

Management of *KRAS*-Mutated Non–Small Cell Lung Cancer

Jyoti Malhotra, MD, MPH^{1,2}; Danny Nguyen, MD^{1,2}; Tingting Tan, MD, PhD^{1,2}; and George B. Semeniuk III, MD^{1,2}

¹City of Hope Orange County, Irvine, California

²City of Hope National Medical Center, Duarte, California

Corresponding author:
Jyoti Malhotra, MD, MPH
City of Hope Orange County
1000 FivePoint
Irvine, CA 92618
Email: jymalhotra@coh.org

Abstract: Kirsten rat sarcoma virus (*KRAS*) is the most frequently mutated oncogene in human cancers, particularly in non–small cell lung cancer (NSCLC), where mutations are present in 32% of lung adenocarcinoma and 4% of squamous cell lung cancer. The most common *KRAS* variant is *KRAS* G12C, which accounts for nearly 40% of all *KRAS* mutations. Although it is the most common oncogenic driver in NSCLC, *KRAS* was considered a “nondruggable target” until recently, owing to the lack of any progress in developing targeted therapies for this oncogene. With the recent development and approval of selective *KRAS* G12C inhibitors such as sotorasib and adagrasib for the treatment of advanced or metastatic NSCLC in the second-line setting and beyond, the standard of care for managing these tumors has undergone a significant change. Mechanisms of resistance to *KRAS* G12C inhibitors are highly heterogeneous, including both on-target and off-target resistance as well as morphologic switching, thus limiting the activity of these drugs when used as monotherapy. New-generation inhibitors and different combination strategies are being developed in early-phase trials to overcome or delay the onset of resistance as well as to target non-G12C mutations. Owing to the biological heterogeneity of *KRAS*-mutant NSCLC, treatment will likely need to be individualized based on factors such as co-occurring mutations.

Introduction

The treatment landscape for patients with advanced non–small cell lung cancer (NSCLC) has dramatically evolved over the last 2 decades owing to the integration of tumor genomic sequencing into treatment paradigms and the approval of highly effective targeted therapies aimed against oncogenic driver alterations in *EGFR*, *ALK*, *ROS1*, *HER2*, *BRAF*, *MET*, *RET*, and *NTRK*. In addition, programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1)-targeting immune checkpoint inhibitors, used alone or in combination

Keywords

KRAS G12C, lung adenocarcinoma, non–small cell lung cancer (NSCLC), squamous cell lung cancer

with chemotherapy, have become the standard of care for NSCLC without a targetable genomic alteration. These therapeutic advances in the treatment of advanced NSCLC have led to significant improvements in clinical outcomes and survival.

The Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene is the most frequently mutated oncogene in human cancers, particularly NSCLC. Mutations in *KRAS* are detected in up to 32% of lung adenocarcinomas and 4% of squamous cell lung cancers.¹ In contrast to other oncogene drivers, *KRAS*-driven NSCLC is frequently associated with a history of smoking, high tumor mutational burden, and genomic signatures of tobacco smoke exposure with predominant G→C or G→T transversion mutations at codon 12.^{2,3} The most common *KRAS* variant is *KRAS* G12C, which accounts for nearly 40% of all *KRAS* mutations (12%-15% of all NSCLC).⁴ Although the most common oncogenic driver in NSCLC, *KRAS* was considered a “nondruggable target” until recently owing to the lack of any progress in developing targeted therapies for this target. This was likely because of the lack of classic drug-binding sites, as well as heterogeneity observed in *KRAS*-mutated NSCLC from different genotypes, and the presence of different co-mutations that in turn impact drug sensitivity patterns. With the recent development and approval of selective *KRAS* G12C inhibitors such as sotorasib (Lumakras, Amgen) and adagrasib (Krazati, Mirati Therapeutics) for the treatment of advanced or metastatic NSCLC in the second-line and beyond setting, the standard of care for managing these tumors has undergone a significant change. Here, we review the approaches for managing *KRAS*-mutated NSCLC and highlight emerging treatment strategies.

KRAS Gene in NSCLC

The proto-oncogene *KRAS* is located on the 12p12.1 chromosome and encodes the intracellular membrane-bound RAS protein.⁵ The RAS protein undergoes a transition from the active guanosine triphosphate (GTP) state to the inactive guanosine triphosphate (GDP) state, a process promoted by guanine nucleotide exchange factors such as the Son Of Sevenless (SOS) protein. The RAS-GTP complex activates several downstream signaling pathways, such as Raf/MEK/ERK and phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin, which play key roles in cell proliferation, differentiation, and survival. *KRAS* mutations are mostly missense point mutations in exon 2 (codons 12 and 13) of the G domain, impairing its ability to either hydrolyze GTP or interact with GTPase-activating proteins, thus leading to a permanent and constitutive activation of the RAS oncoprotein,

ultimately promoting tumorigenesis.⁵ The most frequent codon 12 mutation subtype is p.G12C, consisting of the replacement of a native glycine with a cysteine due to a G9 T transversion, followed by the G12V (22%) and G12D (16%) mutations.

