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COMMENTARY

Adagrasib in KRYSTAL-12 has Broken the *KRAS*^{G12C} Enigma Code in Non-Small Cell Lung Carcinoma

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Abstract: Kirsten rat sarcoma viral oncogene homolog *(KRAS)*^{G12C}-mutant non-small cell lung carcinoma (NSCLC) accounts for approximately 10–13% of advanced nonsquamous NSCLC cases in Western populations, presenting a significant therapeutic challenge owing to the difficulty of directly targeting KRAS. Adagrasib, an oral small-molecule covalent inhibitor, irreversibly and selectively targets KRAS^{G12C} in its inactive state. It received accelerated Food and Drug Administration (FDA) approval on December 12, 2022, following the KRYSTAL-1 Phase II trial. The Phase III KRYSTAL-12 trial demonstrated that adagrasib significantly improved median progression-free survival (mPFS) compared with docetaxel (HR, 0.58; 95% CI: 0.45–0.76; P<0.0001) and increased the intracranial objective response rate (ORR) to 40% in the central nervous system (CNS) evaluable population. This paper evaluates the clinical efficacy of adagrasib in *KRAS*^{G12C}-mutated advanced NSCLC discussing its potential advantages over other inhibitors such as sotorasib. Despite not reaching the 6-month mPFS benchmark, adagrasib offers significant clinical benefits, particularly for the management of CNS metastases. In this pros and cons debate, we argue that adagrasib has broken the *KRAS*^{G12C} enigma code in NSCLC.

Keywords: non-small-cell lung cancer, *KRAS*^{G12C} mutations, adagrasib, sotorasib, KRYSTAL, targeted therapy, intracranial efficacy

Introduction

Kirsten rat sarcoma viral oncogene homolog (*KRAS*) is a common oncogene in human tumors and is associated with various cancer types including 31–35% lung cancers, with the most common histological subtype being non-small cell lung cancer (NSCLC).[1–3] The most frequently found mutations primarily occur in codons 12, 13, or 61 of *KRAS* gene, with single-base missense mutations being the most common type of mutation. In NSCLC, *KRAS*^{G12C}, with glycine substituted by cysteine at codon 12, is the dominant mutation subtype, comprising approximately 40% of *KRAS*-mutated adenocarcinoma and 10–13% of advanced nonsquamous NSCLC in Western countries.[1,4]

KRAS gene encodes KRAS proteins that function as guanosine triphosphatases (GTPases). These proteins are activated when guanosine diphosphate (GDP) is replaced by guanosine triphosphate (GTP) after cells receive appropriate stimuli. Once activated, KRAS proteins activate multiple downstream signaling pathways, including the RAF-MEK-ERK and PI3K-AKT-mTOR pathways. The *KRAS*^{G12C} mutation favors the active form of KRAS, resulting in the hyperactivation of downstream oncogenic pathways and dysregulation of cell growth.[1,5]

KRAS mutations are incredibly heterogeneous and RAS proteins did not appear to present suitable binding pockets to which drugs could bind; thus, direct targeting of KRAS has been a challenge for decades, leading to limited fully approved treatment options, aside from chemotherapy for *KRAS*^{G12C}-mutant NSCLC. Fortunately, novel inhibitors targeting the specific KRAS^{G12C}, including AMG510 (sotorasib) and MRTX849 (adagrasib), have demonstrated promising results in recent preclinical and clinical trials. KRAS^{G12C} inhibitors are a class of small molecules that selectively inhibit the KRAS^{G12C} isoform via binding to a site on KRAS known as switch II pocket (S-IIP). This results in decreased signal transduction, particularly by the RAF-MEK-ERK/MAP pathway, ultimately preventing tumor progression. However, chemotherapy currently remains the standard of care for *KRAS*^{G12C}-mutated NSCLC due to lack of data on KRAS^{G12C} inhibitors as first-

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line therapy. Here, we argue that adagrasib offers significant clinical benefit compared to other KRAS^{G12C} inhibitors and anticipate its potential as first-line therapy in *KRAS*^{G12C}-mutated NSCLC.

