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REVIEW

KRAS^{G12C} Inhibitors in Non-Small Cell Lung Cancer: A Review

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Abstract: Rat sarcoma virus (*RAS*) GTPase is one of the most important drivers of non-small cell lung cancer (NSCLC). *RAS* has three different isoforms (Harvey rat sarcoma viral oncogene homolog [*HRAS*], Kirsten rat sarcoma viral oncogene homolog [*KRAS*] and Neuroblastoma ras viral oncogene homolog [*NRAS*]), of which *KRAS* is most commonly mutated in NSCLC. The mutated KRAS protein was historically thought to be "undruggable" until the development of KRAS^{G12C} inhibitors. In this review, from the aspect of brain metastasis, we aim to provide an overview of the advances in therapies that target KRAS^{G12C}, the limitations of the current treatments, and future prospects in patients with *KRAS* p.G12C mutant NSCLC.

Keywords: KRAS, G12C, non-small cell lung cancer, brain metastases

Introduction

Lung cancer (LC) is the leading cause of cancer-related deaths worldwide.[1] It is broadly classified as non-small cell lung cancer (NSCLC) or small-cell lung cancer, based on its clinicopathological features. NSCLC accounts for >85% of all LC cases.[1] Brain metastases (BMs) affect up to 50% of patients with advanced NSCLC,[2] resulting in particularly low survival rates,[3] with a median overall survival (mOS) from BM diagnosis of approximately 2.5 years; meanwhile, central nervous system (CNS)-progression-free survival (PFS) is approximately 1.2 years.[4] Mutations in oncogenic genes that drive NSCLC occur in epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), ROS proto-oncogene 1 (*ROS1*), Kirsten rat sarcoma (*KRAS*), mesenchymal epithelial transition factor (*MET*) and rearranged during transfection proto-oncogene (*RET*). Thanks to the detection of such drive gene mutations, we have entered a new era of personalized therapy in the treatment of patients with LC driven by genotyping.[5] The prevalence of *KRAS* mutations is as high as 30% in NSCLC.[6] The most common codon variants in the protein was mutation from amino acid glycine to cysteine (G12C), which accounted for about 39%[7] of *KRAS* mutation and occurs in roughly 14% of lung adenocarcinomas (LUADs).[8] However, *KRAS* has long been considered an untreatable target.

The brain microenvironment affects the development of BMs, and plays a crucial role in the proliferation, migration, and survival of tumor cells.[9] The blood-brain barrier (BBB) is an important part of this microenvironment[9] and can affect the influx and efflux of molecules into the CNS, preventing drug entry.[10] In addition, the BBB prevents drugs from passively permeating through the high levels of expressed efflux transporters and tight intracellular junctions.[11] Consequently, antitumor activity of first- and second-generation EGFR tyrosine kinase inhibitors, such as gefitinib, erlotinib, and afatinib, seems limited by the BBB. These agents are all substrates of multidrug efflux transporters adenosine triphosphate-binding cassette subfamily members B1 and G2 (ABCB1/MDR1/P-glycoprotein and ABCG2/BCRP).[12–14] Kpu,u, the ratio of free brain to free plasma exposure, is considered a reliable predictor of the BBB diffusion rate, with a value greater than 0.3 indicating satisfied BBB permeability.[15] The CNS drug design guidelines consider that the molecular properties of drugs with high brain exposure include a polar surface area (PSA) < 76 Å^2 (preferred in the range of 25–60 Å^2) and a hydrogen bond donor (HBD) < 3 (ideally 0 or 1).[16.]

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Achieving high drug exposure in the CNS remains a challenge and is much more difficult than achieving exposure elsewhere in the body.[11] Thus, the treatment of CNS metastases from solid tumors is challenging.[17] Many modern antitumor therapies, such as most chemotherapeutic agents, use large hydrophilic molecules that cannot cross the BBB,[18,19] and the effective rate of chemotherapy ranges from 15% to 30%.[19] Although the presence of CNS lesions can impact the BBB penetration rate, effective treatment of CNS metastases relies on a drug's ability to cross the barrier.[20] Active drug transport can affect drug accumulation rates at the tumor site, especially for intracranial (IC) lesions.[21] As outcomes improve for patients with *KRAS* p.G12C mutant NSCLC, BMs may limit treatment efficacy due to the BBB effects. Herein, we review the preclinical and clinical data on the efficacy and CNS penetration of $KRAS^{G12C}$ inhibitors in patients with *KRAS* p.G12C mutant NSCLC and BMs.

