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KRAS Inhibitors in Lung Cancer: Current Strategies and Future Approaches

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Introduction

RAS (rat sarcoma viral oncogene homolog) proteins were among the earliest identified proteins that regulate cell growth, differentiation, and survival.[1,2] The seminal work of Harvey and Kirsten in the 1960s paved the way for discovering these proteins that are encoded by retroviral oncogenes initially observed in rat sarcoma viruses.[3,4] Among the different RAS proteins discovered to date, the *KRAS* (Kirsten Rat Sarcoma viral oncogene) isoform is the most frequently mutated in human cancers, occurring in 75% to 80% of cancers, followed by neuroblastoma RAS (*NRAS*), occurring in 12%, and Harvey RAS (HRAS), occurring in 3% of RAS cancers.[1,5,6] *KRAS*, together with Epidermal Growth Factor (*EGFR*) and Anaplastic Lymphoma Kinase (*ALK*), are the most commonly identified oncoproteins, with known mutations in non-small cell lung cancer (NSCLC), and have been the focus of many research studies over the years.[7,8] Despite significant success in targeting both *EGFR* and *ALK* mutations in NSCLC, more progress has yet to be made in developing therapies for *KRAS* mutations.[9]

Geographic variations have been observed in NSCLC patients harbouring *KRAS* mutations. The highest incidence has been observed in the Western hemisphere, particularly in Europe and North America (20–25% prevalence among Caucasians) and a lower prevalence has been observed in East Asian regions and India, with a range of (10–15%).[5,6,10,11] *KRAS* mutations are frequently detected in lung adenocarcinoma (32%) and are rarely identified in squamous cell carcinoma.[5,12,13] *KRAS*-mutant lung cancers are more common among smokers [14–17], and those with high programmed death-ligand 1 (PD-L1) expression,[18] causing increased immune invasion hypothesized to be due to chronic exposure to particulate matter from smoking.[19,20] The use of immunotherapy in *KRAS*-driven lung cancer remains unclear as co-mutations such as *STK11* and *KEAP1* may diminish the benefit of immunotherapy, especially among those with *KRAS* mutant NSCLC.[21,22] Therefore, developing *KRAS*-specific drugs is essential to improve the treatment outcomes of this patient population. There are several subtypes of *KRAS*, with most point mutations occurring at exons 2 and 3, representing hotspots at codons G12, G13, and Q61.[5,23,24] *KRAS* G12C is the most frequent subtype at 41–43% among NSCLC patients, making it a reasonable target for drug development.[25,26] Moreover, NSCLC patients with G12C mutations tend to have a poorer prognosis and usually present with metastatic disease upon diagnosis compared to other *KRAS* subtypes or patients with *KRAS* wild-type.[13,27].

Two small-molecule inhibitors are currently approved by the FDA for NSCLC patients harbouring *KRAS* G12C mutations, namely sotorasib[27,28] and adagrasib.[29] A few molecules that target *KRAS* G12C, in addition to other *KRAS* mutations, are also in early to mid-clinical development. In this review, we will focus on *KRAS* G12C inhibitors.

KRAS Mutations in Lung Cancer

RAS proteins function as finely regulated molecular switches in the cell membrane that cycle between an activated GTP (guanosine triphosphate)-bound and an inactivated GDP (guanosine diphosphate)-bound state. Two regulatory proteins govern the switching process to the active and inactive state: **1)** guanine nucleotide exchange factor (GEF), which helps GTP to bind to RAS, leading to its activation, while **2)** GTPase activating protein (GAP) leads the hydrolysis of GTP to GDP, causing RAS inactivation. Mutations in *KRAS*

impair the hydrolysis of GTP to GDP; thus, *KRAS* remains in its active state, leading to unregulated activation of several downstream intracellular pathways, including the RAF-MEK-ERK pathway, PI3K-AKT-mTOR pathway, and ral guanine nucleotide dissociation stimulator (RALGDS) which are responsible for cellular proliferation, differentiation, cell migration, and survival.[30,31]