Accelerated Approval of Adagrasib (MRTX849) Based on KRYSTAL-1 (NCT03785349) Trial

Adagrasib (MRTX849) is an oral, small-molecule, covalent KRAS^{G12C} inhibitor that irreversibly and selectively binds to the cysteine in the S-IIP of KRAS^{G12C} in its inactive state, inhibiting KRAS-dependent signaling.[6] Moreover, adagrasib is pharmacokinetically favorable in several ways, including its long half-life (23 hours), central nervous system (CNS) penetration, and dose dependence.[6]

In KRYSTAL-1 (NCT03785249), a multicenter, single-arm, open-label, Phase 1–2 multiple expansion cohort trial, adagrasib was evaluated in patients with advanced solid tumors harboring the *KRAS*^{G12C} mutation. Adagrasib was found to have promising results with an objective response rate (ORR) of 42.9% (95% confidence interval (CI): 33.5–52.6), median progression-free survival (mPFS) of 6.5 months (95% CI: 4.7–8.4) among 112 patients.[5] Among the 33 patients with CNS metastases at baseline, the intracranial ORR was 33.3% (95% CI: 18–51.8). The median intracranial PFS in 42 patients with baseline CNS metastases was 5.4 months (95% CI: 3.3–11.6).[6] (Table 1)

Based on these results, adagrasib was granted accelerated approval for previously treated *KRAS*^{G12C}-mutated locally advanced or metastatic NSCLC by the Food and Drug Administration (FDA) on December 12, 2022.[7] As with the most accelerated approvals, continued approval for this indication is contingent upon confirmatory trial(s) and verification of

Table 1 Comparison of Efficacy and Safety Between KRYSTAL 1 and KRYSTAL 12

	KRYSTAL-1	**KRYSTAL-12**
Trial Phase	2	3
Patient selection	*KRAS*^{G12C}-mutated, advanced NSCLC, previously treated	*KRAS*^{G12C}-mutated, advanced NSCLC, previously treated
N (adagrasib treated)	116	301
Prior chemotherapy	100%	100%
Prior immunotherapy	100%	100%
BIRC-assessed ORR	43% (95% CI: 33.5–52.6)	32 [95% CI: 2.56–8.56)
DOR (months)	8.5 (95% CI: 6.2–13.8)	8.3 (95% CI: 6.1–10.4)
PFS (months)	6.5 (95% CI: 4.7–8.4)	5.5 (95% CI: 4.5–6.7)
Intracranial ORR	12.5%	24% (in all patients with baseline CNS metastases), 40% (in CNS evaluable population)
OS (months)	12.6 (95% CI: 9.2–19.2)	Not mature
AEs	100%	94%
Grade 3–4 AE rate	44.8%	47%
AE-associated death rate	1.7%	1%
Common AEs	Diarrhea (70.7%) Nausea (69.8%) Fatigue (59.5%) Vomiting (57%) Anemia (36.2%)	Diarrhea(53%) Vomiting (35%) Nausea (34%) AST increase (30%) ALT increase (30%)

Abbreviations: AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; BIRC, blind independent central review; CNS, central nervous system; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression free survival; RCT, randomized controlled trial.

clinical benefit, which in this case led to the KRYSTAL-12 trial. The results of this trial were presented at the annual meeting of the American Society of Clinical Oncology (ASCO) 2024.

KRYSTAL-12 (NCT04685135) Trial, a Confirmatory Randomized Phase III Trial of Adagrasib versus Docetaxel

KRYSTAL-12 (NCT04685135) is a randomized, open-label Phase 3 trial comparing adagrasib with docetaxel in patients with *KRAS*^{G12C}-mutated, locally advanced, or metastatic NSCLC who were previously treated with platinum-based chemotherapy and anti-PD1 or anti-PDL1 therapy, either concurrently or sequentially. A total of 453 patients were randomized in a 2:1 ratio to either oral adagrasib (600 mg twice daily) or IV docetaxel (75mg/m^2 once every three weeks).[8,9]