KRAS Pathway and Non-Small Cell Lung Cancer

The *KRAS* gene is considered the most frequently mutated oncogenic driver of human malignancies.[22,23] It undergoes alternative splicing and encodes two highly related protein isomers, K-RAS4A and K-RAS4B (also known as isoforms 2A and 2B), composed of 189 and 188 amino acids, respectively.[24] Considering its wide and high expression levels in human tumors, KRAS is generally referred to as K-RAS4B.[25,26]

KRAS is a membrane-bound protein, with a molecular weight of 21 kDa. It belongs to the guanosine triphosphatase (GTPase) family,[27] functions as a guanosine diphosphate (GDP)/triphosphate (GTP) binary switch, controls vital signal transduction from activated membrane receptors to intracellular molecules,[28] and regulates cell growth and differentiation. KRAS shifts between the GTP-bound and GDP-bound states; the former leads to signal activation and the latter indicates signal deactivation. In general, this shift is controlled by GTPase-activating proteins (GAP) and their counterparts, guanine nucleotide exchange factors (GEF).[28] The binding of GTP to KRAS promotes the binding of effectors to trigger signal transduction pathways, including the mitogen-activated protein kinase pathway.[29,30] Figure 1 shows the *KRAS* signaling pathway.

Clinical and Pathological Characteristics of NSCLC Patients with KRAS p.G12C Mutation

In NSCLC, the identified *KRAS* mutations accounts for up to 25% of LUADs and approximately 3% of squamous cell carcinomas.[31,32] G12A, G12C, G12D, G12R, G12S, G12V, G13C, G13D, Q61H, and Q61L are common oncogenic *KRAS* mutations in NSCLC patients. G12C accounts for the highest proportion of *KRAS* mutations in NSCLC.[33–36] Figure 2 shows hotspot *KRAS* mutations in patients with NSCLC. A recent study examined the distribution of the $KRAS^{G12C}$ mutations in 32,138 patients with cancer across race (Asian, Black, and White) and sex and in 10 cancer types.[8] $KRAS^{G12C}$ mutations were identified in 1867 samples, most frequently in patients with NSCLC (1443 [13.8%]). Among them, females harbored more $KRAS^{G12C}$ mutations than males. Notably, within the same ethnicity, the risk of developing G12 mutations differed between males and females. Additionally, smoking is a significant risk factor for the development of *KRAS* mutations in LC. In fact, these mutations are often detected in smokers (30%) and rarely detected in non-smokers (11%).[37] In addition, the pathological type of LC is closely related to *KRAS* mutations, and such mutations are more common in LUADs than in squamous NSCLC (20–40% versus approximately 5%, respectively).[38]

Incidence, Prognosis, and Treatment of KRAS p.G12C Mutant NSCLC with BMs

Presentations involving BMs are more complex in NSCLC patients with specific oncogene addiction.[40] The disease biological characteristics can guide treatment. According to a retrospective review[41] of 579 patients with metastatic NSCLC, the incidence of BMs was highest in patients with mutations/fusions of *ROS1* (36%) and *ALK* (34%), followed by *EGFR* (28%) and *KRAS* (28%), which occurred in only 21% of patients with NSCLC without a driver oncogene. BMs are associated with poor outcomes and compromised quality of life.[42] A retrospective analysis has shown that patients with *KRAS*-mutant NSCLC, particularly those with G12C mutation, have a high risk of developing BMs,[8] while among patients with *KRAS* p.G12C mutant NSCLC, approximately 27–42% are diagnosed with CNS metastases.[43–46] Within 6 to 12 months of diagnosis, the cumulative incidence of BMs may reach 48.2% and 42.2%, respectively.[47] Patients with