In addition to their effects on the downstream signalling pathways, it has also been established that *KRAS* mutations have a role in immune system modulation through their interaction with the tumour microenvironment (TME), which can influence tumour progression and anti-tumour response.[2,32]

Strategies for *KRAS* G12C inhibition

The FDA granted approval to two targeted agents for *KRAS* G12 mutated NSCLC, which are sotorasib and adagrasib, while Health Canada has only granted approval of sotorasib. Both agents are covalent allosteric inhibitors of *KRAS* G12C, which prevents the release of GDP and subsequent binding of GTP, locking the mutant *KRAS* in an inactive state by wedging into a cleft around the Switch II domain.

Sotorasib is the first *KRAS* G12C inhibitor to enter a clinical trial. The phase 2 CodeBreaK 100 trial demonstrated a clinical benefit of sotorasib in patients who had received at least one prior systemic therapy. The results showed an objective response rate (ORR) of 37.1%, a median progression-free survival (PFS) of 6.8 months, a median duration of response (DOR) of 11.1 months, and a median overall survival (OS) of 12.5 months.[27] The clinical benefit was further supported by the subsequent phase 3 study, CodeBreak 200, which compared the *KRAS* G12C inhibitor to docetaxel in NSCLC patients who had progressed on platinum-based chemotherapy and checkpoint inhibitor therapy. The median PFS and ORR were superior, with the PFS for sotorasib at 5.6 months vs 4.5 months with docetaxel, and an ORR of 28.1% for sotorasib vs 13.2% for docetaxel. There was no difference in OS between the treatment arms.[33] Docetaxel-treated patients reported more severe symptoms and more significant negative impact from toxicity than sotorasib-treated patients. The quality-of-life as measured by the EQ5D visual analog scale started to deteriorate within 5 days after docetaxel was initiated and continued to deteriorate over time; with sotorasib, QOL was preserved over time.[34]

Adagrasib is the second irreversible and selective *KRAS* G12C inhibitor approved for use among NSCLC patients harbouring this mutation who were previously treated with chemotherapy and immunotherapy. Adagrasib has also demonstrated clinical efficacy with an ORR of 42.9%, a median PFS of 6.5 months, a median DOR of 8.5 months and a median OS of 12.6 months.[28] The phase 3 study (NCT04685135) comparing adagrasib and docetaxel in patients with *KRAS* G12C mutation-positive NSCLC who had received prior platinum-based chemotherapy and immunotherapy has finished enrolment, and the results are pending.

Since the availability of these two molecules, clinicians are now concerned about the most appropriate drug for their patients. As noted previously, sotorasib and adagrasib have a similar PFS and OS. In contrast, adagrasib has shown a numerically higher ORR along with higher drug-related adverse events and, consequently, a higher treatment discontinuation rate (although caution must be exercised when performing cross-trial comparisons). Both molecules cause substantial gastrointestinal side effects including diarrhea, nausea or vomiting, and elevations in liver enzymes (**Table 1**).[26,28,35]

One preclinical study reported a high concentration of adagrasib in the cerebrospinal fluid, which is comparable to other targeted therapies for other oncogenic mutations that have good activity against brain metastasis (osimertinib, alectinib, lorlatinib).[36–40] Moreover, in the phase II KRYSTAL-1 study, the use of adagrasib showed an intracranial (IC) ORR and disease control rate (DCR) of 33% and 85%, respectively. The IC PFS was 5.4 months, supporting the utility of adagrasib in NSCLC patients with brain metastases.[29] Conversely, sotorasib has limited data on central nervous system (CNS) activity. A posthoc analysis of the CodeBreak 100 trial, including 16 patients with stable brain metastases, demonstrated an IC DCR of 88%[39]. In the subgroup analysis of patients who presented with brain metastases at the time of enrollment in CodeBreak 200, those treated with sotorasib had a decrease in the risk of progression and a trend to delay in the development of new brain metastases.[40]

