

The Potential Treatment Options and Combination Strategies of KRAS-Mutated Lung Cancer

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Abstract: In non-small cell lung cancer (NSCLC), Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations are found in up to 30% of all cases, with the most prevalent mutations occurring in codons 12 and 13. The development of *KRAS*-targeted drugs like sotorasib and adagrasib has generated significant excitement in the clinical arena, offering new therapeutic options. Their potential for combination with other treatments broadens the scope for clinical exploration. Acquired resistance to *KRAS* exon 2 p.G12C inhibitors is a significant challenge, with several reported mechanisms. In this scenario, combination therapy strategies that include targeting Src Homology Region 2 Domain-Containing Phosphatase-2 (SHP2), Son of Sevenless Homolog 1 (SOS1), or downstream effectors of *KRAS* exon 2 p.G12C are showing promise in overcoming such resistance. However, the efficacy of immune checkpoint inhibitors in this context still requires comprehensive evaluation. The response to anti-Programmed Cell Death Protein 1/Programmed Cell Death Protein 1 Ligand (anti-PD-1/PD-L1) drugs in NSCLC may be significantly influenced by co-occurring mutations, underscoring the need for a personalized approach to treatment based on the specific genetic profile of each tumor.

Keywords: targeted therapies, sotorasib, adagrasib, resistance

Introduction

Lung cancer remains the leading cause of cancer-related deaths globally, with nearly 1.8 million fatalities annually. Among these, NSCLC represents the majority, accounting for about 85% of all lung cancer diagnoses, with adenocarcinoma being the most prevalent histological subtype. In recent years, advancements in molecular profiling and the development of novel targeted therapies have significantly transformed the treatment landscape for NSCLC. Simultaneously, the rise of immune checkpoint inhibitors has broadened the spectrum of therapeutic strategies available for lung cancer. Notably, combination therapies that incorporate immune checkpoint inhibitors alongside targeted drugs have shown superior efficacy compared to monotherapy approaches. Previously, certain molecular alterations like *KRAS* mutations were deemed untreatable, but the advent of new targeted drugs has opened up promising treatment possibilities for these challenging cases. This shift marks a pivotal moment in the ongoing efforts to effectively treat and manage NSCLC.

The *KRAS* protein, a small membrane-bound Guanosine Triphosphatase (GTPase), plays a critical role as a molecular switch regulating various cellular signaling functions. Its activity within the cell is determined by the balance between nucleotide hydrolysis and exchange, which governs the amount of active *KRAS*. In its GDP-bound form, *KRAS* remains in an “off” state. However, upon exposure to growth factors, *KRAS* transitions to the “on” state through the exchange of GDP for GTP. This activation process is facilitated by guanine nucleotide exchange factors (GEFs) like SOS1 and SOS2. Once activated, *KRAS* triggers downstream effector pathways, notably the Mitogen-Activated Protein Kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways, which are essential for cell proliferation and survival. The return of

KRAS to the “off” state occurs when GTP is hydrolyzed back to GDP, a reaction catalyzed by GTPase-activating proteins (GAPs) such as neurofibromatosis type 1 (NF1).¹ This dynamic cycle of activation and deactivation is crucial for the precise regulation of cellular processes influenced by *KRAS*. This article comprehensively explores various aspects of *KRAS* mutations in NSCLC, with a focus on targeted therapies and combination treatment strategies for *KRAS*-mutant NSCLC.

Epidemiology of *KRAS* Mutations

KRAS mutations represent the most prevalent carcinogenic driver in NSCLC, with their incidence varying significantly based on the lung cancer’s pathological type, ethnicity, smoking history, and gender. In Caucasian populations, *KRAS* mutations are found in approximately 30% of lung adenocarcinomas, whereas they occur less frequently in lung squamous cell carcinoma, with an incidence ranging from 1.6% to 7.1%.² In large cell lung cancer and adenosquamous carcinoma, the incidence rates are 12.8% and 10%, respectively. Beyond ethnic differences, *KRAS* mutations tend to be more common among women and individuals with a history of smoking.³

A strong correlation has been established between PD-L1 expression and *KRAS* mutations.^{4,5} NSCLC patients who are PD-L1 positive (TPS \geq 1%) are more likely to have *KRAS* mutations, particularly the *KRAS* exon 2 p.G12C mutation, compared to those who are PD-L1 negative.⁵ The mutation rate in patients with high PD-L1 expression levels (\geq 50%) is significantly higher than in those with low levels (1–49%).⁴ This phenomenon may be associated with *KRAS* mutations that induce PD-L1, as confirmed in human NSCLC cell lines.^{6–8} Notably, the p.G12C mutation, characterized by the substitution of glycine with cysteine, is one of the most prevalent types of *KRAS* mutations, accounting for 40% of all such mutations in NSCLC.⁹ Nassar et al recently reported that specifically in NSCLC patients, the incidence of the *KRAS* exon 2 p.G12C mutation is 13.8%.¹⁰ In contrast, other significant mutations, such as p. G12V and p. G12D, represent 21% and 17% of *KRAS* mutations in NSCLC, respectively.⁹ Additionally, research by Dogan et al and Osta et al has highlighted that *KRAS* exon 2 p.G12C mutations are particularly prevalent among female patients and smokers.¹¹ It has also been noted that there is no statistically significant difference in age among different *KRAS* mutation subtypes.¹²

Biological Characteristics of *KRAS*: Structure, Function, Downstream Pathway

KRAS is a gene that encodes a membrane-bound GTPase. This protein plays a pivotal role in cellular signaling and functions in an inactive state when bound to guanosine diphosphate (GDP) and in an active state when bound to guanosine triphosphate (GTP).¹³ The transition of *RAS* proteins to their active, GTP-bound state is facilitated by GEFs, such as the effector protein SOS1.¹⁴ Upon activation, *KRAS* can bind to downstream effector molecules either as monomers or dimers, initiating a variety of signaling pathways (Figure 1). Conversely, the inactivation of *KRAS* is regulated by GAPs, which increase the GTPase activity of *KRAS*, leading to a greater affinity for GDP and thus maintaining *KRAS* in its inactive state. This dynamic interplay between the active and inactive states of *KRAS* is fundamental to the regulation of various cellular processes and is a key focus in understanding the molecular mechanisms driving cancer and other diseases.

KRAS Mutation Subtypes and Genetic Heterogeneity

Incidence of Different Mutant Subtypes

KRAS mutations predominantly involve chromosome 12p12.1, with the most common alterations occurring at codons 12 and 13, and less frequently at codon 16. Remarkably, over 80% of oncogenic *KRAS* mutations are found at codon 12, which is strategically located near the nucleotide binding pocket and the adjacent effector protein switch of the *KRAS* protein.¹⁵ These mutations often result in the substitution of glycine at codon 12 with other amino acids, except proline. This alteration can lead to genomic heterogeneity in tumors harboring *KRAS* mutations, thus impeding GAP binding and promoting GTP hydrolysis. Consequently, this facilitates the accumulation of active *KRAS*-GTP, driving carcinogenic cell signaling.¹⁶ Among these, the most frequent mutations at *KRAS* codon 12 are the glycine-cysteine (*KRAS* exon 2 p. G12C), glycine-valine (*KRAS* exon 2 p. G12CV), and glycine-aspartic acid (*KRAS* exon 2 p. G12D) mutations.