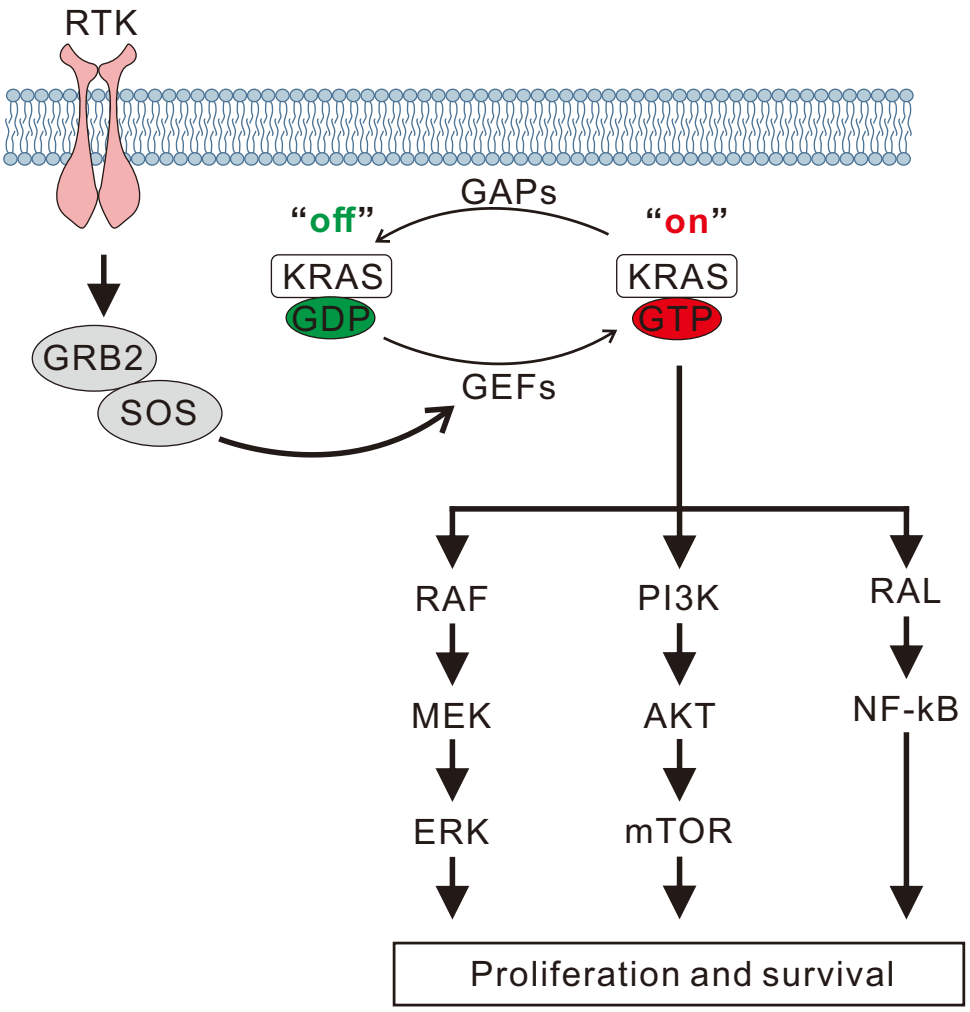

Figure 1 *KRAS* signaling pathway. Binding of extracellular ligands activates the receptor tyrosine kinase (RTK). The phosphorylating tyrosine on the intracellular domain of RTK recruits SH2 domain-containing adaptor protein GRB2. GEFs are allosterically activated by GRB2. The activated GEFs activate *KRAS* by exchanging KRAS-GDP to KRAS-GTP. The GTP-bound KRAS activates the downstream signaling molecule such as RAF, PI3K, and RAL, leading to the expression of the target genes that participate in cellular proliferation and survival.

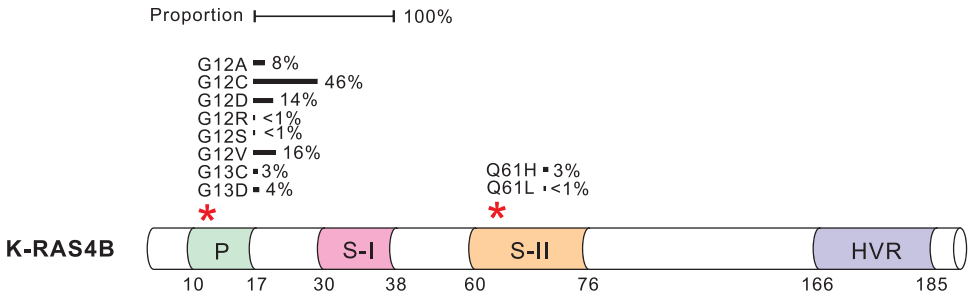

Figure 2 Hotspot *KRAS* mutations in NSCLC. Domain architecture of K-RAS4B, P (P-loop), S-I (switch-I), S-II (switch-II), HVR (hypervariable region). The frequency of different *KRAS* mutations.[33,39] The asterisk represents the location of mutations.

KRAS mutations respond poorly to chemotherapy and have poor overall prognosis.[48] In this patient group, the mOS since the initial diagnosis of metastatic disease has been estimated at 19.1 months.[47] The corresponding OS values were significantly lower in patients with than in those without BMs (13.2 months vs 16.0 months, respectively).[49.]

Owing to the low permeability of the BBB to most conventional antitumor agents, radiotherapy (RT)/radiosurgery and/or surgery remain at the core of disease management in patients with NSCLC.[40] However, the treatment of patients with oncogene-driven NSCLC may differ.[40] In oncogene-addicted NSCLC patients with BMs, targeted therapy can achieve a high IC response rate.[50,51] Targeted therapy can help prevent adverse effects (AEs) of radiation, such as necrosis and cognitive impairment.[52,53] The incidence of BMs is higher in patients with *KRAS*^{G12C} mutation than in those with *EGFR* mutations or *ALK*-rearranged NSCLC, which further underlines the need for efficient treatments for this cohort.

The first KRAS^{G12C} inhibitor, AMG510, was approved in 2021 by the United States Food and Drug Administration to treat patients with *KRAS* p.G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy.[54] The key exclusion criteria were untreated active BMs, systemic antitumor therapy within 28 days before the initiation of sotorasib therapy, and radiation therapy within 2 weeks before the initiation of sotorasib therapy.[55] Several inhibitors of KRAS^{G12C} have been developed to date. Sotorasib[55] and adagrasib[56] have already shown some promising results in early phase clinical trials, which is encouraging for developing CNS-targeted therapies.[57–59] *KRAS*-mutated NSCLC constitute a molecularly diverse and clinically heterogeneous group, and standard treatment options provide only modest clinical benefit.[17–19] A summary of the published clinical trials of KRAS^{G12C} inhibitors in patients with NSCLC is presented in Table 1.