KRAS mutations are usually mutually exclusive with other targetable oncogenic drivers, such as *EGFR* or *ALK* mutations, likely owing to underlying synthetic lethality that may take place with the co-occurrence of these 2 mutations.^{6,7} Notably, about half of *KRAS* G12C-mutant tumors have co-occurring mutations within nontargetable oncogenes, such as *TP53* (39%), serine/threonine kinase 11 (*STK11*; 20%-28%), and kelch-like ECH-associated protein 1 (*KEAP1*; 13%-24%). These co-mutations modulate the tumor microenvironment and the clinical responses to current treatments.² Inactivation of *STK11* (or its protein product, LKB1) is associated with a “cold” tumor immune microenvironment with a reduced CD8-positive (CD8+) T-cell density and predicts primary resistance to anti-PD-1/PD-L1 therapies. Conversely, co-occurring mutations within the *TP53* gene are associated with increased CD8+ T-cell infiltration and predict improved clinical response to immunotherapy.^{2,8} Ricciuti and colleagues reported clinical outcomes for lung adenocarcinoma patients with high PD-L1 expression treated with first-line anti-PD-1/PD-L1 therapy. Both *STK11* and *KEAP1* mutations were associated with worse clinical response and survival outcomes among the *KRAS*-mutant population, whereas *KRAS* wild-type NSCLC patients experienced a clinical benefit from anti-PD-1/PD-L1 therapy regardless of *STK11/KEAP1* mutation status, suggesting a deleterious impact of these co-mutations on the efficacy of immune checkpoints limited to *KRAS*-mutant disease.⁹ This highlights the importance of next-generation sequencing testing for all patients with advanced or metastatic NSCLC to inform clinical decisions. A circulating tumor DNA-based assay or other form of liquid biopsy may be a viable and minimally invasive option for patients who cannot undergo tissue biopsy or have insufficient tumor tissue available.

Treatment Approach to KRAS-Mutated NSCLC

Currently, treatment algorithms for *KRAS*-mutant NSCLC continue to mirror those for NSCLC without a targetable genomic alteration. The only exception is the treatment of advanced NSCLC in the second-line and beyond setting, as two *KRAS* G12C inhibitors (sotorasib and adagrasib) have become the standard of care for patients who have tumor progression on first-line chemoimmunotherapy.¹⁰ The *KRAS* G12C mutation impairs GTP hydrolysis, keeps the protein in a constitutively activated form, and ultimately

Table 1. Management of Toxicities With Approved KRAS G12C Inhibitors

	Treatment for toxicity	Guidelines for dose modifications and discontinuations	
		Sotorasib	Adagrasib
Hepatotoxicity	(1) Evaluate for other contributing factors (2) For significant hepatotoxicity, consider treatment with glucocorticoids	Hold if grade 2 AST/ALT elevation with symptoms or grade 3-4 AST/ALT, resume at lower dose level once recovered to grade ≥ 1 Permanently discontinue if AST/ALT $>3 \times$ ULN with total bilirubin $>2 \times$ ULN in the absence of alternative causes	Decrease to the next lower dose level if grade 2 AST/ALT elevation. Hold if grade 3-4 AST/ALT elevation, resume at lower dose level once recovered to grade ≥ 1 Permanently discontinue if AST or ALT $>3 \times$ ULN with total bilirubin $>2 \times$ ULN in the absence of alternative causes
Interstitial lung disease/pneumonitis		Hold if suspected, permanently discontinue if confirmed	
Diarrhea	(1) BRAT diet and fluid intake (2) Antidiarrheals, such as diphenoxylate-atropine or loperamide (3) Monitor electrolytes if severe or persistent diarrhea	Supportive care including antidiarrheal if grade 1-2 Hold if grade 3-4, resume at lower dose level once recovered to grade ≥ 1	
Nausea/vomiting	(1) Antiemetics and fluid intake (2) Monitor electrolytes if severe or persistent vomiting	Supportive care including antiemetics if grade 1-2 Hold if grade 3-4, resume at lower dose level once recovered to grade ≥ 1	
QTc interval prolongation	(1) Monitor electrolytes and replete as needed		Hold if QTc >500 ms or >60 ms increase from baseline. Resume when <481 ms at a lower dose level Permanently discontinue if torsades de pointes, polymorphic ventricular tachycardia, or signs or symptoms of serious or life-threatening arrhythmia

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BRAT, bananas, rice, applesauce, and toast; ms, milliseconds; QTc, corrected QT; ULN, upper limit of normal.

promotes cell proliferation. Owing to the visibility of the switch-II binding pocket in the GDP-bound state of the KRAS oncoprotein, selective direct KRAS G12C inhibitors have been developed that bind and block the KRAS G12C protein in its inactive GDP-bound state (off).^{11,12} Among these, both sotorasib (AMG-510) and adagrasib (MRTX849) are now US Food and Drug Administration (FDA) approved, and several other direct, covalent KRAS G12C inhibitors, such as GDC-6036, D-1553, JAB-21822, JDQ443, and LY3537982, are in the early phases of clinical development. Trials are also underway to test the efficacy of these KRAS G12C inhibitors in the adjuvant

and neoadjuvant settings for the treatment of early-stage NSCLC.

Role of PD-1/PD-L1 Inhibitors for Treating KRAS-Mutated NSCLC

Immunotherapy represents a promising approach in KRAS-mutant NSCLC, as PD-L1 is upregulated by KRAS mutation through sustained phosphorylation of ERK activation. Furthermore, this upregulation induces CD3+ T-cell apoptosis, which can be reversed by anti-PD-1/PD-L1 antibody or ERK inhibitor treatment, suggesting

that PD-1 blockade potentially restores the antitumor immunity of T cells in *KRAS*-mutated NSCLC.^{13,14} *KRAS*-mutant NSCLC, often linked to smoking, is frequently associated with high mutational burden.^{15,16} A meta-analysis of 6 studies showed that immunotherapy combined with chemotherapy significantly prolonged the overall survival (OS; hazard ratio [HR], 0.59; $P < .00001$) and progression-free survival (PFS; HR, 0.58; $P = .0003$) in patients with *KRAS*-mutant NSCLC compared with chemotherapy alone, and the OS was significantly longer in patients with *KRAS* mutations than in the *KRAS* wild-type group ($P = .001$).¹⁷