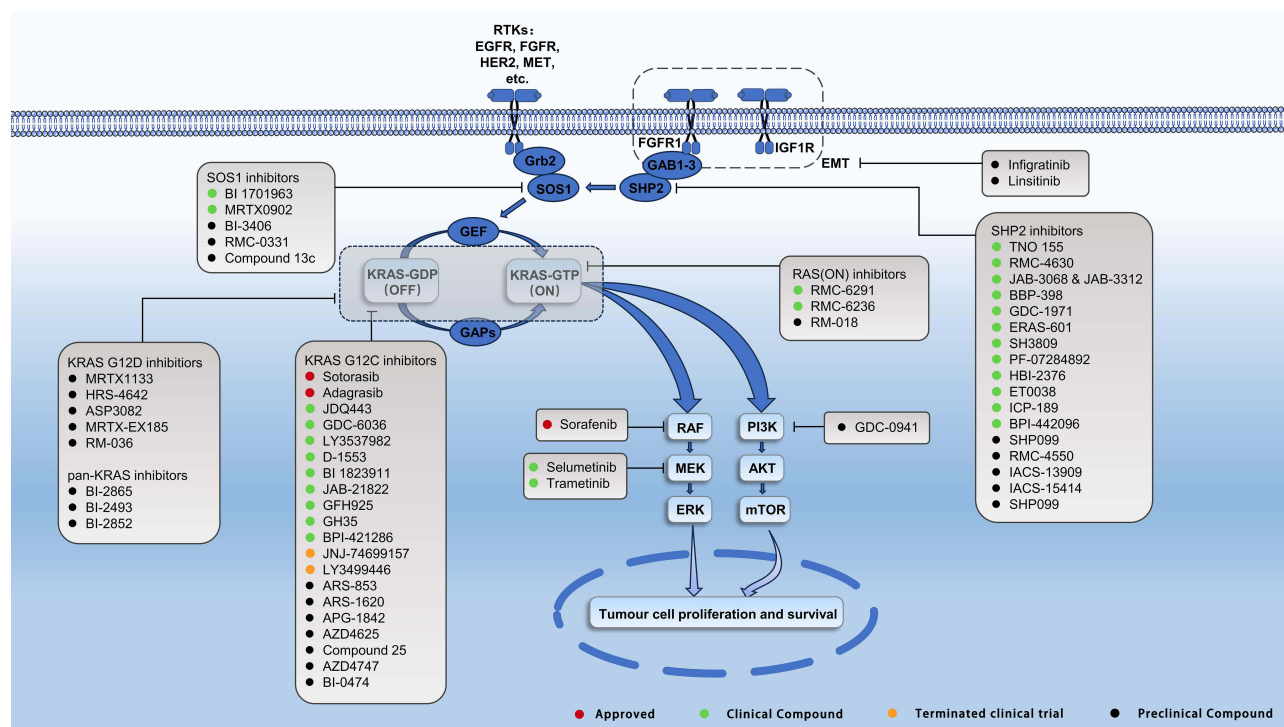


Figure 1 [KRAS signaling pathway and targeted therapeutic agents].

Different Mutant Subtypes Have Different Prognoses

The prognostic implications of various *KRAS* mutation subtypes are currently unclear and subject to debate. While some studies indicate no significant differences in prognosis among the *KRAS* mutation subtypes,¹⁷ conflicting evidence exists. For example, several studies suggest that patients with the *p. G12D* mutation experience worse progression-free survival (PFS) and overall survival (OS),¹⁸ in contrast to those with the *o. G12C* mutation, who demonstrate better objective response rates (ORR), PFS, and OS.¹⁹ Conversely, other research has reported that the *p. G12D* mutation may be associated with better PFS and OS.²⁰

Effects of Different Mutant Subtypes on Downstream Signaling Pathways

Different *KRAS* mutation subtypes have distinct impacts on downstream signaling pathways. For instance, in cell lines harboring *KRAS exon 2 p.G12C* or *KRAS exon 2 p.G12CV* mutations, there is a notable increase in RAS-related protein (RAL) A/B signaling,²¹ accompanied by a decrease in phosphorylated Protein Kinase B (AKT) levels. This pattern differs significantly compared to cell lines with other types of *KRAS* mutations or those with wild-type *KRAS*. In contrast, cell lines featuring *KRAS exon 2 p.G12CD* mutations show more effective activation of the PI3K-AKT pathway.^{22,23} The identification of these differing effects highlights the importance of developing treatment strategies for *KRAS*-mutated NSCLC that are specifically tailored to the unique characteristics of each mutation subtype. Such targeted approaches are likely to be more effective due to their precise alignment with the underlying molecular alterations.

Prognostic Impact of KRAS Mutations

The prognostic impact of *KRAS* mutations in NSCLC patients at both early and advanced stages is increasingly recognized. According to the 2022 National Comprehensive Cancer Network (NCCN) guidelines, *KRAS* mutations are considered an adverse prognostic factor relative to tumors without these mutations.²⁴ These mutations are associated with poor prognosis across all stages of NSCLC and present a higher risk of recurrence post-early complete resection.^{3,11,25} Tumors with *KRAS exon 2 p.G12C* mutations are particularly noted for their higher rates of lymphatic invasion and elevated tumor mutation burdens.²⁶ Research involving surgically resected lung adenocarcinoma patients demonstrates

that those with *KRAS*-mutant tumors experience worse disease-free survival (DFS) and overall survival (OS) compared to those with wild-type tumors, a difference that persists even when Epidermal Growth Factor Receptor (EGFR) mutations are excluded.^{3,27}

It is crucial to recognize that prognosis varies significantly with different *KRAS* mutation subtypes and co-mutations. For instance, a single-center retrospective observational study of advanced NSCLC patients treated with at least one therapy reported that those with *KRAS* exon 2 *p.G12C* mutations had a notably better response rate than those without this subtype (50% vs 29.4%; Odds Ratio: 2.4; 95% Confidence Interval: 0.70–8.18; *P*=0.162).²⁰ Furthermore, in multivariate analysis, the *KRAS* exon 2 *p.G12C* mutation was significantly associated with improved PFS (HR: 0.37; 95% CI: 0.12–0.84; *P*=0.021) and OS (HR: 0.22; 95% CI: 0.07–0.66; *P*=0.007).