KRAS^{G12C} Inhibitors and Their Efficacy in NSCLC

Sotorasib

Sotorasib (LUMAKRAS™, AMG510) (molecular weight [MW] = 561, PSA = 92 Å^2, HBD = 1, and Log D = 2.3),[11] is a covalent KRAS^{G12C} small molecule developed by Amgen for the treatment of solid tumors with *KRAS*^{G12C} mutation. Sotorasib is a first-in-class KRAS^{G12C} inhibitor. It covalently binds to the switch II pocket and irreversibly binds to the cysteine residue of the KRAS^{G12C} mutant.[77] Consequently, trapping the KRAS protein in the inactive GDP-bound state blocks its downstream signaling effects without affecting wild-type KRAS.[77] In a mouse bearing *KRAS* p.G12C tumors, treatment with sotorasib once daily (QD) led to tumor regression.[78] Durable responses to sotorasib in patients with locally advanced or metastatic *KRAS* p.G12C mutant NSCLC have been demonstrated in a multicenter Phase 1/2, open-label CodeBreaK 100 trial.[55,60] The trial reported an objective response rate (ORR) and disease control rates (DCR) in NSCLC patients of 32.2% (19/59) and 88.1% (52/59), respectively, with no observed dose-limiting toxic effects or treatment-related deaths.[55] Specifically, the confirmed ORR and DCR in the NSCLC set administered AMG510 960 mg QD were 37.1% and 80.6%, respectively.[60] In later analysis (data cutoff date: 20 Jun 2021), the median duration of response (mDoR) was 11.1 months.[79] In the first pooled analysis of 174 NSCLC patients enrolled in Phase I and II CodeBreaK 100 studies, the ORR was 41%.[61] The CodeBreaK 200 trial[62] was the first Phase III trial of KRAS^{G12C} inhibitors for the treatment of NSCLC. Sotorasib was associated with an increase in the median PFS (mPFS) rate, compared with that associated with docetaxel (mPFS 5.6 months vs 4.5 months; hazard ratio [HR] 0.66).[62] However, the OS was comparable in both groups (HR 1.01).

Little is known about the impact of sotorasib in the CNS of patients with NSCLC. Sixteen patients were assessed by the Response Assessment in Neuro-Oncology tool; three (19%) had complete response (CR), 11 (69%) had stable disease (SD), and 14 (88%) had IC DCR.[61] Although patients with untreated active BMs were excluded from the CodeBreaK 100 trial, in post-hoc analysis, patients with stable BMs previously treated with RT or surgery had an mOS of 8.3 months and a mPFS of 5.3 months with a DCR of 77.5% and a mDOR of 11.1 months.[63] Notably, 14 (87.5%) patients with assessable BMs achieved IC disease control.[63] Brain magnetic resonance imaging (MRI) with contrast or brain contrast-enhanced computed tomography scanning was performed during screening.[62] Patients with treated and stable BMs were eligible, while those with new or progressive untreated brain lesions or symptomatic brain lesions were excluded from the study.[62] Compared to the docetaxel group, the sotorasib group had a longer median time to recurrence of the CNS disease (15.8 months vs 10.5 months; HR 0.52).[62] In subgroup analyses, the mPFS was 4.4 m vs 2.9 m (AMG510 vs docetaxel) in patients with a history of CNS involvement; the corresponding values were 5.7 months vs 5.7 months for those without any history of CNS involvement.[62] The first randomised clinical trial data evaluating the IC efficacy of