The presence of co-mutations and their potential impact on efficacy was also explored. CodeBreak 100 and KRYSTAL-1 showed a higher ORR and PFS for those with *STK11* alone and those with *STK11* and/or *KEAP1* and *TP53* mutations.[41,42] However, CodeBreak 200 did not show any

Event	Any Grade *number of patients (%)*	Grade ≥ 3 *number of patients (%)*
Sotorasib (N=126)[28]		
Diarrhea	40 (31.7)	5 (4.0)
Nausea	24 (19.0)	0
Alanine aminotransferase (ALT) increase	19 (15.1)	8 (6.3)
Aspartate aminotransferase (AST) increase	19 (15.1)	7 (5.6)
Fatigue	14 (11.1)	0
Vomiting	10 (7.9)	0
Adagrasib (N=116)[29]		
Diarrhea	82 (70.7)	1 (0.9)
Nausea	81 (69.8)	5 (4.3)
Fatigue	69 (59.5)	8 (6.9)
Vomiting	66 (56.9)	1 (0.9)
Anemia	41 (36.2)	17 (14.7)
Dyspnea	41 (35.3)	12 (10.3)
Alanine aminotransferase (ALT) increase	33 (28.4)	6 (5.2)
Aspartate aminotransferase (AST) increase	31 (26.7)	6 (5.2)

Table 1. Adverse Events Reported during Treatment with Sotorasib and Adagrasib; *courtesy of Kenneth Samala, MD and Qunicy S-C Chu, MD.*

difference in benefit for those with *STK11*, *KEAP1*, and *TP53* but showed less benefit for those with other co-mutations.[33] More studies in predictive biomarkers are warranted.

Several molecules targeting *KRAS* G12C mutations are currently being developed and studied. Most have shown promising preliminary clinical activity and tolerable side effects and are summarized in **Table 2**.

Challenges in managing *KRAS* mutated NSCLC

KRAS and *CNS* metastases

The lifetime incidence of brain metastases in NSCLC patients with *KRAS* G12C mutations is approximately 40%. Hence, effective treatment options for CNS disease are a significant unmet need in this population.[35] Although data have demonstrated the preliminary IC activities of both sotorasib and adagrasib in patients with *KRAS* G12C mutant NSCLC,[29,39,40] further studies on patients with known brain metastases are needed.

Resistance mechanisms

One of the significant challenges in targeted therapies is the invariable development of acquired resistance. The lower ORR for both sotorasib and adagrasib (compared to other drugs against EGFR and ALK mutations)[46–48] may be explained by the intrinsic mechanisms of resistance to *KRAS* G12C inhibitors, including an adaptive RAS-MEK pathway feedback reactivation.[28,29,50,51] There are three main acquired mechanisms of resistance, namely **1)** on-target mechanisms,[52,53] **2)** bypass mechanisms,[53,54] and **3)** lineage plasticity and epithelial-to-mesenchymal transition (**Table 3**).[53] Undiscovered mechanisms could still exist, which supports the need for and importance of investigating resistance mechanisms to develop tolerable combination strategies with superior outcomes compared to the *KRAS* G12C inhibitor alone.

Development of *KRAS* G12C combinations can be challenging, such as the combination with PD(L)1. Li et al. reported 30–50% of secondline and beyond *KRAS* G12C positive metastatic NSCLC patients who received either sequential or concurrent sotorasib at 120–960 mg daily and pembrolizumab or atezolizumab, developed >grade 3 hepatotoxicity with the majority occurring beyond the first 30 days of therapy, which resolved with corticosteroid treatment. The phase II study of adagrasib at 400 mg BID in combination with pembrolizumab at 200 mg intravenously Q3W in treatment-naïve, advanced *KRAS* G12C mutation positive NSCLC still reported 16% of patients experiencing >grade 3 hepatotoxicity and 6.7% required corticosteroid treatment.[55] Dose reductions and interruptions were reported in 46% and 59% of patients, respectively. Treatment-related adverse event discontinuation of adagrasib, pembrolizumab and both agents were 6%, 11% and 4%, respectively.[56] The preliminary results of the phase I dose expansion of MK-1084 at 400 mg daily and pembrolizumab, reported hepatoxicity in up to 13% of treatmentnaïve *KRAS* G12C mutation positive, advanced NSCLC patients.[43]