The predictive significance of *KRAS* mutations as prognostic biomarkers for immune-oncology drugs, cytotoxic chemotherapy, and targeted therapy is of great importance to clinicians treating metastatic NSCLC.²⁸ With the advent of immune checkpoint inhibitors, the presence of Serine/Threonine Kinase 11 (STK11) co-mutations is increasingly significant for prognosis.

Co-mutations

The most frequent co-mutations in NSCLC with *KRAS* exon 2 *p.G12C* mutations are *STK11*, Tumor Protein p53 (*TP53*), and Kelch-like ECH-associated protein 1 (*KEAP1*). These mutations occur in 10.3–28.0% of cases for *STK11*, 17.8–50.0% for *TP53*, and 6.3–23.0% for *KEAP1*.^{29,30} Co-mutations can significantly influence the effectiveness of chemotherapy, immunotherapy, and molecular targeted therapies in treating tumors. Inactivation of the *STK11* gene is linked to a tumor immune microenvironment that excludes T-cells, reducing the efficacy of PD-L1 inhibition. This resistance is observed in *KRAS*-mutant lung adenocarcinoma, which often results in poor clinical outcomes when treated with PD-L1 inhibitors and chemo-immunotherapy.^{31–33} Furthermore, co-alterations in *STK11* and *KEAP1* are associated with unfavorable clinical outcomes in *KRAS*-mutant NSCLC treated with platinum-based chemotherapy,^{31,34} as well as in advanced NSCLC treated with docetaxel.^{34,35} Co-mutations of *TP53* and *KRAS* correlate with genomic instability, a higher tumor mutational burden, and increased PD-L1 expression, leading to variable responses.³⁶ While patients with *TP53/KRAS* mutations may show enhanced responses to PD-L1 inhibitors, these mutations also predict a shortened overall survival when patients receive platinum-based adjuvant chemotherapy.³⁷

The CodeBreak 100 and KRYSTAL-1 clinical trials explored the impact of co-occurring genomic alterations in *STK11*, *KEAP1*, and *TP53* on the clinical outcomes of NSCLC patients with *KRAS* exon 2 *p.G12C* mutations treated with sotorasib and adagrasib.^{38,39} In these studies, the response rates to sotorasib and adagrasib across key co-mutated subgroups were as follows: *STK11* (40–41%), *TP53* (39–51%), with *KEAP1* co-mutations resulting in numerically lower (ORR) of 20–29% for both inhibitors. Additionally, the exploratory data from the CodeBreak 200 trial showed that sotorasib, when compared to docetaxel in advanced NSCLC patients with prior platinum treatment and *KRAS* exon 2 *p.G12C* mutations, consistently benefited patients across these key co-mutated subgroups.⁴⁰ This research underscores the importance of understanding how genomic alterations co-occur in *KRAS* *G12C*-mutated NSCLC, providing a valuable framework for stratifying patients by co-mutation status for targeted therapy with *KRAS* exon 2 *p.G12C* inhibitors, thereby potentially enhancing patient outcomes.

Inhibitors Targeted on KRAS Exon 2 P. G12C Mutation

For over forty years, targeting *KRAS* mutations was deemed a formidable challenge, with limited progress in developing effective chemotherapy or targeted treatments specifically for these mutations, leading to few clinically approved options. However, recent advancements in understanding the *KRAS* signaling pathway have paved the way for the development of targeted therapies (Figure 1). A significant milestone was reached with Sotorasib, which became the first direct *KRAS* inhibitor to enter clinical trials in 2018. It was subsequently approved in 2021 by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treating second-line *KRAS* exon 2 *p.G12C* mutated locally advanced or metastatic NSCLC. In clinical trials, Sotorasib demonstrated a disease remission rate of 32.2% and a control rate of 88.1%, with an objective response rate of 37.1% in 124 patients with *KRAS* exon 2 *p.G12C* mutated NSCLC.^{38,41} Similarly, Adagrasib has also gained FDA approval, showing promising results in both preclinical and clinical trials, with

a recent study reporting a remission rate of 45% and a disease control rate of 96.1%.^{42,43} Both drugs achieve their therapeutic effect by covalently and irreversibly binding to cysteine in the mutated protein, thereby inhibiting its function and biological activity. This approach, targeting the switch II pocket structure of the mutated *KRAS* protein, marks a significant breakthrough in the field of oncology, offering new treatment avenues for what were once considered “undruggable” oncogenic proteins (Figure 1).

Sotorasib

The results from the Phase 2 CodeBreak100 trial demonstrate that sotorasib, when used as a monotherapy in patients with advanced NSCLC harboring the *KRAS* exon 2 *p.G12C* mutation and who had previously undergone other anticancer treatments, offered sustained clinical benefits. The trial reported an overall response rate of 37.1%, with a median PFS of 6.8 months and a median OS of 12.5 months. Notably, the incidence of treatment-related adverse events was generally mild and manageable.^{38,44} Further, the Phase 3 CodeBreak200 trial data revealed that sotorasib, compared to docetaxel, significantly improved PFS in patients with advanced NSCLC with the *KRAS* exon 2 *p.G12C* mutation and prior antitumor drug treatments, while also exhibiting a more favorable safety profile.⁴⁵ Although the primary endpoint PFS for CodeBreak 200 reached statistical significance the median PFS difference was low, raising concerns about the actual clinical benefit in the Sotorasib arm.

The FDA’s denial of sotorasib (Lumakras) supplemental new drug application (sNDA) was primarily due to limited clinical efficacy and the inability to reliably interpret the primary endpoint. One key issue was that the actual PFS benefit of Lumakras was smaller than reported by Amgen, with the PFS difference between Lumakras and chemotherapy possibly as brief as 5 days. Additionally, the FDA attributed the limited clinical benefits to potential biases and trial execution flaws. Several indicators suggested systematic bias in the confirmatory trial, such as dropout, discordance, crossover, and a independence. These factors may have led to an overestimation of sotorasib’s PFS benefit.

In the trial, only 2 patients in the sotorasib group were untreated, while 23 patients (13%) in the control group withdrew consent within the first 5 weeks, with no post-baseline imaging. This severe early dropout imbalance introduces significant uncertainty, as control group patients who withdrew consent may have been in better health and more motivated for treatment, leading to a potential underestimation of the control group’s outcomes. Although imaging discordance is common in clinical studies, the discordance pattern in the CodeBreak 200 trial raised concerns. Early discordance was higher in the control group (58% vs 69%), while late discordance was more prevalent in the experimental group (42% vs 31%). These discrepancies suggest a potential bias in favor of the experimental group, especially given that the PFS gain was only 5 weeks—shorter than the study’s imaging assessment interval.

Despite allowing crossover in the control group to minimize dropout, the FDA found that early crossover patients who were censored for PFS had better prognoses. Specifically, the 19 patients who crossed over early had better OS outcomes than the 27 patients who crossed over after BICR confirmation, with median OS of 18.9 months versus 11.8 months. This raises the question: would the trial outcomes have been different if early crossover patients had better prognoses? Hypothetical analysis suggests that if the 20 early dropout control patients and the 19 early crossover patients had a 50% or greater lower risk of disease progression compared to the trial group, the PFS hazard ratio (HR) would have lost its statistical significance.