Table 1 $KRAS^{G12C}$ Inhibitors in Non-Small Cell Lung Cancer

NCT /Phase	Detail	Objective	Active BMs Included	CNS Efficacy	Classification*	ORR*	DCR*	mDoR*	mPFS*	mOS*
AMG510										
NCT03600883/I[55]	180/360/720/960 mg QD	Solid tumors	No	NR		32.2%	88.1%	10.9 m	6.3 m	NR
NCT03600883/II[60]	960 mg QD	NSCLC	No	NR		37.1%	80.6%	11.1 m	6.8 m	12.5 m
NCT03600883/ I/II[61]	960 mg QD	NSCLC	No	IC-DCR 88%		41%	84%	12.3 m	6.3 m	12.5 m
NCT04303780/III[62]	AMG510 960 mg QD or docetaxel 75 mg/m² q3wks	NSCLC	No	Median time to recurrence of CNS disease (15.8 m vs 10.5 m; HR 0.52)	AMG510 docetaxel HR (AMG510 vs docetaxel)	28.1% 13.2% NR	82.5% 60.3% NR	8.6 m 6.8 m NR	5.6 m 4.5 m 0.66	10.6 m 11.3 m 1.01
NCT03600883/ I/II[63]	960 mg QD	NSCLC with stable BMs	No	IC-DCR 87.5%	BM Non-BM	25% 41.7%	77.5% 84.1%	11.1 m 10.0 m	5.3 m 6.7 m	8.3 m 13.6 m
NCT04303780/III[64]	AMG510 960 mg QD or docetaxel 75 mg/m² q3wks	NSCLC with treated, stable BMs	No	Time to CNS recurrence (9.6 m vs 5.4 m; HR 0.84) TRAEs (77.5% vs 89.7%)	AMG510 docetaxel HR (AMG510 vs docetaxel)	NR NR NR	NR NR NR	NR NR NR	6.1 m 4.5 m 0.57	NR NR NR
MRTX849										
NCT03785249/II[56]	600 mg BID	NSCLC (Cohort A)	No	IC-ORR 33.3% IC-mDoR 11.2 m IC-mPFS 5.4 m		42.9%	79.5%	8.5 m	6.5 m	12.6 m
NCT03785249/IB[59]	600 mg BID	NSCLC with untreated CNS metastases	Brainstem metastases, leptomeningeal carcinomatosis, carcinomatous meningitis	IC-ORR 42.1% IC-DCR 89.5% IC-mDoR 12.7 m IC-mPFS 5.4 m		30.0%	80.0%	5.6 m	5.3 m	11.4 m
NCT03785249/I/II[65]	600 mg BID	NSCLC	No	NR		45%	96.1%	NR	NR	NR
NCT03785249/I/IB[66]	150/300/600/1200 mg QD, 600 mg BID	Solid tumors	No	NR	RP2D: 600 mg BID	53.3%	NR	16.4 m	11.1 m	NR
D1553										
NCT05383898/I[67]	600/800/1200 mg QD, 400/600 mg BID	NSCLC	No		Across dose levels RP2D: 600 mg BID With BMs	40.5% 38.7% 17%	91.9% 90.3% 100%	7.1 m 6.9 m NR	8.2 m 7.6 m NR	NR NR NR

(*Continued*)

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Table 1 (Continued).

NCT /Phase	Detail	Objective	Active BMs Included	CNS Efficacy	Classification*	ORR*	DCR*	mDoR*	mPFS*	mOS*
JDQ443										
NCT04699188/IB/II[68]	200/400 mg QD, 200/300 mg BID	Solid tumors	No	NR	Across dose levels	30.0%	NR	NR	NR	NR
					RP2D: 200 mg BID	43.0%	NR	NR	NR	NR
NCT04699188/IB/II[69]	200/400 mg QD, 200/300 mg BID	Solid tumors	No	NR	Across dose levels	41.7%	NR	NR	NR	NR
					RP2D: 200 mg BID	54.5%	NR	NR	NR	NR
JAB-21822										
NCT05009329/I/II[70]	200/400/800 mg QD, 400mg BID, 400mg TID	Solid tumors	NR	NR		70%	100%	NR	NR	NR
GEC255										
CTR20212486/I[71]	200/400/600/800/1000 mg QD	Solid tumors	No	NR	Across dose levels	76.9%	92.3%	NR	NR	NR
					600 mg dose group	83.3%	100%	NR	NR	NR
LY3537982										
NCT04956640/I[72]	50/100/150/200 mg BID	Solid tumors	No	NR	KRAS-G12Ci naïve	60%	80%	NR	NR	NR
					Prior KRAS-G12Ci treated	0%	67%	NR	NR	NR
GFH925										
NCT05005234/ I/II[73]	Accelerated titration design for 250mg QD and a BOIN design with 450/700/900mg QD.	Solid tumors	No	NR		16.7%	83.3%	NR	NR	NR
NCT05005234/ I/II[74]	Accelerated titration design for 250mg QD and a BOIN design with 450–900mg QD and 450–750mg BID.	Solid tumors	No	NR	Across dose levels	44.8%	92.5%	NR	NR	NR
					RP2D: 600mg BID	50.0%	96.7%	NR	NR	NR
GDC-6036										
NCT04449874/I[75] JNJ-74699157	50/100/200/400 mg QD	Solid tumors	No	NR	NR	37%	NR	NR	NR	NR
NCT04006301/I[76]	100/200mg QD	Solid tumors	No	NR	Median treatment duration: 2.91 m. Based on dose-limiting skeletal muscle toxicities and the lack of efficacy at the 100 mg dose, further enrollment was stopped.					

Note: *Only the data on non-small cell lung cancer are presented.

Abbreviations: BMs, Brain metastases; CNS, Central nervous system; ORR, Objective response rate; DCR, Disease control rate; mDoR, Median duration of response; mPFS Median progression-free survival; mOS, Median overall survival; QD, Once daily; NSCLC, Non-small cell lung cancer; NR, Not reported; IC, Intracranial; q3wks, Every 3 weeks; HR, Hazard ratio; TRAEs, Treatment-related adverse events; BID, Twice a day; RP2D, Recommended Phase 2 dose; TID, Three times a day; KRAS, Kirsten rat sarcoma; BOIN, Bayesian optimal interval.

sotorasib was reported in 2023 by the American Society of Clinical Oncology (ASCO).[64] Efficacy analysis revealed a reduced risk of progression in patients treated with sotorasib vs docetaxel (systemic mPFS was 6.1 months versus 4.5 months, respectively) and some delays to CNS recurrence (9.6 months vs 5.4 months, respectively) in NSCLC patients with previously treated stable BMs.[64] Nevertheless, as patients with active BMs were excluded from the trials,[55,60–64] treatment efficacy in this patient group remains unclear.