The mPFS was significantly increased with adagrasib compared to docetaxel, at 5.49 vs 3.84 months respectively (hazard ratio [HR]: 0.58 [95% CI: 0.45–0.76], P<0.0001). The ORR was also significantly improved with adagrasib (31.9% [95% CI: 2.56–8.56]) compared to docetaxel (9.2% [95% CI: 5.1–15]), with an odds ratio (OR) of 4.68 [95% CI: 2.56–8.56], P<0.0001). Additionally, the intracranial ORR was higher with adagrasib (24%, 19/78) than with docetaxel (11%, 4/36). Specifically, for the CNS evaluable population, which was defined as patients with at least one CNS target lesion at baseline and at least one post-baseline CNS tumor assessment, the intracranial ORR with adagrasib was 40% (10/25) compared with 11% (1/9) with docetaxel. The safety profiles of adagrasib and docetaxel were consistent with those in previous reports, with no new safety signals.[8,9] (Table 1)

Discussion

Adagrasib is not the first KRAS^{G12C} inhibitor to be approved for NSCLC

Prior to adagrasib, AMG510 (sotorasib) was the first KRAS^{G12C}-targeted inhibitor that entered clinical trials (CodeBreaK 100 / NCT03600883) and was approved by the FDA on May 28, 2021, for patients with locally advanced or metastatic *KRAS*^{G12C}-mutated NSCLC who had received prior systemic therapy.[10] Similar to adagrasib, sotorasib is a small molecule that selectively and irreversibly binds to cysteine 12 in the S-IIP of KRAS protein, locking the protein in an inactive state.[1] FDA approval was based on CodeBreaK 100, a Phase 2 trial that demonstrated durable clinical benefit of sotorasib therapy in patients with *KRAS*^{G12C}-mutated NSCLC that was previously treated with both platinum-based chemotherapy and PD-1 or PD-L1 inhibitors.[5]

Subsequently, Codebreak 200 (NCT04303780), a phase 3 randomized trial, compared the efficacy and safety of sotorasib with docetaxel, standard-of-care treatment, in patients with *KRAS*^{G12C}- mutated NSCLC who had previously received platinum-based chemotherapy and anti-PD1 or anti-PDL1 therapy. Overall, 171 patients were randomized to oral sotorasib (960 mg once daily) and 174 patients to IV docetaxel (75mg/m^2 once every three weeks). The mPFS was statistically significant for improvement in sotorasib compared to docetaxel, at 5.6 months (95% CI: 4.3–7.8) vs 4.5 months (95% CI: 3–5.7), respectively (HR 0.66 [95% CI 0.51–0.86], P=0.0017). ORR was also significantly improved with sotorasib (28.1% [95% CI: 21.5–35.4]) compared with docetaxel (13.2% [95% CI: 8.6–19.2], P<0.001).[11]

Unfortunately, OS was not significantly different between sotorasib (mOS 10.6 months [95% CI: 8.9–14]) and docetaxel (mOS 11.3 months (95% CI: 9–14]), with HR 1.01 [95% CI: 0.77–1.33]. For patients with previous CNS disease, median time to recurrence of CNS disease was delayed for the sotorasib arm (15.8 months [95% CI 0.7-not estimable] compared to docetaxel arm (10.5 months [95% CI: 5.8-not estimable], HR 0.52 (95% CI: 0.26–1).[11] In terms of safety, treatment-related adverse events (TRAEs) of Grade ≥3 were reported in 33% (n=56) of sotorasib recipients and 40% (n=61) of docetaxel recipients.[11] (Table 2)

How does adagrasib compare to sotorasib in *KRAS*^{G12C}-mutant NSCLC?

Adagrasib and sotorasib are both inhibitors that covalently bind to the cysteine in the G12C region of KRAS^{G12C} mutant, locking KRAS in its inactive, GDP-bound state.[5,6,11] Given such mechanistic similarities, it is not surprising that both agents have been approved by the FDA for the clinical use of *KRAS*^{G12C}-mutant NSCLC as second-line agents. Now, the question is whether adagrasib or sotorasib is superior for treating previously treated *KRAS*^{G12C}-mutated NSCLC. Overall, the KRYSTAL and Codebreak phase 3 trials demonstrated that both adagrasib and sotorasib elicited statistically