The study also included a confirmation of progression (COP) process, separate from investigator and central imaging assessments. While the FDA typically views the COP process as minimally affecting the independence of results, concerns arose that irregular implementation may have biased the study’s final outcomes. Additionally, some critics questioned potential manipulation of the blinded independent central review (BICR) for PFS, raising concerns about the study’s integrity.

Adagrasib

Adagrasib, notable for its favorable pharmacokinetic properties, has a long half-life of 23 hours, exhibits dose-dependency, and is capable of penetrating the central nervous system.^{42,43,46} During the 2023 European Society for Medical Oncology (ESMO) meeting, the KRYSTAL-7 study presented promising results on the effectiveness and safety of adagrasib combined with pembrolizumab as a first-line treatment for patients with advanced NSCLC harboring the

KRAS exon 2 *p.G12C* mutation.⁴⁷ Specifically, for patients with a PD-L1 Tumor Proportion Score (TPS) of $\geq 50\%$, the regimen showed an ORR of 63% and a disease control rate (DCR) of 84%, offering preliminary evidence of its potential for long-lasting effects. This confirmed ORR of 63% notably surpasses the 39–45% ORR achieved with pembrolizumab monotherapy, underscoring the combination's superior efficacy. Moreover, the median PFS has yet to be reached, even after a median follow-up of 10.1 months, indicating sustained benefits over time. In terms of safety, adagrasib and pembrolizumab together maintained the expected safety profiles seen when administered separately, with a lower incidence of treatment-related adverse events (TRAEs). Notably, only 4% of patients discontinued treatment due to TRAEs. Specifically, treatment-related liver events were reported in less than 10% of cases, with most being of minor severity, and no patients discontinued the treatment duo due to elevated Alanine Aminotransferase/Aspartate Aminotransferase (ALT/AST) levels or liver-associated TRAEs. Encouraged by these results, Mirati is preparing to launch a Phase III clinical trial to further investigate adagrasib with pembrolizumab as a first-line therapy in NSCLC patients with the *KRAS* exon 2 *p.G12C* mutation and a PD-L1 TPS of $\geq 50\%$. Complementing this, the ongoing confirmatory Phase III KRYSTAL-12 study is evaluating adagrasib against docetaxel in NSCLC patients with the *KRAS* exon 2 *p.G12C* mutation who have previously undergone treatment, aiming to validate the effectiveness of adagrasib in a broader treatment context.⁴⁸

JDQ-443

JDQ-443 is another novel *KRAS* exon 2 *p.G12C* inhibitor reported in 2022, which exhibits superior structural features and enhanced therapeutic efficacy compared to existing *KRAS* inhibitors such as Sotorasib and Adagrasib. It binds covalently and irreversibly to the Switch II pocket of the *KRAS* exon 2 *p.G12C* protein. Uniquely, JDQ-443 also engages the C12 residue through a novel binding mode that avoids direct interaction with the H95 residue, which is associated with resistance.^{49,50} This interaction effectively locks the *KRAS* exon 2 *p.G12C* in an inactive state, inhibiting the excessive activation of the oncogenic pathway in tumors. In preclinical studies, JDQ-443 demonstrated potent inhibition of the *KRAS* exon 2 *p.G12C* signaling pathway and cellular proliferation, and exhibited dose-dependent anti-tumor activity.⁵¹ The ongoing KonTRASt-01 study, an exploratory phase Ib/II trial, assesses the efficacy of JDQ-443 both as a monotherapy and in combination with TNO155 (an SHP2 inhibitor) and/or a PD-1 monoclonal antibody. The study reported an ORR of 45% according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) criteria, which increased to 57% at the recommended 200mg BID dose level. This ORR surpasses those of Sotorasib and Adagrasib, marking it as the highest among current *KRAS* inhibitors. Regarding safety, most TRAEs were mild (grade 1–2). There were four instances of grade 3 TRAEs, but no severe adverse events (grade 4–5) were reported. These results affirm JDQ-443's reliability and efficacy for treating NSCLC patients with *KRAS* exon 2 *p.G12C* mutations.⁵²

Other *KRAS* Exon 2 *p.G12C* Inhibitors

The landscape of *KRAS* exon 2 *p.G12C* inhibitors has rapidly expanded following the successes of Sotorasib and Adagrasib. Currently, over 20 inhibitors targeting *KRAS* exon 2 *p.G12C* are in various stages of clinical research (Table 1). Notable among these are LY3537982, GFH925, JAB-21822, IBI351 (also known as GFH925), Garsorasib (D-1553), and others. In November 2023, the Center for Drug Evaluation (CDE) officially accepted the new drug application for IBI351,⁵³ granting it priority review status. This decision was based on its potential to treat advanced NSCLC patients harboring the *KRAS* exon 2 *p.G12C* mutation, particularly those who have already received at least one systemic treatment. Furthermore, GDC-6036 is a promising *KRAS* exon 2 *p.G12C* inhibitor. According to the results of the Phase I trial,⁵⁴ GDC-6036 treatment achieved durable clinical remission in patients with *KRAS* exon 2 *p.G12C* mutation-positive solid tumors, and the majority of adverse events were low-grade. In patients with NSCLC, the confirmed response rates was 53.4% (95CI 39.9% to 66.7%) and the median progression-free survival was 13.1 months (95% CI 8.8 months to unestimated). Of the 58 NSCLC patients with measurable disease, complete response rates were 2%, partial response rates were 59%, and disease stabilization was the best response in 29%. And Divarasib had a very rapid onset of action, with a median time from treatment initiation to achieving response of only 1.3 months and a median duration of response (DoR) of 14 months. In comparison to established drugs like Sotorasib (Lumakras) and Adagrasib (MRTX849), GDC-6036 demonstrates superior potency and selectivity in vitro, showing promise for