KRAS co-occurring mutations are critical factors dictating distinct immune phenotypes within *KRAS*-mutant NSCLCs, with co-mutations in *TP53* and *STK11* profoundly influencing the tumor-immune contexture. In the Stand Up to Cancer cohort, PFS and OS were shorter in the *KRAS/STK11* co-mutant lung adenocarcinoma group than in patients with *KRAS/TP53* co-mutated tumors.⁸ Other reports have also demonstrated that *KRAS/TP53* co-mutant lung tumors show remarkable benefits with single-agent PD-1 blockade.¹⁸ In a study investigating the impact of mutations in *SWI/SNF* genes, including *SMARCA4*, on immunotherapy outcomes in *KRAS*-mutant NSCLC, the worst OS and prognosis were associated with *SMARCA4* mutations, indicating the unfortunate outcome of this gene alteration with *KRAS*.¹⁹ Notably, *STK11* mutations are a major determinant of primary resistance to PD-1 blockade in PD-L1-positive NSCLC, regardless of *KRAS* mutational status.⁸ Therefore, despite PD-1/PD-L1 inhibitors being promising biological therapy for *KRAS*-mutant lung adenocarcinomas, these drugs do not benefit all patients equally. Instead, immunotherapy for these patients should be individualized according to the presence of major co-mutations. For instance, single-agent anti-PD-1/PD-L1 therapy is an effective therapy and might be sufficient to obtain tumor regression in at least a subset of patients with *KRAS/TP53* co-mutant tumors. Conversely, patients with *KRAS/STK11* co-mutated NSCLC may benefit more from a regimen incorporating a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody to the chemotherapy and PD-1/PD-L1 inhibitor backbone. In POSEIDON, a phase 3 trial of first-line treatment in patients with metastatic NSCLC, those who received a combination of the anti-CTLA-4 agent tremelimumab, the anti-PD-L1 agent durvalumab (Imfinzi, AstraZeneca), and chemotherapy reported a survival benefit compared with those who received chemotherapy alone, irrespective of *KRAS*, *STK11*, or *KEAP1* mutational status.²⁰

The combination of sotorasib and PD-1 inhibition increases the infiltration of CD8+ T cells into the tumor microenvironment and confers a complete and durable

response to the combined treatment in most models.²¹ In *KRAS* G12C-mutated mouse models, adagrasib reduces intratumor myeloid-derived suppressor cells and increases M1 macrophages, dendritic cells, and CD4+/CD8+ T cells, positively modulating the tumor microenvironment immune composition.²² These observations provided a strong biological rationale for combining *KRAS* G12C inhibitors and immune checkpoint inhibitors. The first data on the safety and efficacy of this combined approach came from the phase 1b CodeBreak 100/101 study.²³ Overall, 58 NSCLC patients with *KRAS* G12C mutations received sotorasib in combination with either atezolizumab (Tecentriq, Genentech) or pembrolizumab (Keytruda, Merck). At a median follow-up of 12.8 months, confirmed responses were 29%, with a median duration of 17.9 months and a median OS of 15.7 months (95% CI, 9.8-17.8). Combination therapy resulted in a high rate of grade 3/4 toxicities, which were reported in 60% to 80% of patients and led to treatment discontinuation in approximately 50% of them. The incidence of hepatotoxicity was similar in checkpoint inhibitor-naïve and -pretreated patients. Lowering the dose of sotorasib as well as making use of lead-in administration of sotorasib followed by combination treatment with pembrolizumab may be strategies to address this.²³ Clinical trials combining either sotorasib or adagrasib with anti-PD-1/PD-L1 inhibitors are currently ongoing (NCT03600883, NCT03785249, NCT04613596)

Direct *KRAS* Inhibitors

Sotorasib

Sotorasib is an oral covalent *KRAS* G12C inhibitor that irreversibly and selectively binds to the mutant cysteine in a small pocket on the *KRAS* G12C protein 2, locking the *KRAS* G12C-mutant protein in an inactive state, thus preventing oncogenic signaling without affecting wild-type *KRAS*.^{21,24} It received regulatory approval by the FDA in May 2021, and by the European Medicines Agency in January 2022, for the treatment of patients with *KRAS* G12C-mutant advanced NSCLC treated with at least 1 prior line of systemic therapy. The recommended dosage of sotorasib is 960 mg (eight 120-mg tablets) orally once daily. The dose can be reduced to 480 mg or 240 mg daily for intolerable toxicities. Coadministration of sotorasib with gastric acid-reducing agents decreases sotorasib concentrations, which may reduce the efficacy of sotorasib.²⁵ Therefore, coadministration of sotorasib with proton pump inhibitors, H₂ receptor antagonists, or antacids should be avoided. If coadministration with an acid-reducing agent cannot be avoided, sotorasib should be administered 4 hours before or 10 hours after the agent. Coadministration of sotorasib with a strong CYP3A4 inducer decreases

sotorasib concentrations, which may reduce the efficacy of sotorasib. Coadministration of sotorasib with a P-glycoprotein substrate such as digoxin increases concentrations of the P-glycoprotein substrate in the plasma, which may increase adverse reactions. Therefore, the coadministration of sotorasib with strong CYP3A4 inducers and P-glycoprotein substrates should be avoided.²⁵

Clinical Data. Hong and colleagues reported the results of the phase 1 CodeBreak 100 clinical trial (NCT03600883), an open-label multicenter study of sotorasib in heavily pretreated patients with *KRAS* G12C-mutated metastatic solid tumors.²⁶ Sotorasib was administered orally once daily at a dose of 960 mg in the expansion cohort. No dose-limiting toxicities or deaths related to sotorasib treatment were reported. In the NSCLC subgroup with 59 patients, 32% had a confirmed objective response (a complete or partial response) and 88% had disease control (objective response or stable disease). The median PFS was 6.3 months. Treatment-related adverse events (TRAEs) were reported in 56.7% of patients, with grade 3 or 4 TRAEs reported in 11.6% of patients. The most common grade 3 TRAEs were gastrointestinal (nausea, 1.6% and diarrhea, 3.9%) and hepatic (elevated transaminases, 7%). Pharmacokinetic analysis demonstrated that the half-life of sotorasib was approximately 5.5 hours.

