4/5 TRAEs were observed.[75]

DISCUSSION

Despite decades of failed attempts to target KRAS, there have been substantial advances in treating *KRAS*^{G12C} mutant NSCLC. Two KRAS^{G12C} inhibitors, sotorasib and adagrasib, are currently approved in the second-line settings for these patients. Furthermore, many next-generation KRAS^{G12C} inhibitors and agents targeting other mutant variants or WT KRAS are currently being tested in preclinical and clinical studies. However, the efficacy of existing KRAS^{G12C} inhibitors is short-lived with rapid emergence of drug resistance. Furthermore, due to the complexity and plasticity of RAS signaling pathways, resistance mechanisms can be heterogeneous, and several resistance mechanisms can be present simultaneously, representing a significant hurdle when selecting treatment for these patients.

One promising approach to address primary and acquired resistance is using multi-agent treatment strategies with combination therapies. Combining KRAS^{G12C} inhibitors with ICIs to augment treatment response or tumor debulking strategies using systemic chemotherapy or drugs targeting KRAS upstream or downstream signaling pathways may effectively target emerging co-mutations and bypass track pathways. Introducing these combinations in the first line or eventually in the early-stage setting may also improve outcomes. Several clinical trials are currently investigating KRAS^{G12C} inhibitors in first-line settings. Additionally, the CodeBreak202 study is exploring the combination of sotorasib with chemotherapy versus chemoimmunotherapy in PD-L1 negative, *KRAS*^{G12C} mutant NSCLC (NCT05920356). Several novel strategies targeting KRAS are being explored in various cancer types. A phase 1 study of mRNA-5671/V941 vaccine, which targets multiple *KRAS* mutations (*G12C*, *G12D*, *G12V*, and *G13D*) is currently evaluating safety and tolerability of mRNA-5671/V941 as monotherapy or in combination with pembrolizumab in patients with advanced solid malignancies including NSCLC (NCT03948763). Additionally, T-cell receptor gene targeting of KRAS mutations or proteolysis-targeted chimeras to target KRAS G12C mutations such as PROTACs may offer a promising a therapeutic alternative in patients harboring KRAS alterations.[76]

Finally, newer RAS-ON inhibitors are either in clinical trials or advanced stages of preclinical development and may eventually surpass the RAS-OFF inhibitors. It will be interesting to follow the efficacy, safety, and resistance mechanisms of these inhibitors as they mature in the clinic. Furthermore, moving KRAS^{G12C} inhibitors in the neoadjuvant and adjuvant settings in monotherapy or combination with ICIs is also being explored in resectable *KRAS*^{G12C} mutant NSCLC (NCT05472623, NCT04302025). In summary, significant progress has been made in treating *KRAS*^{G12C} mutant NSCLC. However, we are likely only scratching the surface of what is possible for the treatment of these patients.

AUTHOR CONTRIBUTIONS

Khvaramze Shaverdashvili: Conceptualization, writing—original draft, and writing—review and editing. **Timothy F. Burns:** Conceptualization, supervision, and writing—review and editing.

CONFLICT OF INTEREST STATEMENT

Timothy F. Burns reports 2 years of compensation as a DSMB member: Advarra, Inc (Lantern Pharma); participation on a scientific advisory board for Janssen Scientific Affairs, LLC, Amgen, AstraZeneca, Eli Lilly, Inc, Genentech, and Takeda Pharmaceuticals USA, Inc; consulting fees from Pfizer; and institutional research funds from Novartis (all to institution). The other author declares no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in public.

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