Several relevant case reports and retrospective studies have been reported in the literature. One patient[57] experienced disseminated intravascular coagulation caused by rapid tumor progression and a worsened PS status due to multiple active BMs. After 2 weeks of AMG510 administration, the symptoms improved and multiple BMs disappeared, providing some support for the use of this treatment in patients with poor PS. Meanwhile, the benefit of sotorasib in NSCLC patients with active, previously untreated BMs was also reported.[58,80] Notably, a repeat brain MRI scan one month after the discontinuation of sotorasib revealed an ongoing IC response, although the treatment was discontinued due to transaminase deterioration.[80] Subsequently, to further examine whether there was preliminary evidence of IC activity, the researchers identified six patients who developed active, untreated BMs (at any point in their disease course) before sotorasib initiation, with an mOS "not reached" (8.7, not estimable) at a median follow-up time of 8.8 months.[49] A confirmed IC disease response to treatment was observed in three of the four patients, with an mDoR of 4.1 months and a median IC PFS of 4.7 months.[49] In 2023, Inno et al[81] reported an IC response to sotorasib in a patient with both pretreated and untreated symptomatic BMs, with an IC response duration of 16 months, supporting the use of this treatment in this patient group and showing the need for further studies in this context.

A phase Ib, open-label study (NCT04185883)[82] evaluated sotorasib monotherapy in NSCLC with BMs and in combination regimens (treatment groups included sotorasib + TKI, sotorasib + anti-programmed cell death 1 ligand 1 [PD-L1] therapy, sotorasib + chemotherapeutic regimen, and sotorasib + anti-programmed cell death protein 1 [PD1] therapy) in patients with advanced *KRAS* p.G12C mutant NSCLC. Enrolment began in December 2019 and the trial is currently ongoing.

Adagrasib

Adagrasib (MRTX849, Mirati Therapeutics) (MW = 604, PSA = 71 Å^2, HBD = 0, and Log D = 3.6)[11] is an oral, potent, small-molecule KRAS^{G12C} inhibitor that selectively modifies mutant cysteine 12 in GDP-bound KRAS^{G12C} and inhibits *KRAS*-dependent signaling. Adagrasib has favourable pharmacokinetics (PK) properties, such as oral bioavailability, long half-life (24h), dose-dependent PK, and extensive tissue distribution.[83] In studies, MRTX849 induced pronounced tumour regression in 17 (65%) *KRAS^{G12C}*-positive cell lines and in patient-derived xenograft models of multiple tumour types.[83]

Data presented at the 2021 ASCO meeting showed adagrasib tolerability and clinical activity in patients with previously treated *KRAS* p.G12C mutant NSCLC.[65] The KRYSTAL-1 trial (NCT03785249) evaluated the safety, PK, and clinical activity of adagrasib in patients with *KRAS* p.G12C mutant advanced solid tumours.[66] After a median follow-up time of 19.6 months, the confirmed ORR was 53.3%, the mDoR was 16.4 months, and the mPFS was 11.1 months. A total of 23 (92.0%) patients experienced treatment-related AEs (TRAEs).[66]

Additionally, preclinical data have demonstrated target pathway inhibition, tumour regression, and increased survival in multiple BM mouse models treated with a clinically relevant dose of adagrasib.[47] Among the two NSCLC patients with active and untreated BMs from the KRYSTAL-1 trial, cerebrospinal fluid concentrations of adagrasib measured above the target cellular IC50 and the average Kp,uu were calculated at 0.47, which are comparable to those of other targeted agents known to have high activity against BMs (eg, osimertinib [0.39], alectinib [0.63–0.94], and lorlatinib [0.75]).[84–86] Moreover, both patients demonstrated corresponding BM regression.[47] Overall, this evidence was first to show proof-of-concept for adagrasib use in this patient population. The results from cohort A of the phase I/II KRYSTAL-1 trial have confirmed objective response in 48 (42.9%) patients.[56] The mPFS was 6.5 months, and the mOS was 12.6 months. Notably, among 33 patients with previously treated stable CNS metastases, the median IC PFS was 5.4 months. The IC-confirmed ORR was 33.3%, with a DCR of 85%. Additionally, for patients with untreated CNS metastases, adagrasib monotherapy showed acceptable efficacy.[59] Patients with brainstem metastasis, leptomeningeal carcinomatosis, and/or carcinomatous meningitis were excluded.[59] Patients with focal leptomeningeal disease were

eligible for the study.[59] With a median follow-up of 13.7 months, the IC DCR was 90%, and the confirmed IC ORR was 42% (8/19). Among them, three patients had a complete IC response, and five patients had a partial IC response. The median IC-PFS was 5.4 months. Grade 3 TRAEs occurred in 10 (40%) patients; only one (4%) patient experienced grade 4 TRAEs; no grade 5 TRAEs were reported, which was consistent with previous reports.[56,66] Regarding CNS-specific TRAEs, most patients experienced grade 1–2 CNS-specific TRAEs, four patients experienced grade 3, and there was no grade 4 or higher CNS-related event.[59] To date, MRTX849 is the first $KRAS^{G12C}$ inhibitor to prospectively demonstrate IC activity with manageable safety in patients with untreated BMs.