Table 1 Ongoing Trials with KRAS Exon 2 P. G12C Inhibitors in Lung Cancer

	Drug Inhibitor	Clinical Trial	Phase	Drug Combined
01	GDC-6036	NCT04449874	I/II	Atezolizumab, cetuximab, bevacizumab, erlotinib, GDC1971, inavolisib
02	JDQ-443	NCT04699188	Ib/II	TNO155, tislelizumab
03	D-1553	NCT04585035 NCT05379946	I/II	Pembrolizumab, cetuximab, INI0018
04	LY3537982, LY3499446	NCT04956640	I/II	Abemaciclib, erlotinib, pembrolizumab, temuterkib, LY3295668, cetuximab, TNO155
05	JAB-21822	NCT05002270	I/II	Cetuximab
06	BI 1823911	NCT04973163	Ia/Ib	BI 1823911, BI 1701963, Midazolam
07	JAB-21822	NCT05288205	I/IIa	JAB-3312
08	D-1553+INI0018	NCT05379946	I/II	D-1553+INI0018
09	MK-1084	NCT05067283	Ia/Ib	Pembrolizumab, carboplatin, pemetrexed, cetuximab, oxaliplatin, leucovorin, 5-fluorouracil
10	JNJ-74699157 (ARS-3248)	NCT04006301	I	NA
11	ARS-853		Preclinical	NA
12	ARS-1620		Preclinical	NA
13	ARS-3248	NCT04006301	I	NA
14	Compound I		Preclinical	NA
15	SML-10-70-I		Preclinical	NA
16	SML-8-73-I		Preclinical	NA

advancing the treatment of *KRAS* mutations. The GO42144 study will subsequently explore the combination of Divarasib with a variety of other anticancer agents, such as PD-L1 inhibitors, PI3K alpha inhibitors, bevacizumab, and cetuximab, in an effort to delay the emergence of acquired resistance as much as possible, with the hope that Divarasib will bring greater therapeutic benefits.

Inhibitors Targeted on KRAS Exon 2 P. G12D Mutation

KRAS exon 2 p.G12D mutations are more prevalent than *KRAS* exon 2 p.G12C mutations, yet, as of now, there are no approved targeted therapies for *KRAS* exon 2 p.G12CD worldwide. Drawing on the successful development strategies of *KRAS* exon 2 p.G12C inhibitors, several *KRAS* exon 2 p. G12D inhibitors have been developed (Table 2). Notably, MRTX1133 by Mirati Therapeutics is the first reported reversible inhibitor targeting *KRAS* exon 2 p. G12D.⁵⁵ This compound selectively and reversibly inhibits *KRAS* exon 2 p. G12D, while sparing *KRAS* wild-type cells. In animal tumor models of pancreatic and colorectal cancer, MRTX1133 consistently shows dose-dependent inhibition of *KRAS*-dependent signaling. At a dosage of 3 mg/kg, it effectively inhibits the growth of G12D-mutant xenografts. However, MRTX1133 has not yet been reported to enter clinical trials. Other *KRAS* exon 2 p. G12D inhibitors are also predominantly in the early stages of clinical development. The research into *KRAS* exon 2 p. G12D inhibitors includes both small molecules and degraders, which vary in their methods of administration, including intravenous and oral dosing.

Table 2 Ongoing Trials with KRAS Exon 2 p. G12D Inhibitors

	Drug Inhibitor	Phase	Cancer Type	Clinical Trial
01	MRTX-1133	I/II	NSCLC, PDAC, CRC, Other Solid Tumors	NCT05737706
02	HRS-4642	I	With Advanced Solid Tumors Harboring KRAS exon 2 p. G12D Mutation	NCT05533463
03	ASP3082	I	Solid Tumors	NCT05382559
04	INCB161734	I	Solid Tumors	NCT06179160
05	RMC-9805	I	NSCLC, CRC, PDAC, Advanced Solid Tumors	NCT06040541
06	AST2169	I	With Advanced Solid Tumors Harboring KRAS exon 2 p. G12D Mutation	CXHL2301442
07	QLC1101	Clinical approval	With Advanced Solid Tumors Harboring KRAS exon 2 p. G12D Mutation	NCT06403735
08	JAB-22000	Preclinical	PDAC, NSCLC, CRC	NA
09	UA022	Preclinical	Tumors	NA

Abbreviations: NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal cancer.

Pan-KRAS Inhibitors

Beyond the drug therapies targeting *KRAS exon 2 p. G12D*, pan-*KRAS* targeted therapies, which aim at multiple or all *KRAS* mutation variants, have provided new therapeutic choices for numerous cancer types with *KRAS* mutations. Among the recent developments, the Memorial Sloan Kettering Cancer Center in the USA has reported promising results with an inhibitory molecule, BI-2865. This molecule is noted for its ability to deactivate 18 of the 24 most commonly observed *KRAS* mutant proteins in cancer.⁵⁶ Additionally, the company Revolution is making strides with RMC-6236, a pan-*RAS* inhibitor. Specifically targeting advanced solid tumors with *KRAS G12* mutations (except *KRAS exon 2 p. G12C*), RMC-6236 is currently undergoing Phase 1 clinical trials. Notably, in animal models of non-small cell lung and pancreatic cancers, which were implanted with tumors exhibiting various *KRAS* gene mutations, RMC-6236 showed potent anticancer effects.⁵⁷

BI-2865

Recently, Boehringer Ingelheim (BI) and the Memorial Sloan Kettering Cancer Center (MSKCC) unveiled a new Pan-*RAS* inhibitor, BI-2865, in a publication in Nature.⁵⁶ Originating from the *KRAS G12C* inhibitor BI-0474, BI-2865 emerged as an optimized version after researchers removed its covalent warhead. This modification reduced its potency against the *p.G12C* mutation alone but expanded its inhibitory effect to cover other *KRAS* mutations, including *p.G12D* and *p. G12V*. In vitro experiments demonstrated that BI-2865 effectively inhibits the growth of cancer cells with various *KRAS* mutations, including *G12C*, *G12V*, and *G12D*. Its inhibitory effect on *G12C* mutations is comparable to that of Sotorasib. Out of the 24 common *KRAS* mutations found in human cancers, BI-2865 can inhibit 18, showcasing its broad potential in targeting *KRAS*-driven malignancies.

RMC-6236

The revised text effectively presents RMC-6236, an innovative oral, non-covalent RASMULTI(ON) inhibitor that specifically targets mutations and variants within classical *RAS* subtypes, exhibiting selectivity in both GTP-bound and dissociated states.⁵⁸ In preclinical studies, RMC-6236 has been shown to consistently and powerfully suppress the growth of diverse *RAS* mutant tumors, particularly in cases of pancreatic and NSCLC with *KRAS G12X* mutations, where X represents A, D, R, S, or V. The Phase I clinical trials involved patients who had progressed after standard treatments, predominantly those with NSCLC featuring *KRAS exon 2 p. 12D* and *12V* mutations. For NSCLC treated solely with RMC-6236, the ORR reached 38%, with a DCR of 85%. The median response time recorded was 1.4 months, the average duration of treatment was 3.1 months, and the longest PFS spanned nearly one year.^{59,60}

Acquired Resistance to KRAS Exon 2 P. G12C Mutation

Mechanisms of Acquired Resistance to KRAS Exon 2 P. G12C

The development of acquired resistance to *KRAS* inhibitors in cancer treatment can be understood through two primary categories: on-target and off-target mechanisms. On-target resistance mechanisms are specifically associated with mutations occurring in the switch-II binding pocket of the *KRAS* protein. These mutations can alter the binding affinity of the drug, thereby diminishing its efficacy.⁶¹ Acquired *KRAS* activating mutations and the amplification of the *KRAS* gene are key factors that mediate resistance via on-target mechanisms. They achieve this by reactivating the *RAS* signaling pathway, which the *KRAS* inhibitors initially aim to suppress. Understanding these mechanisms is crucial for developing more effective strategies to overcome or prevent resistance to *KRAS* inhibitors in cancer therapy (Figure 1).