Table 2 Comparison of Efficacy and Safety Between KRYSTAL 12 and CodebreaK 200

	KRYSTAL-12	CodebreaK 200
Trial Phase	3	3
Trial Design	Arm A: Adagrasib 600mg twice a day (N=301) Arm B: Docetaxel 74mg/m^2 every 3 weeks (N=152)	Arm A: Sotorasib 960 mg daily (N=171) Arm B: Docetaxel 75 mg/m² every 3 weeks (N=174)
Patient selection	*KRAS*^{G12C}-mutated, advanced NSCLC, previously treated	*KRAS*^{G12C}-mutated, advanced NSCLC, previously treated
Prior chemotherapy	100%	100%
Prior immunotherapy	100%	100%
BIRC-assessed ORR	A: 32% B: 9%	A: 28.1% B: 13.2%
DOR (months)	A: 8.3 (95% CI: 6.1–10.4) B: 5.4 (95% CI: 2.9–8.5)	A: 10.6 (95% CI: 8.9–14.0) B: 6.8 (95% CI: 4.3–8.3)
PFS (months)	A: 5.5 (95% CI: 4.5–6.7) B: 3.8 (95% CI: 3.0–4.5)	A: 5.6 (95% CI: 4.3–7.8) B: 4.5 (95% CI: 3.0–5.7)
Intracranial ORR	A: 24% (in all patients with baseline CNS metastases), 40% (in CNS evaluable population) B: 11%	Not reported
OS (months)	A: Not mature B: Not mature	A: 10.6 (95% CI: 8.9–14.0) B: 11.3 (95% CI: 9.0–14.9)
AEs	A: 94% B: 86%	A: 98% B: 95%
Grade 3–4 AE rate	A: 47% B: 46%	A: 33% B: 40%
AE-associated death rate	A: 1% B: <1%	A: <1% B: <1%
Common AEs	A: Diarrhea (53%), Vomiting (35%), Nausea (34%), AST increase (30%), ALT increase (30%) B: Anemia (29%), Asthenia (28%), Alopecia (25%), Diarrhea (24%), Neutropenia (16%)	A: Diarrhea (34%), Nausea (14%), Appetite decrease (11%), AST increase (10%), ALT increase (10%) B: Fatigue (25%), Alopecia (21%), Nausea (20%), Diarrhea (19%), Anemia (18%)

Abbreviations: AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; BIRC, blind independent central review; CNS, central nervous system; DOR, duration of response; NR, not reported; ORR, overall response rate; OS, overall survival; PFS; progression free survival; RCT, randomized controlled trial.

significant improvements in mPFS and ORR compared to docetaxel, which is the current standard of care. Specifically, the mPFS was 5.5 months with adagrasib (vs 3.84 with docetaxel; HR 0.58; P<0.0001)[8,9] and 5.6 months with sotorasib (vs 4.5 with docetaxel; HR 0.66; P=0.0017).[11] The median ORR was 31.9% for adagrasib (vs 9.2% for docetaxel; OR 4.68, P<0.0001)[8,9] and 28.1% for sotorasib (vs 13.2% for docetaxel, P<0.001)[11] (Table 2).

The similarity in how KRYSTAL-12 and CodebreaK 200 were conducted allow us to compare the results of both studies in attempt to evaluate adagrasib compared to sotorasib. The difference between mPFS of adagrasib and docetaxel was 1.6 months, while there was a 1.1-month difference between that of sotorasib and docetaxel. As for the median ORR, there was a 22.7% difference between adagrasib and docetaxel, and a 14.9% difference between sotorasib and docetaxel. Numerically, adagrasib and sotorasib lead to a similar mPFS and ORR; however, when comparing the relative difference between adagrasib vs docetaxel and sotorasib vs docetacel, it appears that adagrasib may be slightly more effective in

prolonging PFS and inducing overall response to therapy. Importantly, caution should be exercised when performing cross-trial comparisons.