Skoulidis and colleagues published the efficacy results of the phase 2 expansion cohort of the CodeBreak 100 study, including 126 *KRAS* G12C-mutated pretreated advanced NSCLC patients.²⁷ The activity profile of sotorasib was confirmed in this larger population, with an objective response rate (ORR) of 37%, a disease control rate of 80.6%, and a median duration of response of 11.1 months. Median PFS was 6.8 months and median OS was 12.5 months (95% CI, 10.0 to not evaluable). Two-year follow-up data from the CodeBreak 100 study were presented at the American Association for Cancer Research Annual Meeting 2022.²⁸ In this updated analysis, including 174 patients with *KRAS* G12C-mutant advanced NSCLC, 1-year and 2-year survival rates were 50.8% and 32.5%, respectively. Biomarker analysis showed that sotorasib activity was independent of PD-L1 expression or *STK11* co-mutation status. Among 104 patients who were evaluated for co-occurring mutations in *STK11*, *KEAP1*, or *TP53* genes, response rates were 50% for *STK11*-mutant/*KEAP1* wild-type tumors, 23% for *STK11*-mutant/*KEAP1*-mutant tumors, and 14% for *STK11* wild-type/*KEAP1*-mutant tumors.

More recently, the primary analysis of the randomized phase 3 CodeBreak 200 study (NCT04303780) comparing sotorasib with docetaxel in pretreated patients with *KRAS* G12C-mutant NSCLC was presented at the European Society for Medical Oncology Congress 2022.²⁹ All 345 enrolled patients had progressed to first-line treatment

with platinum-based chemotherapy and a checkpoint inhibitor, and were randomized 1:1 to receive sotorasib or docetaxel. The study met its primary endpoint of a statistically significant improvement in median PFS (5.6 vs. 4.5 months; HR, 0.66; $P=.002$). The 1-year PFS was 24.8% for sotorasib and 10.1% for docetaxel, whereas the ORR was 28.1% vs 13.2%, respectively. OS did not significantly differ between the 2 groups, with more than one-third of the patients experiencing a crossover from chemotherapy to sotorasib at the time of disease progression. The safety profile was manageable, with a higher incidence of grade 3 or higher toxicity in the docetaxel group vs the sotorasib group (33.1% vs 40.4%, respectively). The most frequent grade 3 or higher toxicities were diarrhea (11.8%), increased alanine aminotransferase (ALT; 7.7%) and increased aspartate aminotransferase (AST; 5.3%) with sotorasib, whereas fatigue (6%), neutropenia (8.6%), and febrile neutropenia (5.3%) were more frequently reported in the docetaxel arm. For patient-reported outcomes, the times to deterioration in general health, physical function, and cancer-related symptoms were significantly delayed with sotorasib compared with docetaxel.²⁹ These data support the use of sotorasib as the new standard of care in pretreated patients harboring *KRAS* G12C mutations, although the lack of survival data highlights the need to develop more novel combinations and therapies for this target. Sotorasib is currently being investigated as first-line monotherapy in the treatment-naïve cohorts of the phase 1/2 CodeBreak 100/101 studies as well as in the phase 2 prospective CodeBreak 201 study (NCT04933695).

Adverse Events and Monitoring. In the CodeBreak 100 trial,²⁷ the most common TRAEs were diarrhea (31.7%), nausea (19.0%), transaminitis (increase in ALT/AST, 15.1%), and fatigue (11.1%). TRAEs led to dose modification in 22.2% of patients and the discontinuation of therapy in 7.1%. The most common TRAEs that led to dose modification were diarrhea, transaminitis, an increase in the blood alkaline phosphatase level, and nausea. Therefore, patients on sotorasib should have liver function tests (ALT, AST, and total bilirubin) before the initiation of therapy, then every 3 weeks for the first 3 months of treatment, and then once a month or as clinically indicated, with more frequent testing in patients who develop transaminitis and/or bilirubin elevations.²⁵ Also, interstitial lung disease (ILD) or pneumonitis, which is a rare but serious TRAE, occurred in about 1.6% of patients. Therefore, patients on sotorasib should be monitored for new or worsening pulmonary symptoms, and sotorasib should be permanently discontinued in patients who develop ILD/pneumonitis. Table 1 lists common adverse events that may occur with sotorasib and the approach to managing them.

Table 2. Emerging Drugs in Development to Target KRAS in NSCLC

Class of drugs	Drug name	Trial number
KRAS G12C inhibitors	BI 1823911	NCT04973163
	MK-1084	NCT05067283
	JAB-21822	NCT05288205
	LY3537982	NCT04956640
	GDC-6036	NCT04449874, NCT05789082
	JDQ-443	NCT05445843, NCT05132075
SOS1 inhibitors	BI 1701963	NCT04111458
SHP2 inhibitors	JAB-3312	NCT05288205
	BBP-398	NCT04528836
	TNO155	NCT04330664
RAF/MEK inhibitor	VS-6766	NCT05375994, NCT04620330, NCT05074810

NSCLC, non–small cell lung cancer.

Adagrasib

Adagrasib (MRTX849) is an oral covalent KRAS G12C inhibitor that irreversibly binds to the mutant cysteine in KRAS G12C and locks the mutant KRAS protein in its inactive state that prevents downstream signaling without affecting the wild-type KRAS protein.³⁰ In December 2022, adagrasib was approved by the FDA for the treatment of advanced or metastatic *KRAS* G12C–mutated NSCLC. Adagrasib is taken at 600 mg orally twice daily; the dose can be reduced to 400 mg twice daily or 600 mg once daily if needed. Concomitant use of adagrasib with P-glycoprotein substrates or with any agent that may prolong the QTc interval should be avoided.³¹ If concomitant use cannot be avoided, cardiac monitoring with electrocardiography and electrolyte monitoring should be used while the patient is on adagrasib therapy. Adagrasib should be held if the QTc interval is greater than 500 ms or the change from baseline is greater than 60 ms. Adagrasib is a CYP2C9 and CYP2D6 inhibitor and a CYP3A4 substrate. Concomitant use of adagrasib with strong CYP3A inhibitors should be avoided until adagrasib concentrations have reached a steady state (after approximately 8 days). Concomitant use of adagrasib with strong CYP3A inducers, sensitive CYP3A substrates, or sensitive CYP2C9 or CYP2D6 substrates should be avoided.³¹