Secondary mutations in *KRAS* play a significant role in the development of resistance to *KRAS exon 2 p.G12C* inhibitors. In cases of resistance to sotorasib, secondary mutations in *KRAS* are observed in 87.3% of cases. Among these, *KRAS exon 2 p. G13D* is the most frequent mutation in sotorasib-resistant clones, accounting for 23%, followed by *R68M* and *A59S* mutations, each constituting 21.2%.⁶² In the context of resistance to adagrasib, *KRAS Q99L* emerges as the most prevalent secondary mutation, found in 52.8% of cases, with *Y96D* and *R68S* mutations following at 15.3% and 13.9% respectively.

Off-target resistance mechanisms to *KRAS* inhibitors involve a range of biological processes including the activation of bypass signaling pathways, epithelial-mesenchymal transition (EMT) mechanisms, and shifts toward cellular senescence. These mechanisms enable cancer cells to maintain signal activation and continue proliferating, even under the stress of *KRAS* inhibitor treatment. A key discovery in this area was made by Suzuki et al, who identified substantial upregulation of Mesenchymal to epithelial transition factor (MET) and hepatocyte growth factor (HGF) in cells that had developed resistance to sotorasib. They found that amplification of the MET gene played a crucial role in the acquired resistance to this drug. Importantly, the deletion of MET in resistant cells restored their sensitivity to sotorasib in vitro. This re-sensitization to the drug was also accompanied by the resumption of sustained Extracellular Regulated Protein Kinases (ERK) phosphorylation, highlighting the significance of MET in the resistance mechanism and offering a potential therapeutic target to overcome resistance in *KRAS*-mutated cancers.⁶³

EMT represents another key non-genomic transcriptional reprogramming mechanism that contributes to acquired resistance in targeted cancer therapies.⁶⁴ In the context of *KRAS exon 2 p.G12C* mutated NSCLC, the adoption of EMT characteristics has been linked to the development of acquired resistance to sotorasib, both in vitro and in xenograft models.⁶⁵ This phenomenon was observed in H358 and LU65 cell lines that developed resistance to sotorasib, as evidenced by a decrease in e-cadherin and an increase in vimentin expression, which are hallmarks of EMT.⁶⁵

Overall, despite the recent development of sotorasib and adagrasib, biological mechanisms of acquired resistance have yet been described in both pre-clinical and clinical specimens. Numerous emerging resistance mechanisms are being identified, and the resistance mechanisms related to *KRAS* resemble a vast network that requires exploration.^{66,67}

Targeting Acquired Resistance to KRAS Exon 2 P. G12C Inhibitors

As detailed by Canon et al sotorasib may augment the efficacy of targeted therapies, including those that inhibit both upstream and downstream effectors of *KRAS exon 2 p.G12C*.⁶⁸ Their synergy scoring analysis with various targeted therapies supports the concept that sotorasib can enhance therapeutic efficacy and help overcome acquired resistance. In studies involving the H358 xenograft model, combining sotorasib with Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase (MEK) inhibitors led to a substantial reduction in tumor volume, markedly greater than using either monotherapy.⁶⁸

Additionally, the *KRAS exon 2 p.G12C/Y96D* mutation is known to cause cross-resistance to both sotorasib and adagrasib by modifying drug binding.^{62,69} In response, Tanaka et al identified structurally and functionally distinct *KRAS exon 2 p.G12C* inhibitors that are effective against the *Y96D* mutation.⁶⁹ RM-018, a novel *KRAS exon 2 p.G12C* inhibitor, exemplifies this by using cyclophilin A to bind and inhibit the GTP-bound state of *KRAS exon 2 p.G12C*. Both in vitro and in vivo studies demonstrate RM-018's capability to decrease cell viability and significantly reduce RAS-MAPK signaling in cell lines with the *KRAS exon 2 p.G12C* mutation.^{70,71} When administered to the H358 *KRAS G12C*-

NSCLC xenograft model, RM-018 induced dose-dependent tumor regression and was well tolerated. Importantly, RM-018 also showed in vitro efficacy against acquired resistance.⁶⁹

Combination therapies that target both upstream and downstream signaling pathways of *KRAS* offer another avenue to circumvent acquired resistance.^{63,65,72} Additionally, the simultaneous inhibition of SOS1 and SHP2 presents a novel strategy for overcoming resistance to *KRAS* exon 2 *p.G12C* inhibitors.⁴²

Combined with Inhibitors of Other Signaling Pathways

The potential synergy between the PI3K/AKT/mTOR and RAS/RAF/MEK signaling pathways suggests that targeting both pathways simultaneously, or even just one, could be an effective approach in treatments centered on signal transduction pathways (Table 3). Notably, the combined blockade of PI3K/mTOR and MEK has demonstrated significant effectiveness in mouse models with *KRAS*-induced adenocarcinoma.⁷³ The activation of the PI3K pathway is dependent on *RAS* and its catalytic subunit p110 α . By inhibiting this subunit, the PI3K pathway can be effectively suppressed, leading to hindered tumor growth. This effect is further enhanced when MEK inhibition is applied concurrently, showcasing the potential of a dual inhibition strategy in managing *KRAS*-driven cancers.^{74,75}

Targeting RTKs Involved in by-Pass Signaling Pathways and Epithelial-to-Mesenchymal Transition

The strategy of dual inhibition, targeting both MET and *KRAS* exon 2 *p.G12C*, has proven effective in reducing tumor growth in sotorasib-resistant xenograft mouse models. This approach suggests that combining MET and *KRAS* exon 2 *p.G12C* inhibitors could be a viable treatment option for NSCLC patients who have both MET amplification and *KRAS* exon 2 *p.G12C* mutations.⁶³ The efficacy of such dual blockade underscores the potential of combination therapies in overcoming resistance mechanisms and improving treatment outcomes for patients with complex genetic profiles in NSCLC.