Notably, KRYSTAL-12 also demonstrated a statistically significant increase in intracranial ORR in patients treated with adagrasib compared to docetaxel.[8] In all patients with baseline CNS metastases, the intracranial ORR was 24% in the adagrasib group and 11% in the docetaxel group. Even more significantly, in the CNS evaluable population, the intracranial ORR with adagrasib was 40%.[8,9] This improvement is crucial because neurological symptoms can greatly impact a patient's quality of life. While CodebreaK 200 reported delayed CNS recurrence with sotorasib with a median time to recurrence of CNS disease delayed for a median of 5.3 months, there are no specific reports on intracranial ORR with sotorasib.[11] Therefore, sotorasib may have similar effects; however, further studies are warranted.

Furthermore, OS was not significantly different between sotorasib (mOS 10.6 months [95% CI: 8.9–14]) and docetaxel (mOS 11.3 months (95% CI: 9–14]), with HR 1.01 [95% CI: 0.77–1.33].[11] For adagrasib, the OS data were immature at the time of analysis. The KRYSTAL-12 study remains ongoing as planned for the final analysis of OS.[9]

Regarding safety, grade ≥3 TRAEs were more frequently reported with adagrasib than sotorasib. Treatment discontinuation due to TRAEs was similar between adagrasib and sotorasib, with 8% in the adagrasib group (vs 14% with docetaxel)[7,8] compared to 10% with sotorasab (vs 11% with docetaxel).[11] The most frequent TRAEs of both adagrasib and sotorasib included diarrhea and increased ALT and AST levels, whereas with docetaxel, neutropenia, fatigue, and febrile neutropenia were more common.[11] (Table 2)

How does adagrasib compare to other KRAS^{G12C} inhibitors?

JDQ443 is another oral, selective, covalent KRAS^{G12C} inhibitor that maintains KRAS in an inactive GDP-bound state. KontRASt-01 (NCT04699188), a Phase Ib/II study demonstrated promising anti-tumor activity of JDQ443 in advanced solid tumors harboring *KRAS*^{G12C} mutation, including NSCLC and colorectal cancer. Preliminary data showed that 57% (4/7) confirmed ORR at 200 mg twice daily of JDQ443 as a single agent in NSCLC and 35% (7/20) confirmed ORR across doses of NSCLC.[12] During the 2023 ASCO Annual Meeting, Cappuzzo et al announced the initiation of KontRASt-02, a Phase III randomized study that, evaluating JDQ443 as monotherapy in comparison to docetaxel in patients with previously treated, advanced, *KRAS*^{G12C}-mutated NSCLC with the primary endpoint of PFS.[13] Despite the 57% ORR observed with the JDQ443 200, this was based on an incredibly small sample size and must be further evaluated. Unfortunately, as of July 2024, Novartis had stopped recruitment for the KontRASt-02 trial, perhaps because of the potential futility of JDQ443 in comparison to other existing KRAS^{G12C} inhibitors.

Divarasib (GDC-6036) is yet another KRAS^{G12C} inhibitor with increased potency and selectivity compared to adagrasib and sotorasib, and promising efficacy (ORR 53.4% and PFS 13.1 months, total n=60) in the NSCLC cohort of a Phase I trial (NCT04449874).[14] However, there is no data regarding divarasib and its efficacy with intracranial metastasis, a crucial missing piece. Despite divarasib being potentially more tolerable, with lower rates of grade 3 or higher adverse events, adagrasib remains a more favorable option in terms of overall efficacy at this time.

Other KRAS^{G12C} inhibitors include olomorasib (LY3537982), garsorasib (D-1553), and BI 1823911. Olomorasib is a potent and highly selective KRAS^{G12C} inhibitor that also acts on the inactive GDP-bound state. LOXO-RAS-20001, a Phase I–II study, demonstrated efficacy of olomorasib monotherapy in *KRAS*^{G12C}-mutant advanced solid tumors. In previously KRAS^{G12C}-inhibitor treated NSCLC, ORR was 41% (n=16/39) and mPFS 8.1 months (95% CI: 5.6–15.6). In KRAS^{G12C} inhibitor-naïve NSCLC, mPFS was 7.9 months (95% CI: 4.1-NE). However, data on CNS metastasis remains lacking.[15]