Clinical Data. The first-in-human study to report on the safety and efficacy of adagrasib was KRYSTAL-1 (NCT03785249), a multicenter, phase 1 study in 25 patients with *KRAS* G12C–mutated solid tumors.³² After a median follow-up of 19.6 months, 8 of 15 patients (53.3%) with NSCLC treated with 600 mg twice a day achieved a confirmed partial response. The median

duration of response was 16.4 months (95% CI, 3.1 to not estimable), and the median PFS was 11.1 months. The most common TRAEs were nausea (80.0%), diarrhea (70.0%), vomiting (50.0%), and fatigue (45.0%). The most common serious TRAE was fatigue (15.0%). In the NSCLC phase 2 cohort of KRYSTAL-1,³⁰ 116 patients with *KRAS* G12C–mutated pretreated NSCLC were treated. The ORR was 42.9%, the median duration of response was 8.5 months, and the median PFS was 6.5 months (95% CI, 4.7–8.4). With a median follow-up of 15.6 months, the median OS was 12.6 months (95% CI, 9.2–19.2). TRAEs occurred in 97.4% of the patients, with grade 3 or higher TRAEs in 44.8% of patients and TRAEs resulting in drug discontinuation in 6.9% of patients.³³ The exploratory biomarker analyses showed that ORR was similar across different PD-L1 expression levels. The ORRs in patients with co-occurring alterations in *STK11*, *KEAP1*, *TP53*, and *CDKN2A* were 40.5%, 28.6%, 51.4%, and 58.3%, respectively, with the lowest response rates noted in tumors with *KEAP1* co-mutations. A phase 3 study comparing adagrasib vs docetaxel monotherapy in patients with pretreated NSCLC is currently ongoing (NCT04685135). Adagrasib as a first-line treatment is also being studied in cohorts of the phase 1/2 KRYSTAL-1 study (NCT03785249).

Adverse Events and Monitoring. In the KRYSTAL-1 study, the most common TRAEs were diarrhea (62.9%), nausea (62.1%), vomiting (47.4%), fatigue (40.5%), increased ALT (27.6%), increased blood creatinine (25.9%), and increased AST (25.0%). A total of 52 patients (44.8%) had grade 3 or higher TRAEs; the most common were fatigue, nausea, increased ALT (4.3% each), and increased AST (3.4%). Two grade 5 fatal events were reported (1

cardiac failure in a patient with a medical history of pericardial effusion and 1 pulmonary hemorrhage). TRAEs led to dose reduction in 51.7% and dose interruption in 61.2% of patients; the most common reasons were gastrointestinal-related events, increased ALT and AST, and fatigue. ILD/pneumonitis occurred in 4.1% of patients (median time to first onset, 12 weeks). Table 1 lists common adverse events that may occur with adagrasib, and the approach to managing these. For patients who start treatment with adagrasib, liver function tests should be conducted before the start of adagrasib and monthly for 3 months after and as clinically indicated. When transaminases are increased, it is important to evaluate other potential contributing factors, such as alcohol use, acetaminophen, other medications, and medical conditions. In the case of more significant hepatotoxicity, treatment with glucocorticoids can be considered.

Central Nervous System Activity of KRAS G12C Inhibitors. Data on the intracranial activity of adagrasib from KRYSTAL-1 in patients with *KRAS* G12C-mutant NSCLC and active, untreated central nervous system (CNS) metastases reported an intracranial ORR of 31.6%, with 3 complete responses.³⁴ Cerebrospinal fluid (CSF) analysis of 2 patients with a complete encephalic response showed that adagrasib concentrations in the CSF exceeded the partition coefficients observed for other therapies, demonstrating penetration and efficacy in the CNS. Ramalingam and colleagues have also reported on the intracranial efficacy of sotorasib in 40 patients with NSCLC and stable brain metastases enrolled in the Code-Break 100 trial, with median intracranial PFS and OS of 5.3 and 8.3 months, respectively.³⁵ These data demonstrate that *KRAS* G12C inhibitors have CNS efficacy, yet it remains unclear how to incorporate this information in treatment paradigms. More research is needed to better delineate the approach to patients with untreated brain metastases.

Resistance to KRAS G12C Inhibitors. Acquired resistance mechanisms of *KRAS* G12C inhibitors can be divided into the following 3 categories³⁶: on-target resistance, histological transformation to squamous cell carcinoma, and off-target resistance. In on-target resistance, *KRAS* G12C mutation transforms to G12D/R/V/W and other subtypes or G12C amplification. In off-target resistance, acquired bypass resistance mechanisms include amplification of *MET*; activation mutations of *NRAS*, *BRAF*, *MAP2K1*, and *RET*; oncogenic fusing of *ALK*, *RET*, *BRAF*, *RAF1*, and *FGFR3*; and loss-of-function mutations in *NF1* and *PTEN*.