D-1553

Patients with BMs are often excluded from clinical trials of novel targeted agents given the unpredictable relationship between systemic and CNS responses.[4] In a phase I dose-escalation and dose-expansion study of D-1553 presented in 2023,[67] 79 patients with $KRAS^{G12C}$ mutation were enrolled across China, and data from 74 patients were available for efficacy analysis. The results demonstrated an ORR of 40.5% (30 for partial response and 38 for SD) and a DCR of 91.9%. The mPFS was 8.2 months, and the mDOR was 7.1 months. In patients with BMs, the ORR was 17% and 100%, respectively. However, it should not be ignored that there are only six patients had BMs at baseline.

Jdq443

JDQ443 is a potent, selective, orally bioavailable covalent inhibitor of GDP-bound $KRAS^{G12C}$ that binds to the Switch II loop, and to the $KRAS^{G12C}$ switch II region of the protein. It is distinct from sotorasib and adagrasib, targeting different regions of the pocket and triggering different interactions.[87] Moreover, JDQ443 inhibits the proliferation and signaling of G12C/H95 double *KRAS* mutants. Its potent and selective antitumor activity was demonstrated in cell lines and in *vivo* models.[87] Preliminary results of JDQ443 monotherapy dose escalation reported by a multicenter dose-escalation trial KontRASt-01 (NCT04699188) were first presented at the 2022 American Association for Cancer Research (AACR).[68] Twenty patients with NSCLC showed an ORR of 30.0% (6/20) across dose levels, and 43.0% (3/7) showed it at the recommended phase 2 dose (RP2D).[68] However, the key exclusion criterion for the JDQ443 monotherapy arm was the presence of active BMs. Another study reported the ORR of 41.7% across dose levels and that of 54.5% at RP2D.[69] KontRASt-02 (NCT05132075) is a global, Phase III, open-label, randomised, multicenter study evaluating JDQ443 as a monotherapy in comparison to docetaxel in patients with $KRAS^{G12C}$-mutated advanced NSCLC, and KontRASt-06 (NCT05445843) is an open-label Phase II trial evaluating the activity and safety of JDQ443 single-agent as first-line treatment for patients with locally advanced or metastatic *KRAS* p.G12C mutant NSCLC with a PD-L1 expression < 1% or a PD-L1 expression ≥ 1% and an STK11 co-mutation. All these studies are currently enrolling patients.[88] Participants with known active CNS metastases and/or carcinomatous meningitis are excluded from both trials.

Other Inhibitors

LY3537982 is a potent inhibitor that delivers sustained target occupancy of > 90%. The initial results of LOXO-RAS -20001 (NCT04956640) demonstrated a favourable safety profile.[72] Patients with treated CNS metastases were eligible for this study if their disease was asymptomatic, radiographically stable for at least 30 days, and did not require steroid treatment in the 2-week period prior to study treatment. IC results have not been reported.

IBI351 (GFH925) is an irreversible covalent inhibitor of $KRAS^{G12C}$. The preliminary efficacy of IBI351 has been demonstrated in previously treated advanced NSCLC.[73] Updated results were reported for the 2023 AACR.[74] Among 67 NSCLC patients, 44.8% of the patients received two or more prior lines of treatment, and 38.8% of the patients had BMs. The investigator-assessed ORR was 58.2%, the confirmed ORR was 44.8%, and the DCR was 92.5%. At 600 mg twice daily dose level (RP2D), the ORR was 63.3%, the confirmed ORR was 50.0%, and the DCR was 96.7%. Although patients with BMs were included in the cohort, the efficacy and safety data for these patients were not presented separately.

JAB-21822 is a highly selective covalent oral inhibitor of $KRAS^{G12C}$. Among patients with NSCLC (400 and 800 mg QD), an ORR of 70%, including non-confirmed partial response (PR) and a DCR of 100%, has been reported.[70] These trials are ongoing. Another phase 1, open-label, multicenter study (CTR20212486) assessing GEC255 in patients with