A retrospective analysis by Chour et al. reported that patients treated with PD(L)1 immediately followed by sotorasib experienced more >grade 3 toxicity (50% versus 13%), especially hepatoxicity (33% versus 11%), than those who were not treated with this regimen. There were no fatal events. The majority of the hepatoxicity occurred within 30 days after initiation of sotorasib.[57]

Future approaches

Advances in drug development for *KRAS* mutations in the last few years has led to the approval of two selective *KRAS* G12C inhibitors, and recently, other inhibitors specific for G12D, G12S, and G12R have been identified.[58–60] Although this progress is promising, *KRAS*-mutated cancers have many other subtypes. Developing a specific drug for each one may be impractical, since nearly 20% of *KRAS* mutations occur at frequencies of, at most, 2%.

A way to resolve this issue is to develop a pan-KRAS-selective inhibitor that targets all *KRAS* subtypes while sparing RAS signalling in normal cells. Currently, two pan-*KRAS*-selective inhibitors are in preclinical development. BI-2865 and its close analogue, BI-2493, have shown activity against *KRAS* mutants and wild-type *KRAS* in cells and in animals, respectively. Both drugs spare the inhibition of NRAS and HRAS proteins.[53]

In opposition to the current inhibitors that are directed to the inactivated "*KRAS*-off" molecule, targeting *KRAS* in its GTP-bound activated "*KRAS*-on" state, may lead to further advances. For example, RMC 6236, which binds to

Molecule (Company)	Phase	Eligibility	Prior G12C Therapy?	Safety (All Grades) *(%)*	Clinical Activity	Recommended Dose
JDQ443 (Novartis)[43] n=68	Ib/II	advanced, *KRAS* G12C-mutated solid tumours (including 38 NSCLC patients); previous standard-of-care treatment; aged ≥18 years; and ECOG PS 0–1	Prior treatment with a *KRAS* G12C inhibitor may be allowed for dose escalations of combinations and a subset of groups in dose expansion; not allowed in the monotherapy arm	Fatigue (16.2) Nausea (17.6) Diarrhea (13.2) Edema (11.8) Vomiting (11.8) Grade ≥3: Neutropenia (2.9)	ORR of 41.27% (for response evaluable NSCLC patients); ORR of 54.5%	200 mg BID
Divarasib (Roche) [44] n=59 (NSCLC patients only)	I	*KRAS* G12C-mutated solid tumours (including 60 NSCLC patients) who had progressed after at least one available standard therapy; aged ≥18 years; and ECOG PS 0 or 1	Not allowed	Nausea (76.3) Diarrhea (61) Vomiting (54.2) Grade ≥3: Diarrhea (3.4) Increased ALT (6.8) Increased AST (5.1)	Response rate of 53.4% and median PFS of 13.1 months for NSCLC patients; confirmed response rate of 56.4% and median PFS of 13.7 months	400 mg OD
LY3537982 (Eli Lilly)[45] n=56	I	Locally advanced, unresectable and /or metastatic solid tumour with KRAS G12C mutation (including 16 NSCLC patients); aged ≥18 years; and ECOG PS 0 or 1	Prior G12C therapy allowed in other groups	Diarrhea (38) Constipation (16) Fatigue (16) Peripheral edema (13) Nausea (11) Grade ≥3: Neutropenia (2)	ORR of 38% in patients with *KRAS* G12C inhibitor-naïve NSCLC and ORR of 7% in NSCLC patients with prior exposure to *KRAS* G12C inhibitors.	100 mg BID
MK-1084 (Merck Sharp & Dohme)[46] n=24 (Arm 2 in combination with Pembrolizumab in patients with untreated NSCLC with PD-L1 TPS ≥1%)	I	Locally advanced unresectable or metastatic solid tumours with a *KRAS* G12C mutation and ≥1 line of prior therapy (Arm 1), or previously untreated metastatic NSCLC with PD-L1 TPS ≥1% (Arm 2); aged ≥18 years; and ECOG PS 0 or 1	No information provided	Increased ALT (79) Increased AST (33) Pruritus (29) Diarrhea (17) Fatigue (13) Grade ≥3: Increased ALT (13) Increased AST (8)	ORR of 19% in Arm 1 (including 4 NSCLC patients) and 47% in Arm 2	800 mg OD monotherapy and 400 mg with Pembrolizumab