The largest assessment of acquired resistance to sotorasib on plasma samples of patients with *KRAS* G12C mutations was conducted in the CodeBreak 100 study, with at least 1 novel acquired genomic alteration detected

upon progression in 28% of patients with NSCLC.³⁷ The most prevalent putative resistance pathway was the receptor tyrosine kinases (RTKs, 24%), highlighting the potential role of combination therapies of sotorasib with upstream RTK inhibitors, such as SHP2 or epidermal growth factor receptor (EGFR) inhibitors.³⁷

On-Target Resistance. Since covalent “off” inhibitors, like sotorasib and adagrasib, bind the *KRAS* G12C-GDP complex in its inactive state, acquired resistance mutations may arise within the *KRAS* G12C domain, by either inactivating GTPase or promoting the guanine exchange from GDP to GTP. Acquired resistance, including mutations or amplifications, was found in half the patients with adagrasib-resistant *KRAS* G12C-mutant advanced NSCLC.³⁶ Preclinical studies in cell lines showed that R68S, H95D/Q/R, and Y96C confer resistance to adagrasib and R68S and Y96C confer resistance to sotorasib.³⁸ These findings suggest the possible sequential use of the 2 drugs in some cases.³⁹

Off-Target Resistance. Another main mechanism of acquired resistance under the selective pressure of targeted therapies is the activation of bypass signaling pathways. Currently approved inhibitors are highly selective for the G12C protein isoform and do not inhibit the wild-type *RAS* receptor coexisting within the same cell. This selective inhibition may provide potential feedback to reactivate the *RAS* signaling pathways. This reactivation is related to increased *NRAS*-GTP and *HRAS*-GTP, suggesting that *KRAS* G12C-mutant cell lines may rapidly adapt to selective inhibition by activating wild-type *RAS* and restoring mitogen-activation pathway kinase (MAPK) signaling.⁴⁰ The increase in wild-type *RAS* activity results from the activation of several RTKs, including EGFR, human epidermal growth factor receptor 2 (HER2), fibroblast growth factor receptor (FGFR), and cMET.⁴¹ Blood-based genomic sequencing of samples collected at the time of adagrasib progression revealed up to 10 distinct mutations affecting effectors of the *RAS*/MAPK pathway, including activating mutations in *NRAS* (Q61L/K/R), *MAP2K1*, and *BRAF* V600E.³⁶ RTK activation was reported in sotorasib-resistant cells that acquired the epithelial-mesenchymal transition (EMT) phenotype.⁴² Recent studies have shown that the activation of EMT leads to primary and acquired resistance to *KRAS* G12C inhibitors. In cells with *KRAS* G12C inhibitor resistance, EMT is induced via activation of the PI3K pathway, which eventually leads to drug resistance.⁴²

Other KRAS-Targeting Drugs in Development

New-generation, tri-complex inhibitors of the GTP-bound isoform of the *KRAS* G12C oncoprotein are currently in development to overcome RTK-mediated tumor escape mechanisms. RMC-6291 is a potent oral

tri-complex inhibitor of both KRAS G12C and NRAS G12C that has shown promising antitumor activity in preclinical models of NSCLC.⁴³ RMC-6236 is another potent selective oral RAS tri-complex inhibitor, with antitumor activity in preclinical models of solid tumors with KRAS G12D and G12V mutations, but also in RAS-dependent wild-type tumors as well as RAS-mediated acquired resistance mechanisms.⁴⁴ Table 2 provides a list of ongoing trials investigating emerging targeted therapies for KRAS-mutated NSCLC.

SRC homology phosphatase 2 (SHP2) is a tyrosine phosphatase that promotes activation of the RAS signaling pathway by activating SOS1 and interacting with the SRC kinase, and it also plays a role in KRAS-mutant NSCLC carcinogenesis.⁴⁵ The preliminary results of the phase 1b CodeBreak 100/101 study, including the combination of sotorasib and the SHP2 inhibitor RMC-4630, were presented at the 2022 World Conference on Lung Cancer.²³ Twenty-one patients with KRAS G12C-mutated NSCLC or other solid tumors were treated with the combination of full-dose sotorasib and RMC-4630 at increasing dose levels. Of the 11 patients with NSCLC, the ORR was 27% and the disease control rate was 64%.²³ The SHP2 inhibitor TNO155 is currently in early-phase development either as monotherapy (NCT03114319) or in combination with the selective KRAS G12C inhibitor JDQ443 (NCT04699188). In cases of acquired resistance to sotorasib, the allosteric SHP2 inhibitor SHP099 significantly reduced tumor growth in orthotopic xenografts.⁴⁵ In sotorasib-resistant cells with EMT characteristics, the addition of both the PI3K inhibitor GDC-0941 and SHP099 to sotorasib effectively suppressed the phosphorylation of PI3K/AKT, MAPK, and S6.⁴²

SOS1 is a guanine nucleotide exchange factor that can bind the catalytic site of KRAS GDP-bound state as well as the allosteric binding site of the KRAS GTP-bound state, ultimately promoting KRAS downstream signaling activation.⁴⁶ SOS1 plays an important role in RAS-mediated carcinogenesis and is a promising target owing to its role in the feedback reactivation of the MAPK pathway.⁴⁷ BI-3406, a recently developed potent and selective SOS1 inhibitor, specifically binds the catalytic site of SOS1, blocking its interaction with the GDP-bound KRAS.⁴⁸ Preclinical studies revealed the therapeutic efficacy of BI-3406 not only on G12C but also on G12V, G12D, and G12S KRAS-mutant models.⁴⁸ BI-3406 also prevents the development of adaptive resistance to MEK inhibitors in KRAS-mutant cell lines and prevents rebound activation of ERK in vitro after treatment with sotorasib.⁴⁸

MEK1/2 is a downstream effector of KRAS in the MAPK signaling pathway and is a promising target for indirect KRAS inhibition.⁴⁹ Initial data from a small (n=87) randomized phase 2 trial suggested a potential

benefit in terms of response rates and PFS with the combination of selumetinib (Koselugo, Alexion) plus docetaxel in pretreated patients with KRAS-mutant NSCLC,⁵⁰ but these data were not validated in the larger phase 3 SELECT-1 study of 510 patients.⁵¹ Median PFS was not significantly different between selumetinib plus docetaxel vs placebo plus docetaxel (3.9 vs 2.8 months, respectively; $P=.44$), nor was there a significant difference in median OS or ORR.⁵¹ The development of directly targeted inhibitors to other KRAS mutations is still ongoing, with the KRAS G12D allele-specific inhibitor MRTX1133 receiving investigational new drug clearance from the FDA in January 2023, enabling the initiation of a phase 1 trial (NCT05737706).⁵²