In the context of *KRAS* exon 2 *p.G12C* inhibitor therapy, the activation of EMT and the PI3K pathway are recognized as contributing factors to both intrinsic and acquired resistance. While SHP2 plays a relatively minor role in activating the PI3K pathway, it is crucial in activating the MAPK pathway, particularly through SOS1 activation. SHP2 facilitates this process by interacting with SRC kinase,⁷⁶ leading to the subsequent activation of the RAS signaling pathway. The use of combination therapy, such as sotorasib or adagrasib with RMC-4550, has shown enhanced efficacy compared to monotherapy. In the first human clinical trial phase 1 results, RMC-4630, used as a monotherapy, achieved a 71% disease control rate in NSCLC patients (n=19) with *KRAS* exon 2 *p.G12C* mutations.⁷⁷

Targeting SHP2 and SOS1

Sotorasib Combined with TNO155

TNO-155, an allosteric SHP2 inhibitor, when combined with sotorasib, has been found to effectively inhibit ERK phosphorylation and reduce *RAS*-GTP levels in met-amplified H23-sotorasib resistant cells, more so than with monotherapy.⁶³ The synergistic effect of combining *KRAS* exon 2 *p.G12C* inhibitors with PI3K and SHP2 inhibitors has been demonstrated to cause tumor regression in mouse models that acquired resistance to AMG510.⁶⁵

JDQ443 Combined with TNO155

SHP2 inhibitors have long been the subject of debate, primarily because they are challenging to develop as standalone drugs. However, since SHP2 is situated upstream of the *KRAS* pathway, there is intense interest in developing SHP2 inhibitors in combination with *KRAS* inhibitors.^{78,79} In preclinical models, the combination of JDQ443 and the SHP2 inhibitor TNO155 has shown to enhance the antitumor efficacy beyond what is achieved with JDQ443 alone as a *KRAS* exon 2 *p.G12C* inhibitor. At the ESMO conference, researchers presented preliminary results from a dose-escalation study involving JDQ443+TNO155 in patients with advanced *KRAS* *G12C*-mutant solid tumors, including NSCLC.⁷⁹ As of February 1, 2023, 50 patients had participated in this dose-escalation treatment. The patient cohort consisted of individuals diagnosed with NSCLC (24 patients, 48%), colorectal cancer (19 patients, 38%), pancreatic cancer (3 patients, 6%), cholangiocarcinoma (2 patients, 4%), duodenal cancer (1 patient, 2%), and ovarian cancer (1 patient, 2%). Notably, 17 of these patients had previously been treated with *KRAS* exon 2 *p.G12C* inhibitors.

Table 3 Clinical Trials Assessing the Safety and Efficacy of Combining KRAS Exon 2 P. G12C Inhibitors with Other Cancer Therapies

Combination Target	Combination Options	NCT Number	Phase
PD1/PD-L1	Sotorasib + Pembrolizumab	NCT04185883 NCT03600883	I/II
	Adagrasib + Pembrolizumab	NCT04613596 NCT03785249	II
	Sotorasib + AMG404	NCT04185883	I/II
	GDC-6036 + Atezolizumab	NCT04449874	I
	LY3537982 + Sintilimab	NCT04956640	I/II
	JDQ443 + Spartalizumab ±TNO155	NCT04699188	Ib/II
SHP2 inhibitors	Sotorasib + RMC4630	NCT04185883 NCT05054725	II
	Sotorasib + TNO155	NCT04449874	I
	Adagrasib + TNO155	NCT04330664	I/II
	GDC-6036 + GDC-1971	NCT04185883	I/II
	JDQ443 + TNO155 ±Spartalizumab	NCT04699188	Ib/II
SOS1 inhibitors	Adagrasib + BII701963	NCT04975256	I/Ib
EGFR and pan ERBB inhibitors	Adagrasib + Afatinib	NCT03785249	I/II
	Sotorasib + Afatinib	NCT04185883	I/II
	Sotorasib + MVASI	NCT05180422	I/II
	JDQ443 + Cetuximab	NCT05358249	Ib/II
	LY3537982 + Cetuximab	NCT04956640	I/II
	LY3537982 + erlotinib	NCT04956640	I/II
	GDC-6036 + Cetuximab	NCT04449874	I
	GDC-6036 + Erlotinib	NCT04449874	I
MEK inhibitor	Sotorasib + Trametinib	NCT04185883	I/II
	Sotorasib + Avutometinib	NCT05074810	I/II
	JDQ443 + Trametinib	NCT05358249	Ib/II
ERK inhibitors	LY3537982 + Temuterkib	NCT04956640	I/II
mTOR inhibitor	Sotorasib + Everolimus	NCT04185883	I/II
CDK4/6 inhibitors	LY3537982 + Abemaciclib	NCT04956640	I/II
	Sotorasib + Palbociclib	NCT04185883	I/II
	Adagrasib + Palbociclib	NCT05178888	I
	JDQ443 + Ribociclib	NCT05358249	Ib/II

Abbreviations: PD-1/PD-L1, programmed cell death protein 1/programmed cell death protein 1 ligand; SHP2, src homology region 2 domain-containing phosphatase-2; SOS1, son of sevenless homolog 1; EGFR, epidermal growth factor receptor; ERBB, The family of ERBB or epidermal growth factor (EGF) receptors includes four members: EGFR/ERBB1, ERBB2, ERBB3 and ERBB4. EGFR and ERBB2; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase; ERK, extracellular regulated protein kinases; mTOR, mammalian target of rapamycin; CDK 4/6, cyclin-dependent kinase 4/6.

Throughout the trial, six different dosing regimens of JDQ443+TNO155 were explored. Forty-four patients experienced TRAEs, with 18 reporting grade 3–4 TRAEs. Fortunately, no grade 5 TRAEs occurred. Efficacy was confirmed in patients with NSCLC, cholangiocarcinoma, duodenal cancer, and ovarian cancer. Of particular note, among the 12 evaluable NSCLC patients who had previously received *KRAS* exon 2 *p.G12C* inhibitor treatment, 4 (33.3%) displayed a confirmed response, achieving a disease control rate of 66.7% (8/12). The maximum tolerated dose (MTD) was not reached, leading to the selection of JDQ443 at 200 mg BID combined with TNO155 at 10 mg BID 2/1 as the recommended dose for further evaluation. This combination has shown strong tolerability and potential to address resistance to *KRAS* inhibitors while also providing synergistic efficacy. Future updates will include detailed biomarker data.

BI-3406 Combined with Adagrasib

SOS1 has emerged as a promising therapeutic target in cancers with *KRAS* mutations, owing to its pivotal role in feedback activation of the Mitogen-activated Protein Kinase (MAPK) pathway. Recently developed BI3406, a selective SOS1 inhibitor, specifically binds to the catalytic site of SOS1, blocking its interaction with GDP-bound *KRAS*.⁸⁰ Preclinical studies of BI-3406 have shown its efficacy extends beyond *KRAS* exon 2 *p.G12C* mutation models, inducing tumor growth inhibition in xenograft models of various *KRAS* mutations including *KRAS* exon 2 *p.G12C* (MIA PaCa-2 cells), *G12V* (SW620 cells), *G13D* (LoVo cells), and *G12S* (A549 cells). In NSCLC and CRC (Colorectal Cancer) models, compared to administering *KRAS* exon 2 *p.G12C* inhibitors alone, combination therapy with SOS1 inhibitors enhances drug efficacy and delays the onset of acquired resistance.^{81,82}