Table 2. Current *KRAS* G12 C Molecules Undergoing Early Clinical Trials; *courtesy of Kenneth Samala, MD and Qunicy S-C Chu, MD.*
Abbreviations: ALT: alanine amino transferase; **AST:** aspartate aminotransferase; **BID:** dosing regimen of twice a day; **ECOG:** Eastern Cooperative Oncology Group; **NSCLC**: non-small cell lung cancer; **OD:** dosing regimen of once daily; **ORR**: overall response rate; **PD-L1**: programmed cell death ligand 1; **PFS**: progression-free survival; **TPS:** tumour proportion score

Mechanism	Details
On-target mechanisms[52,53]	Through secondary mutations affecting *KRAS* (via nucleotide exchange or changing GTPase activity): Example: • Sotorasib – G13D, R68M, A59S, A59T • Adagrasib – Q99L, Y96D, R68S0
Bypass mechanisms[53,54]	Via activation of RTK-RAS-MPK signalling pathways, including mutations in *NRAS*, *BRAF*, *MEK*, and *FGFR3*, to name a few
Lineage plasticity and epithelial-to-mesenchymal transition[53]	Through histological transformation from adenocarcinoma to squamous cell carcinoma and activation of the PI3K pathway

Table 3. Summary of Known Acquired Mechanisms of *KRAS* Resistance; *courtesy of Kenneth Samala, MD and Qunicy S-C Chu, MD*.

Abbreviations: BRAF: v-raf murine sarcoma viral oncogene homolog B1, **FGFR:** fibroblast growth factor receptor, **MEK:** mitogen-activated protein kinase, **NRAS:** neuroblastoma; RAS, **PI3K:** phosphoinositide 3-kinase, **RTK:** receptor tyrosine kinase

cyclophilin A, which, in turn, binds to RAS, which then leads to steric hindrance for RAF binding and activation.[61] In the near future, single-agent molecules that can potentially target almost all *KRAS* mutations will enter clinical trials, and their impact in the treatment landscape of *KRAS* mutated cancers is highly anticipated. One possible significant advantage of targeting several mutations is the prevention of secondary on-target mutations in *KRAS*.

Lastly, the outcomes for patients with CNS metastases are poor. Further investigation on the CNS penetration ability of the new targeted therapies and the development of better strategies for treating brain metastases of *KRAS* mutations in NSCLC patients are warranted to further improve their outcomes.

Conclusion

For many years, tumours harbouring *KRAS* mutations were deemed not targetable. However, recent developments in the understanding of *KRAS*-directed therapies and the approval of two drugs against *KRAS* G12C are steps in the right direction, yet more research is still needed. Admittedly, several challenges still loom in the development of an ideal drug against *KRAS* mutations—one that has good efficacy data (including CNS penetration), a tolerable side effect profile, and the ability to target several *KRAS* mutations simultaneously (hence, reducing the chance of on-target acquired resistance). Ongoing studies are being conducted to further determine the proper treatment approaches, such as the appropriate sequences or therapy combinations (including chemotherapy or immunotherapy), to improve the outcomes for patients with this elusive mutation. Overall, the progress made in the last decade is encouraging, and a highly effective treatment against *KRAS*-mutated NSCLC may be within reach in the next few years.

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