Conclusion

KRAS is no longer considered an undruggable target in NSCLC owing to the recent clinical development of KRAS G12C inhibitors and a better understanding of the biology underlying KRAS-related lung carcinogenesis. Both sotorasib and adagrasib have shown promising efficacy and tolerability in patients with KRAS G12C-mutated, pretreated advanced NSCLC, establishing these as the new standard in second-line treatment for these tumors. Mechanisms of resistance to KRAS G12C inhibitors are highly heterogeneous, including both on-target and off-target resistance as well as morphologic switching, thus limiting the activity of these drugs when used as monotherapy. New-generation inhibitors as well as different combination strategies are being developed in early-phase trials to overcome or delay the onset of resistance as well as to target non-G12C mutations. Owing to the biological heterogeneity of KRAS-mutant NSCLC, treatment will likely need to be individualized based on factors such as co-occurring mutations. Finally, the emergence of new strategies, such as oncolytic cancer vaccines and adoptive T-cell therapy, will likely provide further treatment options in the future.

Disclosures

The authors report no conflicts of interest related to this manuscript.

References

1. Prior IA, Hood FE, Hartley JL. The frequency of Ras mutations in cancer. *Cancer Res.* 2020;80(14):2969-2974.
2. Skoulidis F, Byers LA, Diaio L, et al. Co-occurring genomic alterations define major subsets of KRAS-mutant lung adenocarcinoma with distinct biology, immune profiles, and therapeutic vulnerabilities. *Cancer Discov.* 2015;5(8):860-877.
3. Ricciuti B, Son J, Okoro JJ, et al. Comparative analysis and isoform-specific therapeutic vulnerabilities of KRAS mutations in non-small cell lung cancer. *Clin Cancer Res.* 2022;28(8):1640-1650.
4. Dogan S, Shen R, Ang DC, et al. Molecular epidemiology of EGFR and KRAS mutations in 3,026 lung adenocarcinomas: higher susceptibility of women to smok-