Similarly, garsorasib is a promising option for patients with *KRAS*^{G12C}-mutated NSCLC given its tolerable safety profile (38% reporting grade 3 and 4 events) and anti-tumor activity (ORR of 40.5%, mPFS of 8.2 months among 74 patients in Phase I trial NCT05383898). In patients with brain metastasis, ORR was 17%.[16] BI 1823911 is yet another potent KRAS^{G12C} inhibitor that demonstrated in vivo efficacy in preclinical studies and is now undergoing Phase I trial (NCT04973163) to investigate safety, tolerability, and efficacy as monotherapy and in combination with the pan-KRAS SOS1 inhibitor BI 1701963.[17]

Overall, these emerging KRAS^{G12C} inhibitors demonstrate encouraging antitumor activity and safety profiles, some with potentially more tolerable safety profiles such as divarasib, in comparison to adagrasib and sotorasib. However, they have not yet been directly compared to current standard of care, docetaxel in the second line setting, thus it is difficult to evaluate its relative

efficacy. Additionally, when assessing efficacy in the CNS, adagrasib remains the most favorable option given its significant improvement in intracranial ORR as seen in KRYSTAL-12 and the lack of CNS data with other KRAS^{G12C} inhibitors.

Despite the substantial clinical benefit observed with KRAS^{G12C} inhibitors, acquired resistance to single-agent therapy occurred in most patients on KRAS^{G12C} inhibitor monotherapy and can limit the clinical use of adagrasib and sotorasib, as with all other KRAS^{G12C} inhibitors. Interestingly, Koga et al revealed in vitro studies that demonstrated potential benefit in the sequential use of sotorasib and adagrasib depending on the specific secondary *KRAS* mutation. The study reported secondary *KRAS* mutations that were highly resistant to sotorasib but remained sensitive to adagrasib while mutations resistant to adagrasib remained sensitive to sotorasib. There were also secondary *KRAS* mutations that were resistant to both inhibitors, of which a combination of rametinib and BI-3406, a novel SOS1 inhibitor, had potent activity against.[18] Such nuanced differences amongst adagrasib, sotorasib, and potentially other KRAS^{G12C} inhibitors encourages further investigation regarding strategies involving complementary use of different KRAS^{G12C} inhibitors after development of resistance to a single inhibitor.

Future Directions

KRYSTAL-12 has confirmed adagrasib's efficacy in anti-tumor activity with significant improvement of ORR, mPFS and intracranial ORR. As evidenced, adagrasib has shown promise as a second-line therapy for *KRAS*^{G12C}-mutated advanced NSCLC, making its evaluation as a first-line treatment highly relevant. The KRYSTAL-7 trial (NCT04613596) explores adagrasib both as monotherapy and in combination with pembrolizumab. The Phase II cohort demonstrated that in patients with PD-L1 TPS ≥50%, the combination achieved an ORR of 63% and a disease control rate of 84%, with both the DOR and PFS not yet reached.[19]

The promising findings from the Phase II trial support the initiation of a Phase III trial to randomize patients with *KRAS*^{G12C}-mutated NSCLC and TPS ≥50% to receive either a combination of adagrasib and pembrolizumab, or pembrolizumab alone in the first-line setting. This trial aims to confirm adagrasib's potential to establish a new standard of care for this patient population.[20]

For patients with PD-L1 <50%, the combination of adagrasib and pembrolizumab also demonstrated clinical activity, suggesting that it could be a viable option across different PD-L1 levels.[21] Further research may focus on optimizing the dosage and combination strategies to enhance the efficacy in these patients.

Conclusion

In conclusion, adagrasib met the primary trial endpoint with statistically significant mPFS and ORR compared with docetaxel in the KRYSTAL-12 trial. Although the mPFS of 5.5 months falls slightly below the 6-month benchmark often cited in clinical discussions, it should not diminish its clinical significance. Adagrasib shows promising effectiveness against CNS metastases, highlighting its potential benefits in this area compared to other KRAS^{G12C} inhibitors, offering crucial benefits that extend beyond traditional PFS metrics. Future studies will explore adagrasib's potential as a first-line therapy in combination with immunotherapy, further expanding its role in the treatment of advanced *KRAS*^{G12C}-mutated NSCLC.

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Disclosure

No conflict of interest to declare.

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