Combined Chemotherapy

KRAS exon 2 *p.G12C* inhibitors AMG-510 and MRTX 849 are being explored in combination with carboplatin and the CDK 4/6 (Cyclin-dependent Kinase) inhibitor palbociclib for the treatment of mutant lung cancer.^{42,68} Individual treatments with AMG-510 or carboplatin can inhibit tumor growth in models resistant to MRTX 849, yet their combined use significantly amplifies antitumor activity in mouse xenografts.⁶⁸ Similarly, in MRTX 849-resistant models with a homozygous deletion of Cyclin Dependent Kinase Inhibitor 2A (CDKN 2A), the concurrent administration of MRTX 849 and palbociclib markedly induces tumor regression by targeting the Retinoblastoma (Rb)/E2F transcription factor pathway.⁴² Additionally, the combinations of AMG-510 with erlotinib or afatinib, and MRTX 849 with afatinib, show high efficacy in tumor models that depend significantly on RTK-mediated feedback resistance mechanisms. However, these combinations are less effective in other *KRAS* exon 2 *p.G12C* mutation models.^{83,84}

Moreover, the *KRAS* exon 2 *p.G12C* inhibitor ARS-1620 and the cMET-targeted crizotinib demonstrate synergistic effects.⁸⁵ In preclinical settings, AMG-510 also exhibits efficacy when used with the chemotherapeutic agent carboplatin.⁶⁸ These findings highlight the diverse biological responses of *KRAS* mutant cells to combinations of *KRAS* inhibitors with chemotherapeutic agents. However, the broad applicability of these specific combinations to different tumor types and *KRAS* mutations still requires further validation.

Immunotherapy in *KRAS* Mutation NSCLC

Beyond chemotherapy and targeted therapies, the role of *KRAS* mutations in determining the efficacy of immune checkpoint inhibitors (ICIs) in NSCLC patients has gained attention. At the 2023 ESMO conference, researchers presented the Phase II KRYSTAL-7 study results, which involved combining adagrasib with pembrolizumab as a first-line treatment for patients with advanced NSCLC that harbors *KRAS* exon 2 *p.G12C* mutations.⁴⁷ For patients exhibiting a PD-L1 expression of $\geq 50\%$, the ORR was 63%, and the DCR reached 84%. The median duration of response (DOR) has not yet been reached, with a 95% confidence interval (CI) of 12.6 months to not estimable (NE); similarly, the median PFS was also not reached, with a 95% CI of 8.2 months to NE. These promising results support the advancement to Phase III clinical trials to compare the efficacy of adagrasib combined with pembrolizumab against pembrolizumab monotherapy in treating first-line NSCLC patients with PD-L1 expression of $\geq 50\%$ and *KRAS* exon 2 *p.G12C* mutations.⁸⁶

A single-center retrospective study yielded inconclusive results regarding the correlation between immunotherapy and *KRAS* mutations, finding no significant association.⁸⁷ In contrast, another study reported contradictory findings, suggesting that *KRAS* mutations may serve as predictive markers for extended responses to ICIs in NSCLC patients, particularly those with high PD-1 expression, in future clinical trials.⁸⁸ It is typically observed that patients with *KRAS* mutations have higher PD-L1 expression and a greater tumor mutational burden (TMB) compared to those with wild-type *KRAS*. Tumors characterized by high TMB are known to be highly immunogenic, often described as “hot” or inflammatory tumors. These tumors are distinguished by the infiltration of immune cells, especially cytotoxic T lymphocytes, which can potentially make them more responsive to immunotherapy.⁸⁹

The Choice of Treatment Options

Currently, treatments for NSCLC primarily include surgery, chemotherapy, immunotherapy, and targeted therapies.⁹⁰ Sotorasib is available for patients with locally advanced or metastatic NSCLC harboring *KRAS G12C* mutations who have previously undergone at least one systemic therapy. However, The first-line clinical treatment regimen for *KRAS*-mutant NSCLC patients remains similar to that for patients without driver genes, primarily involving immunotherapy combined with chemotherapy, where bevacizumab plays a significant role. Targeted therapy is typically reserved as a second-line treatment. Additionally, local treatment methods such as surgery and radiotherapy are crucial options. Sequential chemoradiotherapy following chemo-immunotherapy is also one of the available regimens.

For metastatic NSCLC with *KRAS* mutations, the first-line treatment typically involves PD-L1-guided combined chemotherapy and immunotherapy. Although recent data suggest that the effectiveness of this approach requires further validation, it is considered superior to immunotherapy alone for certain patients. Treatment decisions for metastatic *KRAS*-mutated NSCLC, similar to those for NSCLC without driver mutations, are largely dependent on PD-L1 expression levels. Patients with PD-L1 levels $\geq 50\%$ usually receive monotherapy with immunotherapy, while those with PD-L1 $< 50\%$ are typically treated with a combination of immunotherapy and chemotherapy.

In addition to PD-L1 status, other biomarkers like *KRAS* mutation subtypes, co-mutation status, and tumor mutation burden should also be considered to stratify patients and tailor the most effective treatment strategy. Properly evaluating the status of *RAS* gene mutations and interpreting the biological and clinical significance of different *KRAS* and *NRAS* mutations is essential for the comprehensive management of patients with advanced NSCLC and colorectal cancer (CRC). To support healthcare professionals in precision oncology, Malapelle et al have developed an Italian knowledge database (www.rasatlas.com) that summarizes real-world data on *RAS* gene mutations in lung and colorectal cancers.⁹¹

Conclusion

The realm of *KRAS*-targeted drug development is still in its nascent stages, with the advent of *KRAS exon 2 p.G12C* inhibitors marking a breakthrough in the longstanding challenge of targeting *KRAS* mutations. This development represents just the beginning, the first chapter in unraveling the complexities of the *KRAS* enigma. Currently, the field is evolving rapidly, entering a new phase of exploration beyond the confines of *KRAS exon 2 p.G12C* inhibitors. Like other targeted therapies, the mechanisms of acquired resistance to *KRAS exon 2 p.G12C* inhibitors are diverse and complex. In this context, the formulation of combination therapies, particularly those incorporating SHP2 and SOS1 inhibitors, is emerging as a promising approach to tackle both intrinsic and acquired resistance.

Preclinical studies indicate that combining *KRAS exon 2 p.G12C* inhibitors with agents targeting upstream and downstream pathways is often essential for effective treatment. The efficacy of ICIs in *KRAS*-mutant NSCLC, however, remains an area of ongoing research. The response to ICIs appears to be heavily influenced by specific co-existing mutations and the type of *KRAS* mutation variant present. As such, there is a pressing need for continued research and development efforts to expand the therapeutic options available for effectively targeting *KRAS* mutations. Only through such concerted efforts will we be able to build a comprehensive arsenal against *KRAS*-driven cancer.

Disclosure

The authors report no conflicts of interest in this work.

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