- ing-related KRAS-mutant cancers. *Clin Cancer Res.* 2012;18(22):6169-6177.
5. Simanshu DK, Nissley DV, McCormick F. RAS proteins and their regulators in human disease. *Cell.* 2017;170(1):17-33.
 6. Gainer JF, Varghese AM, Ou SH, et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. *Clin Cancer Res.* 2013;19(15):4273-4281.
 7. Unni AM, Lockwood WW, Zejnullahu K, Lee-Lin SQ, Varmus H. Evidence that synthetic lethality underlies the mutual exclusivity of oncogenic KRAS and EGFR mutations in lung adenocarcinoma. *eLife.* 2015;4:e06907.
 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(7):822-835.
 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 Thorac Oncol.* 2022;17(3):399-410.
 10. Ettinger DS, Wood DE, Aisner DL, et al. Non-small cell lung cancer, version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2022;20(5):497-530.
 11. Patricelli MP, Janes MR, Li LS, et al. Selective inhibition of oncogenic KRAS output with small molecules targeting the inactive state. *Cancer Discov.* 2016;6(3):316-329.
 12. Bungaro M, Novello S, Passiglia F. Targeting *KRAS*G12C mutation in advanced non-small cell lung cancer: a new era has begun. *Curr Treat Options Oncol.* 2022;23(12):1699-1720.
 13. Chen H, Fang W, Lin Z, et al. *KRAS* mutation-induced upregulation of PD-L1 mediates immune escape in human lung adenocarcinoma. *Cancer Immunol Immunother.* 2017;66(9):1175-1187.
 14. Lamberti G, Sisi M, Andriani E, et al. The mechanisms of PD-L1 regulation in non-small-cell lung cancer (NSCLC): which are the involved players? *Cancers (Basel).* 2020;12(11):3129.
 15. Spigel DR, Schrock AB, Fabrizio D, et al. Total mutation burden (TMB) in lung cancer (LC) and relationship with response to PD-1/PD-L1 targeted therapies [ASCO abstract 9017]. *J Clin Oncol.* 2016;34(15)(suppl).
 16. Kadara H, Choi M, Zhang J, et al. Whole-exome sequencing and immune profiling of early-stage lung adenocarcinoma with fully annotated clinical follow-up. *Ann Oncol.* 2017;28(1):75-82.
 17. Landre T, Josteau G, Assié JB, et al. Anti-PD-(L)1 for *KRAS*-mutant advanced non-small-cell lung cancers: a meta-analysis of randomized-controlled trials. *Cancer Immunol Immunother.* 2022;71(3):719-726.
 18. 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(12):3012-3024.
 19. 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(7):1176-1187.
 20. Peters S, Cho BC, Luft A, et al. Association between *KRAS*/*STK11*/*KEAP1* mutations and outcomes in POSEIDON: durvalumab ± tremelimumab + chemotherapy in mNSCLC [IASLC abstract OA15.04]. *J Thorac Oncol.* 2022;17(9):S39-S41.
 21. Canon J, Rex K, Saiki AY, et al. The clinical *KRAS*(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature.* 2019;575(7781):217-223.
 22. Briere DM, Li S, Calinisan A, et al. The *KRAS*^{G12C} inhibitor MRTX849 reconditions the tumor immune microenvironment and sensitizes tumors to checkpoint inhibitor therapy. *Mol Cancer Ther.* 2021;20(6):975-985.
 23. Li BT, Falchook GS, Durm GA, et al. CodeBreaK 100/101: first report of safety/efficacy of sotorasib in combination with pembrolizumab or atezolizumab in advanced *KRAS* p.G12C NSCLC [IASLC abstract OA03.06]. *J Thorac Oncol.* 2022;17(9):S10-S11.
 24. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature.* 2013;503(7477):548-551.
 25. Sotorasib package insert. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214665s002lbl.pdf. Updated November 2022. Accessed December 1, 2023.
 26. Hong DS, Fakih MG, Strickler JH, et al. *KRAS*^{G12C} inhibition with sotorasib in advanced solid tumors. *N Engl J Med.* 2020;383(13):1207-1217.
 27. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with *KRAS* p.G12C mutation. *N Engl J Med.* 2021;384(25):2371-2381.
 28. 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(18):3311-3317.
 29. de Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with *KRAS*^{G12C} mutation: a randomised, open-label, phase 3 trial. *Lancet.* 2023;401(10378):733-746.
 30. Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non-small-cell lung cancer harboring a *KRAS*^{G12C} mutation. *N Engl J Med.* 2022;387(2):120-131.
 31. Adagrasib package insert. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/216340s000lbl.pdf. Updated December 2022. Accessed December 1, 2023.
 32. Ou SI, Jänne PA, Leal TA, et al. First-in-human phase I/IB dose-finding study of adagrasib (MRTX849) in patients with advanced *KRAS*^{G12C} solid tumors (KRYSTAL-1). *J Clin Oncol.* 2022;40(23):2530-2538.
 33. Spira AI, Riely GJ, Gadgeel SM, et al. KRYSTAL-1: activity and safety of adagrasib (MRTX849) in patients with advanced/metastatic non-small cell lung cancer (NSCLC) harboring a *KRAS*G12C mutation [ASCO abstract 9002]. *J Clin Oncol.* 2022;40(16)(suppl).
 34. Sabari JK, Spira AI, Heist RS, et al. Activity of adagrasib (MRTX849) in patients with *KRAS*G12C-mutated NSCLC and active, untreated CNS metastases in the KRYSTAL-1 trial [ASCO abstract LBA9009]. *J Clin Oncol.* 2022;40(17)(suppl).
 35. Ramalingam SS, Skoulidis F, Govindan R, et al. Efficacy of sotorasib in *KRAS* p.G12C-mutated NSCLC with stable brain metastases: a post-hoc analysis of CodeBreaK 100 [IASLC abstract P52.03]. *J Thorac Oncol.* 2021;16(10):S1123.
 36. Awad MM, Liu S, Rybkin II, et al. Acquired resistance to *KRAS*^{G12C} inhibition in cancer. *N Engl J Med.* 2021;384(25):2382-2393.
 37. Li BT, Velcheti V, Price TJ, et al. Largest evaluation of acquired resistance to sotorasib in *KRAS* p.G12C-mutated non-small cell lung cancer (NSCLC) and colorectal cancer (CRC): plasma biomarker analysis of CodeBreaK100 [ASCO abstract 102]. *J Clin Oncol.* 2022;40(16)(suppl).
 38. Tanaka N, Lin JJ, Li C, et al. Clinical acquired resistance to *KRAS*^{G12C} inhibition through a novel *KRAS* switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation. *Cancer Discov.* 2021;11(8):1913-1922.
 39. 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 Thorac Oncol.* 2021;16(8):1321-1332.
 40. Ryan MB, Fecce de la Cruz F, Phat S, et al. Vertical pathway inhibition overcomes adaptive feedback resistance to *KRAS*^{G12C} inhibition. *Clin Cancer Res.* 2020;26(7):1633-1643.
 41. Yaeger R, Solit DB. Overcoming adaptive resistance to *KRAS* inhibitors through vertical pathway targeting. *Clin Cancer Res.* 2020;26(7):1538-1540.
 42. 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(22):5962-5973.
 43. Nichols RJ, Yang YC, Cregg J, et al. RMC-6291, a next-generation tri-complex *KRAS*G12C(ON) inhibitor, outperforms *KRAS*G12C(OFF) inhibitors in preclinical models of *KRAS*G12C cancers [AACR abstract 3595]. *Cancer Res.* 2022;82(12)(suppl).
 44. Koltun ES, Rice MA, Gustafson WC, et al. direct targeting of *KRAS*G12X mutant cancers with RMC-6236, a first-in-class, RAS-selective, orally bioavailable, tri-complex RASMULTI(ON) inhibitor [AACR abstract 3597]. *Cancer Res.* 2022;82(12)(suppl).
 45. Mainardi S, Mulero-Sánchez A, Prallahad A, et al. SHP2 is required for growth of *KRAS*-mutant non-small-cell lung cancer in vivo. *Nat Med.* 2018;24(7):961-967.
 46. Freedman TS, Sondermann H, Friedland GD, et al. A Ras-induced conformational switch in the Ras activator Son of sevenless. *Proc Natl Acad Sci USA.* 2006;103(45):16692-16697.
 47. Jeng HH, Taylor LJ, Bar-Sagi D. Sos-mediated cross-activation of wild-type Ras by oncogenic Ras is essential for tumorigenesis. *Nat Commun.* 2012;3:1168.
 48. Hofmann MH, Gmachl M, Ramharter J, et al. BI-3406, a potent and selective SOS1-KRAS interaction inhibitor, is effective in *KRAS*-driven cancers through combined MEK inhibition. *Cancer Discov.* 2021;11(1):142-157.
 49. Chang L, Karin M. Mammalian MAP kinase signalling cascades. *Nature.* 2001;410(6824):37-40.
 50. Jänne PA, Shaw AT, Pereira JR, et al. Selumetinib plus docetaxel for *KRAS*-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. *Lancet Oncol.* 2013;14(1):38-47.
 51. Jänne PA, van den Heuvel MM, Barlesi F, et al. Selumetinib plus docetaxel compared with docetaxel alone and progression-free survival in patients with *KRAS*-mutant advanced non-small cell lung cancer: the SELECT-1 randomized clinical trial. *JAMA.* 2017;317(18):1844-1853.
 52. Wang X, Allen S, Blake JF, et al. Identification of MRTX1133, a noncovalent, potent, and selective *KRAS*^{G12D} inhibitor. *J Med Chem.* 2022;65(4):3123-3133.