advanced solid tumours bearing the *KRAS*^{G12C} mutation revealed that GEC255 is well-tolerated and has encouraging antitumor activity for advanced NSCLC; the trial is still recruiting.[71] The study did not report the effects in patients with BMs. A phase Ia/Ib dose-escalation and dose-expansion study (NCT04449874) evaluated the safety, PK, and activity of divarasib (RG-6330 and GDC-6036) as a single agent in combination with other antitumor therapies in patients with advanced or metastatic solid tumours. GDC-6036 monotherapy exhibits encouraging clinical activity and high target engagement across dose levels in NSCLC with the *KRAS*^{G12C} mutation.[75] Patients with active BMs were excluded. Another KRAS^{G12C} inhibitor, JNJ-74699157 (ARS-3248), was evaluated in a phase I clinical trial (NCT04006301).[76] Patients with asymptomatic BMs were allowed into the trial if they had been treated, had stable disease for at least 4 weeks, as documented by radiographic imaging, and did not require systemic corticosteroid therapy for more than 14 days.[76] However, based on dose-limiting skeletal muscle toxicities and the lack of efficacy at the 100 mg dose, further enrolment was terminated. RMC-6291 is a next-generation mutant-selective inhibitor of KRAS^{G12C} that has overcome the limitations of first-generation inhibitors in preclinical models by directly targeting the active form of this oncogenic driver.[89]

Resistance mechanisms may be ascribed,[90] innate, and acquired in patients with CNS metastatic disease, especially those treated with agents that do not cross the BBB.[11] To address this challenge, Kettle et al[11] proposed structure-based drug design, involving excising a key heterocyclic ring to derive a compound of much smaller size and polarity, a highly potent and selective inhibitor of KRAS^{G12C}, AZD4747, which had molecular properties that can reach into the CNS, showing reductions in human P-gp and BCRP levels. Combination therapies may also reduce the risk of treatment resistance; however, they are associated with toxicity. A phase 1/2 study (NCT04165031) of LY3499446 as oral monotherapy, and in combination with other inhibitors, including abemaciclib, erlotinib, cetuximab, or docetaxel, in patients with advanced solid tumours harboring the *KRAS*^{G12C} mutation was terminated because of unexpected toxicity prior to the initiation of study phase 2. Studies are required to identify protocols that reduce toxicity risk and maximise efficacy in combination therapies, which may help improve outcomes on patients with NSCLC and BMs.

Clinical trials for drug development tend to exclude patients with BMs and meningitis due to poor performance. Consequently, these trials report findings from small sets of patients with stable BMs. Publication of preclinical findings and clinical case reports should be encouraged to build a more robust body of evidence on the treatment of patients with this presentation. Further studies are required to evaluate the safety of these targeted therapies. Additionally, in descriptive exploratory analyses, mutations in *STK11, KEAP1*, and *TP53* were among the most prevalent co-occurring mutations in *KRAS*-mutated NSCLC.[60] Therefore, the presence of co-mutations must be considered when selecting treatment, especially for disease entities and management strategies associated with the risk of treatment resistance.

Conclusions

BMs are common in patients with *KRAS*-mutated NSCLC, reducing life expectancy and quality of life, which represents an area of great unmet need. However, with KRAS inhibitors showing promising anticancer activity in patients with *KRAS*^{G12C} mutation, the therapeutic landscape may also sharply change following the development of KRAS inhibitors with increased CNS bioavailability. Additionally, future prospective studies are required to quantify the IC efficacy of target therapy more accurately. Nevertheless, KRAS^{G12C} inhibitors are still in their infancy (currently only two inhibitors have entered the clinic) with limited studies that have prospectively explored KRAS^{G12C} inhibitors in patients with NSCLC complicated with BMs. Moreover, drug resistance to KRAS^{G12C} inhibitors is growing to be a significant issue, due to several mechanisms of resistance. Therefore, future studies exploring the application of KRAS^{G12C} inhibitor monotherapy or combination therapy are warranted for patients with NSCLC, particularly those with BMs.

Abbreviations

LC, Lung cancer; NSCLC, Non-small cell lung cancer; BMs, Brain metastases; mOS, Median overall survival; CNS, Central nervous system; PFS, Progression-free survival; EGFR, Epidermal growth factor receptor; ALK, Anaplastic lymphoma kinase; ROS1, ROS proto-oncogene 1; KRAS, Kirsten rat sarcoma; MET, Mesenchymal epithelial transition factor; LUADs, Lung adenocarcinomas; BBB, Blood–Brain Barrier; PSA, Polar surface area; HBD, Hydrogen bond donor; IC, Intracranial GTPases, Guanosine triphosphatases; GDP/GTP, Guanosine diphosphate/triphosphate; GAP,

GTPase activating proteins; GEF, Guanine nucleotide exchange factors; RT, Radiotherapy; AEs, Adverse effects; MW, Molecular weight; QD, Once daily; ORR, Objective response rate; DCR, Disease control rate; mDoR, Median duration of response; mPFS, Median progression-free survival; HR, Hazard ratio; CR, Complete response; SD, Stable disease; MRI, Magnetic Resonance Imaging; ASCO, American Society of Clinical Oncology; PD-L1, Programmed cell death 1 ligand 1; PD1, Programmed cell death protein 1; PK, Pharmacokinetics; TRAEs, Treatment-related adverse events; AACR, American Association for Cancer Research; RP2D, Recommended phase 2 dose; PR, Partial response.

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Disclosure

The authors confirm the paper has not been published or submitted for publication elsewhere, and declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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